

NCI Alliance for
Nanotechnology
in Cancer

NCI Alliance for Nanotechnology in Cancer

Program Evaluation

Part 2



VOLUME 2

- **Program Collaborations**
 - List of Alliance Collaborations
 - Geography of Collaborations
 - Joint Publications
 - Alliance Collaborations With Other NCI Programs
 - Training Activities
 - Alliance Bulletin
- **NCL Report**
- **Initial program announcement**
 - Cancer Nanotechnology Plan
 - White Paper – 2004
 - Original RFAs

Collaborative Nature of Research and Technology Development

One of the core features of the Alliance is its heavy emphasis on promoting team science. The NCI program management team spends considerable time working with Alliance investigators to create and drive multidisciplinary teams drawing on synergistic elements of the expertise within different Centers and projects. Alliance members have also developed trans-institutional collaborative projects through their discussions at the annual Investigators Meetings, held each October, and through their interactions as members of the various Alliance working groups. We expect that these joint, inter-project efforts will lead to accelerated scientific progress and will increase common infrastructure to speed up dissemination of data and results.

However, as with all scientific collaborations, large or small, many potential barriers had to be negotiated, including:

- Team members' expertise and flexibility of working with investigators from a different discipline
- Institutional support for cross-disciplinary collaboration
- Spatial proximity of investigators' offices and laboratories
- Overlapping departmental identities of team members

The program office has worked diligently to help ameliorate these potential barriers through planning investigators meetings, hosting working group sessions, and suggesting potential investigator collaborations. To facilitate further discussions among investigators, program staff also developed a visual chart of Alliance projects and their disease (organ) focus against yearly reports of various cancers' incidence and mortality statistics. Our update this year indicates that several projects have expanded their focus to include additional organs in their studies. Ultimately, we anticipate that several technologies developed under this program will facilitate technology platform solutions applicable to several types of cancer.

Spurred by these events, the collaborative nature of the program, and the positive attitude of investigators toward synergistic collaborations, the Alliance community already boasts several inter-Alliance joint projects after first 3 years.

The following pages list: (1) most relevant collaborative efforts established within the Alliance specifying the PIs involved and the topic of their joint research; (2) graphic demonstration of developing these collaborations through the years of the program; (3) list of collaborative publications produced by the Alliance PIs; and (4) interactions of the Alliance PIs with other large NCI programs such as SPOREs, Comprehensive Cancer Centers, and others.

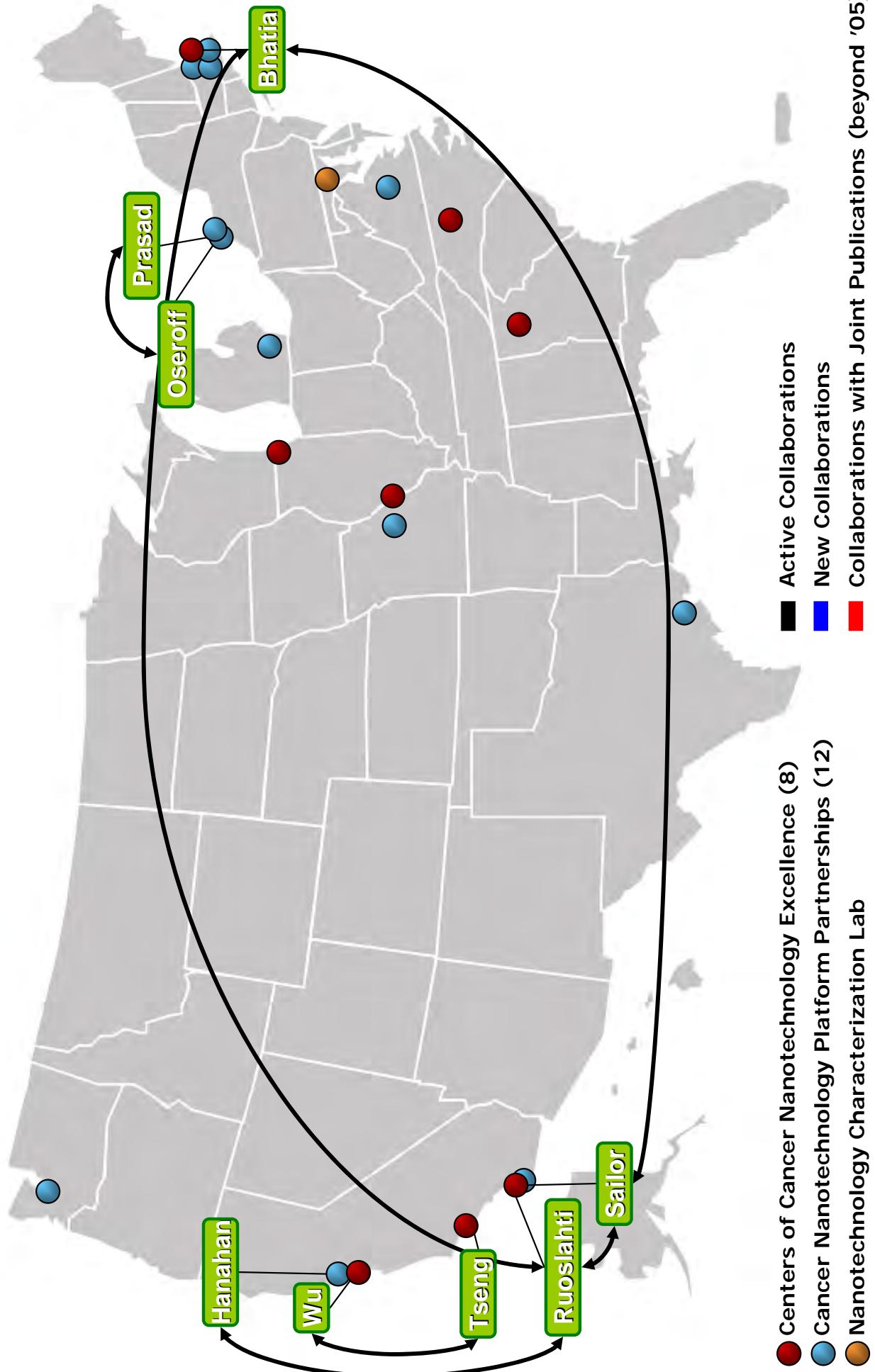
Project PI	PI Affiliation	Collaborating PI(s)	Collaborating PI(s) Affiliation	Collaboration Summary
FY06				
Sangeeta Bhatia	MIT/Harvard CCNE	Erkki Ruoslahti Michael Sailor	UCSD CCNE	Development of protease-triggered nanoparticle solutions for MR imaging and therapeutic delivery.
Paras Prasad	SUNY/Buffalo CNPP	Allan Oseroff	Roswell Park CNPP	Application of organically modified silica (ORMOSIL) nanoparticles in cancer photodynamic therapy.
Hsian-Rong Tseng	Caltech/UCLA CCNE	Anna Wu	Stanford CCNE	Improve PDM/S microchannels for protein repellting, cell immobilization and incubation, semi-quantitative DNA hybridization, and immunoassay applications.
FY07				
Joseph DeSimone	UNC CCNE	David Cheresh	UCSD CCNE	Target PRINT nanoparticles with cRGD for therapeutic delivery of docetaxel.
James Heath	Caltech /UCLA CCNE	Scott Manalis	MIT CNPP	Integration of DEAL technology with SMR nanosensor platform to increase capture efficiency of relevant cancer biomarkers.
Robert Sinclair	Stanford CCNE	Vinayak P. Dravid	Northwestern CCNE	Develop best practices towards synthesis and characterization of nanostructures.
Jianhong Rao	Stanford CCNE	Mounji Bawendi John Frangioni	MIT/Harvard CCNE	Decrease in vivo toxicity of BRET-hemo sensor for medical imaging purposes.
Larry Nishi	Stanford CCNE	Francis Szoka	UNC CCNE	Develop novel nanoparticle delivery system for cancer therapeutics.
Gregory Lanza	Washington U. CCNE	James Baker	U. of Mich CNPP	Facilitate targeted imaging studies examining neovasculature in tumor mouse models.
Michael Sailor	UCSD CCNE	Jan Schnitzer James Baker	SKCC CNPP U. of Mich CNPP	Develop RGP dendrimer constructs for a combined nano-based technology for targeted therapeutics and diagnostics.
Al Charest	MIT/Harvard CCNE	Miqin Zhang	U. of Wash CCNP	Transfer of unique brain tumor mouse model system for MR imaging studies of targeted nanoparticle system.
Sangeeta Bhatia	MIT/Harvard CCNE	Scott Manalis	MIT CNPP	Integrate protease-triggered nanoparticles system with SMR nanosensor platform to detect protease activity in various cancers.
Scott Manalis	MIT CNPP	Karttesh Katti	U. of Missouri CNPP	Test gum-arabic coated gold nanoparticles as functional probes for SMR nanosensor platform
Douglas Hanahan	UCSF CNPP	Francis Szoka	UNC CCNE	Synthesis of nanoparticulate formulations coated with two distinct tumor homing peptides against pancreatic and cervical cancer

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Project PI	PI Affiliation	Collaborating PI(s)	Collaborating PI(s) Affiliation	Collaboration Summary
Miqin Zhang	U. of Wash CNPP	Chun Li	M.D. Anderson CNPP	Evaluate pharmacokinetic and bio-distribution of multifunctional nanoparticles in mouse models.
FY08				
Chad Mirkin	Northwestern U. CCNE	Andrew Ellington	Stanford CCNE	Development of aptamer-based sensors for cancer biomarker detection.
Thomas O'Halloran	Northwestern U. CCNE	William Troger	UCSD CCNE	Arsenic Trioxide loaded silica-based nanospheres for nanodelivery of therapeutics
Douglas Hanahan	UCSF CNPP	Ralph Weissleder	MIT/Harvard CCNE	Synthesis of phage-peptide targeted nanoparticles for SPECT imaging of cancer.
Douglas Hanahan	UCSF CNPP	Leland Chung	Emory/GT CCNE	Targeted imaging of novel pancreatic cancer mouse models for detection of metastatic lesions.
Leland Chung	Emory/GT CCNE	JJ Cheng	Washington U. CCNE	Targeted nanotheranostics for detection of metastatic prostate cancer.
Leland Chung	Emory/GT CCNE	Miqin Zhang	U. of Wash CNPP	Use of CTX nanoparticles for MR imaging detection of prostate metastasis cancer.
Leland Chung	Emory/GT CCNE	Kaitesh Katti	U. of Missouri CNPP	BBN targeted nanoparticles for imaging of metastatic prostate cancer.
Erkki Ruoslahti	UCSD CCNE	Ruth Nussinov	NCI CCR	Computation-assisted development of cancer targeting peptides.
Shawn Chen	Stanford CCNE	Miqin Zhang	U. of Wash CNPP	Evaluate biodistribution VEGF targeted PET nano-imaging agent
Sam Gambhir	Stanford CCNE	Kaitesh Katti	U. of Missouri CNPP	Development of biocompatible gold nanoparticles for use as Raman molecular imaging agents
Brian Kay	UNC CCNE	Scott Manalis	MIT CNPP	Develop SMR nanosensor platform-based detection assay using based on Ankyrin repeat proteins for Her2.
Parag Mallick	Stanford CCNE	Scott Manalis	MIT CNPP	Single cell growth monitor for classifying therapeutic response using SMR nanosensor platform.
Tayyaba Hasan	Mass Gen CNPP	Mansoor Amiji	Northeastern CNPP	Nanomaterial design for PDT in cancer and subsequent evaluation and optimization of PD and PK properties.

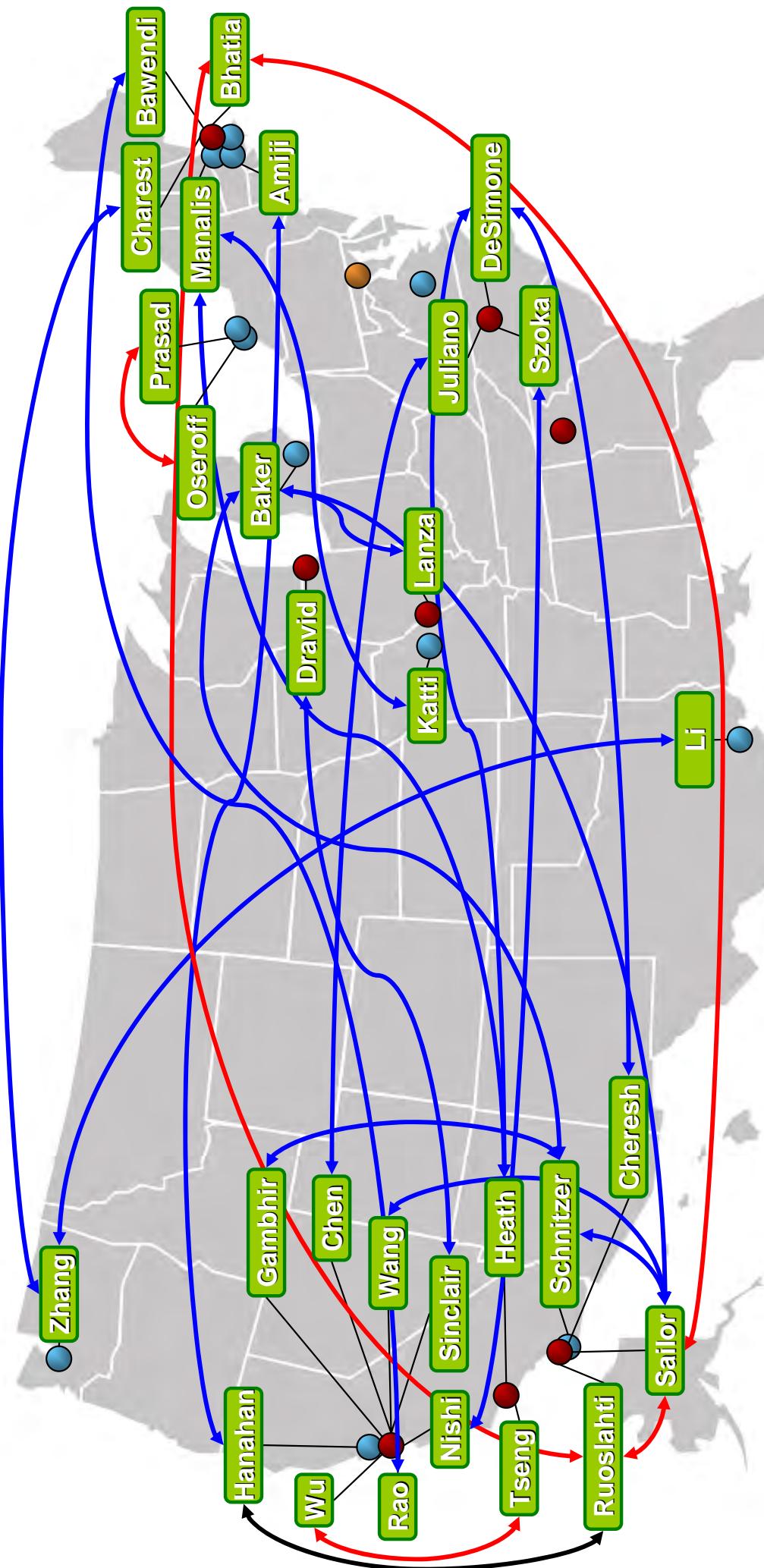
NCI Alliance for Nanotechnology in Cancer: Building Inter-Center Connections and Collaborations Year 1

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NCI Alliance for Nanotechnology in Cancer: Building Inter-Center Connections and Collaborations Year 2

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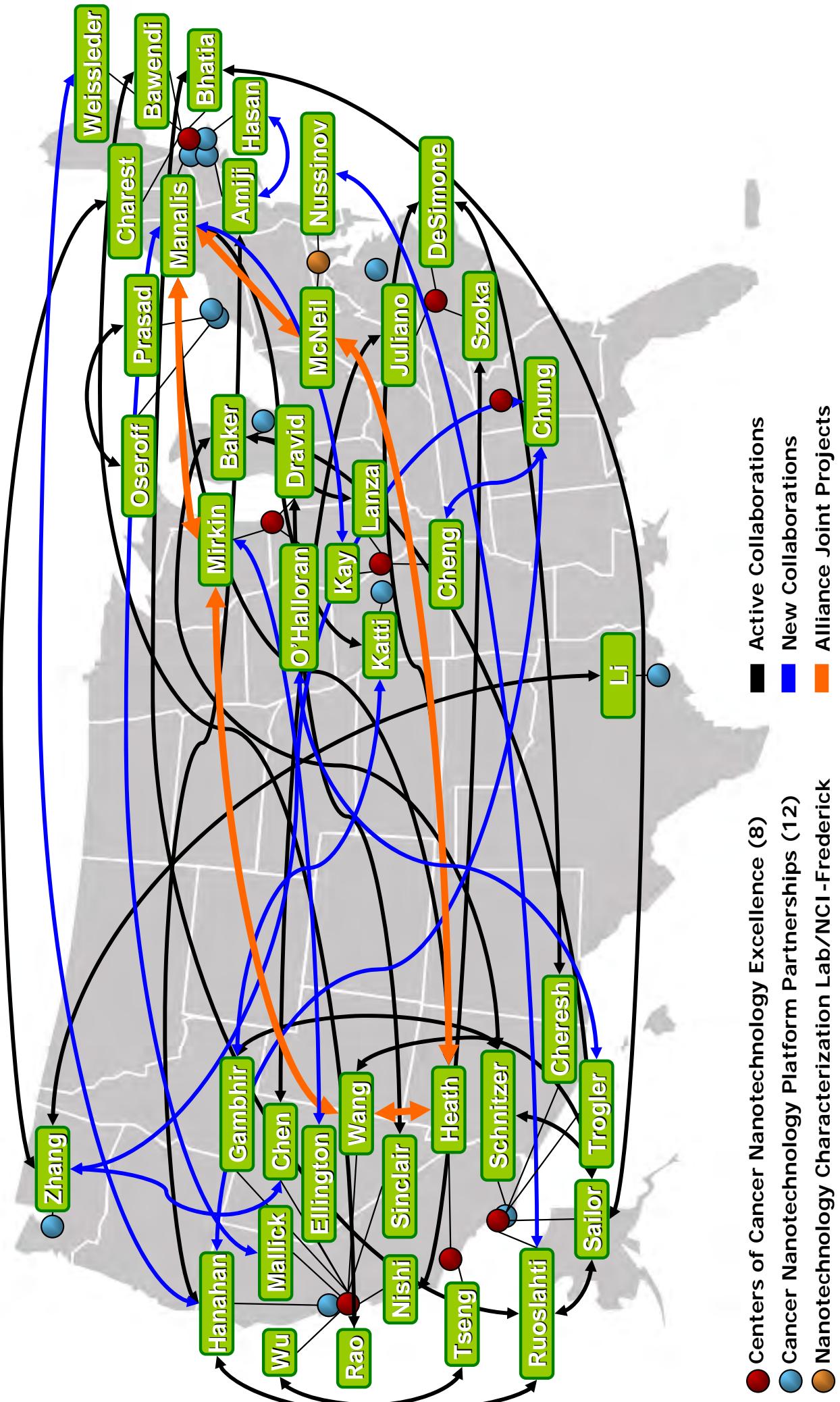
- Centers of Cancer Nanotechnology Excellence (8)
- Cancer Nanotechnology Platform Partnerships (12)
- Nanotechnology Characterization Lab

- Active Collaborations
- New Collaborations
- Collaborations with Joint Publications (beyond '05)

- Centers of Cancer Nanotechnology Excellence (8)
- Cancer Nanotechnology Platform Partnerships (12)
- Nanotechnology Characterization Lab

NCI Alliance for Nanotechnology in Cancer: Building Inter-Center Connections and Collaborations Year 3

NCI Alliance for
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Collaborative Publications

1. Lee, C. C., Sui, G., Elizarov, A., Shu, C. J., Shin, Y. S., Dooley, A. N., Huang, J., Daridon, A., Wyatt, P., Stout, D., Kolb, H. C., Witte, O. N., Satyamurthy, N., Heath, J. R., Phelps, M. E., Quake, S. R. and Tseng, H. R. Multistep Synthesis of a Radiolabeled Imaging Probe Using Integrated Microfluidics. **Science** 310, 1793-6. Dec 16, **2005**. internal Caltech/UCLA CCNE collaboration
2. Wang, S., Garcia, A. J., Wu, M., Lawson, D. A., Witte, O. N. and Wu, H. Pten Deletion Leads to the Expansion of a Prostatic Stem/Progenitor Cell Subpopulation and Tumor Initiation. **Proc Natl Acad Sci U S A** 103, 1480-5. Jan 31, **2006**. internal Caltech/UCLA CCNE collaboration
3. Lei, Q., Jiao, J., Xin, L., Chang, C. J., Wang, S., Gao, J., Gleave, M. E., Witte, O. N., Liu, X. and Wu, H. Nkx3.1 Stabilizes P53, Inhibits Akt Activation, and Blocks Prostate Cancer Initiation Caused by Pten Loss. **Cancer Cell** 9, 367-78. May, **2006**. internal Caltech/UCLA CCNE collaboration
4. Sui, G., Wang, J., Lee, C. C., Lu, W., Lee, S. P., Leyton, J. V., Wu, A. M. and Tseng, H. R. Solution-Phase Surface Modification in Intact Poly(Dimethylsiloxane) Microfluidic Channels. **Anal Chem** 78, 5543-51. Aug 1, **2006**. internal Caltech/UCLA CCNE collaboration
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6. Bailey, R. C., Kwong, G. A., Radu, C. G., Witte, O. N. and Heath, J. R. DNA-Encoded Antibody Libraries: A Unified Platform for Multiplexed Cell Sorting and Detection of Genes and Proteins. **J Am Chem Soc** 129, 1959-67. Feb 21, **2007**. internal Caltech/UCLA CCNE collaboration
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8. Sui, G., Lee, C. C., Kamei, K., Li, H. J., Wang, J. Y., Wang, J., Herschman, H. R. and Tseng, H. R. A Microfluidic Platform for Sequential Ligand Labeling and Cell Binding Analysis. **Biomed Microdevices** 9, 301-5. Jun, **2007**. Caltech/UCLA & Stanford CCNEs collaboration
9. Radu, C. G., Shu, C. J., Nair-Gill, E., Shelly, S. M., Barrio, J. R., Satyamurthy, N., Phelps, M. E. and Witte, O. N. Molecular Imaging of Lymphoid Organs and Immune Activation by Positron Emission Tomography with a New [18f]-Labeled 2'-Deoxycytidine Analog. **Nat Med** 14, 783-8. Jul, **2008**. internal Caltech/UCLA CCNE collaboration
10. He, J. H., Zhang, Y. Y., Liu, J., Moore, D., Bao, G. and Wang, Z. L. Zns/Silica Nanocable Field Effect Transistors as Biological and Chemical Nanosensors. **J. Phys. Chem. C** 111, 12152-56. July **2007**. internal Emory/GT CCNE collaboration
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12. Harris, T. J., von Maltzahn, G., Derfus, A. M., Ruoslahti, E. and Bhatia, S. N. Proteolytic Actuation of Nanoparticle Self-Assembly. **Angew Chem Int Ed Engl** 45, 3161-5. May 5, **2006**. MIT/Harvard & UCSD CCNEs collaboration
13. Park, J. H., Derfus, A. M., Segal, E., Vecchio, K. S., Bhatia, S. N. and Sailor, M. J. Local Heating of Discrete Droplets Using Magnetic Porous Silicon-Based Photonic Crystals. **J Am Chem Soc** 128, 7938-46. Jun 21, **2006**. MIT/Harvard & UCSD CCNEs collaboration

14. Schwartz, M. P., Derfus, A. M., Alvarez, S. D., **Bhatia, S. N. and Sailor, M. J.** The Smart Petri Dish: A Nanostructured Photonic Crystal for Real-Time Monitoring of Living Cells. **Langmuir** 22, 7084-90. Aug 1, **2006**. MIT/Harvard & UCSD CCNEs collaboration
15. Simberg, D., Duza, T., Park, J. H., Essler, M., Pilch, J., Zhang, L., Derfus, A. M., Yang, M., Hoffman, R. M., **Bhatia, S., Sailor, M. J.** and Ruoslahti, E. Biomimetic Amplification of Nanoparticle Homing to Tumors. **Proc Natl Acad Sci U S A** 104, 932-6. Jan 16, **2007**. MIT/Harvard & UCSD CCNEs collaboration
16. Derfus, A. M., Chen, A. A., Min, D. H., **Ruoslahti, E.** and **Bhatia, S. N.** Targeted Quantum Dot Conjugates for Sirna Delivery. **Bioconjug Chem** Jul 14, **2007**. MIT/Harvard & UCSD CCNEs collaboration
17. Hong, R., **Cima, M. J., Weissleder, R.** and Josephson, L. Magnetic Microparticle Aggregation for Viscosity Determination by Mr. **Magn Reson Med** 59, 515-20. Mar, **2008**. internal MIT/Harvard CCNE collaboration
18. Park, J. H., von Maltzahn, G., Zhang, L., Schwartz, M. P., **Ruoslahti, E., Bhatia, S. N.** and **Sailor, M. J.** Magnetic Iron Oxide Nanoworms for Tumor Targeting and Imaging. **Advanced Materials** 20, 1589. **2008**. MIT/Harvard & UCSD CCNEs collaboration
19. Teply, B. A., Tong, R., Jeong, S. Y., Luther, G., Sherifi, I., Yim, C. H., Khademhosseini, A., **Farokhzad, O. C., Langer, R. S.** and **Cheng, J.** The Use of Charge-Coupled Polymeric Microparticles and Micromagnets for Modulating the Bioavailability of Orally Delivered Macromolecules. **Biomaterials** 29, 1216-23. Mar, **2008**. MIT/Harvard & Washington U CCNEs collaboration
20. von Maltzahn, G., Ren, Y., Park, J.-H., Min, D.-H., Kotamraju, V. R., Jayakumar, J., Fogal, V., **Sailor, M. J., Ruoslahti, E.** and **Bhatia, S. N.** In Vivo Tumor Cell Targeting with "Click" Nanoparticles. **Bioconjug Chem** accepted, **2008**. MIT/Harvard & UCSD CCNEs collaboration
21. Harris, T., von Maltzhahn, G., Lord, M. E., Park, J., Agarwal, A., Min, D., **Sailor, M. J.** and **Bhatia, S. N.** Protease-Triggered Unveiling of Bioactive Nanoparticles. **Small** accepted, **2008**. internal MIT/Harvard CCNE collaboration
22. Endres, P. J., Paunesku, T., Vogt, S., **Meade, T. J.** and **Woloschak, G. E.** DNA-TiO₂ Nanoconjugates Labeled with Magnetic Resonance Contrast Agents. **J Am Chem Soc** 129, 15760-1. Dec 26, **2007**. internal Northwestern CCNE collaboration
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25. Cai, W., Shin, D. W., Chen, K., Gheysens, O., Cao, Q., **Wang, S. X., Gambhir, S. S.** and **Chen, X.** Peptide-Labeled near-Infrared Quantum Dots for Imaging Tumor Vasculature in Living Subjects. **Nano Lett** 6, 669-76. Apr, **2006**. internal Stanford CCNE collaboration
26. Cai, W., **Rao, J., Gambhir, S. S.** and **Chen, X.** How Molecular Imaging Is Speeding up Antiangiogenic Drug Development. **Mol Cancer Ther** 5, 2624-33. Nov, **2006**. internal Stanford CCNE collaboration
27. Zhang, Y., So, M. K., Loening, A. M., Yao, H., **Gambhir, S. S.** and **Rao, J.** Halotag Protein-Mediated Site-Specific Conjugation of Bioluminescent Proteins to Quantum Dots. **Angew Chem Int Ed Engl** 45, 4936-40. Jul 24, **2006**. internal Stanford CCNE collaboration
28. Loening, A. M., Fenn, T. D., **Wu, A. M.** and **Gambhir, S. S.** Consensus Guided Mutagenesis of Renilla Luciferase Yields Enhanced Stability and Light Output. **Protein Eng Des Sel** 19, 391-400. Sep, **2006**. internal Stanford CCNE collaboration

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30. Liu, Z., Cai, W. B., He, L. N., Nakayama, N., Chen, K., Sun, X. M., **Chen, X. Y.** and **Dai, H. J.** In Vivo Biodistribution and Highly Efficient Tumour Targeting of Carbon Nanotubes in Mice. **Nat Nanotechnol** 2, 47-52. Jan, **2007**. internal Stanford CCNE collaboration
31. Cai, W., Olafsen, T., Zhang, X., Cao, Q., **Gambhir, S. S.**, Williams, L. E., **Wu, A. M.** and **Chen, X.** Pet Imaging of Colorectal Cancer in Xenograft-Bearing Mice by Use of an 18f-Labeled T84.66 Anti-Carcinoembryonic Antigen Diabody. **J Nucl Med** 48, 304-10. Feb, **2007**. internal Stanford CCNE collaboration
32. Loening, A. M., **Wu, A. M.** and **Gambhir, S. S.** Red-Shifted Renilla Reniformis Luciferase Variants for Imaging in Living Subjects. **Nat Methods** 4, 641-3. Aug, **2007**. internal Stanford CCNE collaboration
33. Schipper, M. L., Cheng, Z., Lee, S. W., Bentolila, L. A., Iyer, G., Rao, J., Chen, X., **Wu, A. M.**, Weiss, S. and **Gambhir, S. S.** Micropet-Based Biodistribution of Quantum Dots in Living Mice. **J Nucl Med** 48, 1511-8. Sep, **2007**. internal Stanford CCNE collaboration
34. Venisnik, K. M., Olafsen, T., **Gambhir, S. S.** and **Wu, A. M.** Fusion of Gaussia Luciferase to an Engineered Anti-Carcinoembryonic Antigen (Cea) Antibody for in Vivo Optical Imaging. **Mol Imaging Biol** 9, 267-77. Sep-Oct, **2007**. internal Stanford CCNE collaboration
35. Lin, S., Xie, X., Patel, M. R., Yang, Y. H., Li, Z., Cao, F., Gheysens, O., Zhang, Y., **Gambhir, S. S.**, **Rao, J. H.** and Wu, J. C. Quantum Dot Imaging for Embryonic Stem Cells. **BMC Biotechnol** 7, 67. Oct, **2007**. internal Stanford CCNE collaboration
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37. Hu, W., Wilson, R. J., Koh, A., Fu, A., Faranesh, A. Z., Earhart, C. M., Osterfeld, S. J., Han, S. J., Xu, L., Guccione, S., **Sinclair, R.** and **Wang, S. X.** High-Moment Antiferromagnetic Nanoparticles with Tunable Magnetic Properties. **Advanced Materials** 20, 1479-83. **2008**. internal Stanford CCNE collaboration
38. Smith, B. R., Cheng, Z., De, A., Koh, A. L., **Sinclair, R.** and **Gambhir, S. S.** Real-Time Intravital Imaging of Rgd-Quantum Dot Binding to Luminal Endothelium in Mouse Tumor Neovasculature. **Nano Lett** Apr 4, **2008**. internal Stanford CCNE collaboration
39. Lee, H. Y., Lee, S. H., Chenjie, X., Xie, J., Lee, J. H., Wu, B., Koh, A. L., Wang, X., **Sinclair, R.**, **Wang, S. X.**, Nishimura, D. G., Biswal, S., Sun, S., Cho, S. H. and **Chen, X.** Synthesis and Characterization of Pvp-Coated Large Core Iron Oxide Nanoparticles as an MRI Contrast Agent. **Nanotechnology** 19, 23 April 2008, **2008**. internal Stanford CCNE collaboration
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41. **Blair, S. L.**, Wang-Rodriguez, J., Cortes-Mateos, M. J., **Messmer, D.**, Sandoval, S., Messmer, B., Troglar, W. and **Kummel, A.** Enhanced Touch Preps Improve the Ease of Interpretation of Intraoperative Breast Cancer Margins. **Am Surg** 73, 973-6. Oct, **2007**. internal UCSD CCNE collaboration
42. Kim, J. S., Valencia, C. A., **Liu, R.** and **Lin, W.** Highly-Efficient Purification of Native Polyhistidine-Tagged Proteins by Multivalent Nta-Modified Magnetic Nanoparticles. **Bioconjug Chem** 18, 333-41. Mar-Apr, **2007**. internal UNC CCNE collaboration

43. Ohulchanskyy, T. Y., Roy, I., Goswami, L. N., Chen, Y., Bergey, E. J., Pandey, R. K., Oseroff, A. R. and Prasad, P. N. Organically Modified Silica Nanoparticles with Covalently Incorporated Photosensitizer for Photodynamic Therapy of Cancer. **Nano Lett** 7, 2835-42. Sep, **2007**. *Roswell Park Cancer Institute & U Buffalo CNPPs collaboration*

Alliance Collaborations With Large NCI Programs

CCNE	Investigator	NCI-related Project Title	Investigator Role
Emory/ GT CCNE	Brian Leyland-Jones	Comprehensive Cancer Center	PI
Emory/ GT CCNE	Dong Shin	Comprehensive Cancer Center, CTEP, U01, NCI Training Program	PI
Emory/ GT CCNE	Dong Shin	Head and Neck Cancer SPORE	
Emory/ GT CCNE	Lily Yang	Comprehesnive Cancer Centers (Arkanasas Cancer Research Center, Fox Chase Cancer Center), NTROI, Emory Head and Neck SPORE	
Emory/ GT CCNE	May Wang	caBIG	PI
Emory/ GT CCNE	Robert Bostick	Comprehensive Cancer Center (P20 planning grant)	
Emory/ GT CCNE	Shuming Nie	Head and Neck Cancer SPORE	Project Pi

Northwestern CCNE	Chung Lee	Robert H. Lurie Comprehensive Cancer Center: Program Leader - Prostate Cancer	Co-PD/PI
Northwestern CCNE	Chung Lee	SPORE in Prostate Cancer - Director, SPORE	PD/PI
Northwestern CCNE	Julian Schink	Robert H. Lurie Comprehensive Cancer Center: Director, Clinical Cancer Center	Co-PD/PI
Northwestern CCNE	Raymond Bergan	ECOG CCOP Research Base: Core Director - ECOG Biomarker Identification Core	PD/PI
Northwestern CCNE	Raymond Bergan	Phase I and II Clinical Trials of Cancer Chemopreventive Agents: (Hemant Roy, Vadim Backman, Raymond Bergan) Spectral Markers in Aspirin Chemoprevention of Colonic Neoplasia	PD/PI
Northwestern CCNE	Raymond Bergan	Robert H. Lurie Comprehensive Cancer Center: Program Leader - Cancer Prevention	Other
Northwestern CCNE	Steve Rosen	Robert H. Lurie Comprehensive Cancer Center	PD/PI
Northwestern CCNE	Susan Crawford	Robert H. Lurie Comprehensive Cancer Center: Director - Mouse Phenotyping Core Facility	Other
Northwestern CCNE	Thomas O'Halloran	Robert H. Lurie Comprehensive Cancer Center: Associate Director, Basic Science Progarms	Co-PD/PI
Northwestern CCNE	Warren Kibbe	caBIG: Task Order 10 NBN Bootcamp	PD/PI
Northwestern CCNE	Warren Kibbe	caBIG-CTMS Workspace Developer-Adopter, Patient Study Calendar (PSC) Module Phase III	
Northwestern CCNE	Warren Kibbe	Robert H. Lurie Comprehensive Cancer Center: Director, Bioinformatics Core	Co-PD/PI

CCNE	Investigator	NCI-related Project Title	Investigator Role
UCSD CCNE	Dennis Carson	Cancer Center Support Grant	Project Leader
UCSD CCNE	Erkki Ruoslahti	Cancer Center Support Grant	Project Leader
UCSD CCNE	Michael Bouvet	T32: Cancer Therapeutics Training Program	Co-PI
UCSD CCNE	Roger Tsien	T32: Growth Regulation & Oncogenesis	Co-PI
UCSD CCNE	Stephen Howell	T32: Cancer Therapeutics Training Program	Co-PI

UNC CCNE	Channing Der	T32 Training grant	Pilot grant co-investigator
UNC CCNE	Channing Der	GI SPORE	
UNC CCNE	David Threadgill	Comprehensive Cancer Center, GI SPORE	Investigator
UNC CCNE	Etta Pisano	Comprehensive Cancer Center, U of Chicago Breast Cancer SPORE	Steering Committee
UNC CCNE	Gary Johnson	Comprehensive Cancer Center	Project 6 Investigator
UNC CCNE	H. Shelton Earp III	Comprehensive Cancer Center and Breast Cancer SPORE	Steering Committee Chair
UNC CCNE	Jim Bear	Comprehensive Cancer Center	Project 6 Investigator
UNC CCNE	Joe DeSimone	Comprehensive Cancer Center, NU-CCNE, CTEP	co-PI
UNC CCNE	Joel Tepper	GI SPORE, CTEP, and Comprehensive Cancer Center	Steering Committee
UNC CCNE	Jonathan Serody	Comprehensive Cancer Center, Breast Cancer SPORE	Project 2 Investigator
UNC CCNE	Klaus Hahn	Comprehensive Cancer Center	Project 6 Investigator
UNC CCNE	MJ Cho	Comprehensive Cancer Center	Project 2 Investigator
UNC CCNE	Otto Zhou	Comprehensive Cancer Center	Project 3 PI
UNC CCNE	P. Kay Lund	Comprehensive Cancer Center	Project 3 Investigator
UNC CCNE	Rihe Liu	Comprehensive Cancer Center	Core 2 PI
UNC CCNE	Rudy Juliano	Comprehensive Cancer Center and T32 Training Grant	PI
UNC CCNE	Terry Van Dyke	MMHCC, NCI Frederick Mouse Cancer Genetics Program, Comprehensive Cancer Center	Core I PI, Project 4 Investigator
UNC CCNE	Weili Lin	Comprehensive Cancer Center	Core 3 PI
UNC CCNE	Wenbin Lin	Comprehensive Cancer Center	Project 4 PI

Multidisciplinary Research Training and Team Development

Multidisciplinary Research Training and Team Development fellowship awards were granted to postdoctoral trainees to allow for multidisciplinary training. New applications for these awards will be also received in 2008. The awards, in alphabetical order by trainee, are:

- **Nanoparticle-Bioconjugates as Cancer-Treating Agents, Texas A&M University, College Station, Texas.** Trainee: Sofi Bin-Salamon, Ph.D.
- **Nanoscale Mechanisms of Hsp90 and Its Co-chaperones, Yale University, New Haven, Connecticut.** Trainee: Ivo P. Doudevski, Ph.D.
- **Targeted Delivery Via Protein-Carbohydrate Interactions, Liquidia, Inc., Research Triangle Park, North Carolina.** Trainee: Ashley L. Galloway, Ph.D.
- **Liposomal Delivery of High LET Emitters to Cell Nuclei, Johns Hopkins University, Baltimore, Maryland.** Trainee: Yah-El Har-El, Ph.D.
- **Geldanamycin-Mediated Uptake of Nanoparticle Probes, Purdue University, West Lafayette, Indiana.** Trainee: Giselle M. Knudsen, Ph.D.
- **Nanolabels of Active Proteases for Cancer Detection, University of California, San Francisco, California.** Trainee: Mark D. Lim, Ph.D.
- **Single Walled Carbon Nanotube Based Tumor Vaccines, Memorial Sloan-Kettering Institute for Cancer Research, New York, New York.** Trainee: Rena J. May, Ph.D.
- **Short-Interfering RNA-Gold Nanoparticle Bioconjugates: A New Cancer Therapy, Northwestern University, Evanston, Illinois.** Trainee: Adam B. Braunschweig, Ph.D.
- **Design of Affinity Capture Agents for Akt1 Using in situ Click Chemistry, California Institute of Technology, Pasadena, CA.** Trainee: Steven W. Millward, Ph.D.
- **Targeted Photoactivated Nanoparticles for the Treatment of Ovarian Cancer, Massachusetts General Hospital, Boston, MA.** Trainee: Daniel Neuman, Ph.D.
- **Nanoprobes and Integrated Nanodevices for Cancer Detection and Treatment, University of Colorado Health Services, Superior, CO.** Trainee: Wounjhang Park, Ph.D.

Multidisciplinary Training and Team Development

1.1 Introduction

Nanotechnology research is by nature an interdisciplinary endeavor. Investigators with basic science, engineering, molecular biology, and clinical backgrounds must work closely together in order to design new drugs and diagnostic tools that combine nanostructured materials, biological molecules, and novel instrumentation. The NCI Alliance has implemented numerous training and career development mechanisms toward building an interdisciplinary, biologically inspired nanotechnology workforce, and to support the research teams working on NCI-funded nanotechnology projects. These mechanisms are highlighted here and include individual postdoctoral fellowships, institutional training awards, and coordinated tutorial events. In addition, we also showcase the many training efforts and activities that have been initiated by Alliance CCNEs.

1.2 Fellowships in Cancer Nanotechnology Research

The Multidisciplinary Fellowships in Cancer Nanotechnology Research were established as part of the NCI Alliance for Nanotechnology in Cancer program. NIH F32 and F33 NRSA award mechanisms are used to provide postdoctoral and senior fellow trainees with interdisciplinary training specifically in the field of cancer nanotechnology. The goal of this fellowship program is to provide research scientists with an opportunity to train outside their current fields of expertise and develop multidisciplinary skill sets that can be applied in the development and testing of nanomaterials and nanodevices in cancer-related applications of diagnosis and treatment. Programmatic analysis shows steady increase in both submitted and awarded applications. The eleven fellows funded by the program (see table) have been prolific and coauthored over ten publications in 2006 and 2007, with several more in the pipeline for 2008.

Trainee	Project Title	Ph.D. Field	F32 Training Field
Ivo P. Doudevski	Nanoscale mechanisms of Hsp90 and its co-chaperones	Chemistry	Biophysics
Rena J. May	Single walled carbon nanotube based tumor vaccines	Cell Biology	Pharmacology
Sofi Bin-Salamon	Nanoparticle-bioconjugates as cancer-treating agents	Mat. Sci.	Chemistry
Mark D. Lim	Nanolabels of active proteases for cancer detection	Chemistry	Pharmacology
Ashley L. Galloway	Targeted delivery via protein-carbohydrate interactions	Organic Chem.	Mat. Sci.
Yah-El Har-El	Liposomal delivery of high LET emitters to cell nuclei	Chem Eng.	Radiology
Giselle M. Knudsen	Geldanamycin-mediated uptake of nanoparticle probes	Chemistry	Pharmacology
Adam Braunschweig	Short-Interfering RNA-Gold Nanoparticle Bioconjugates: A New Cancer Therapy	Chemistry	Molecular Biology
Steven Millward	Design of Affinity Capture Agents for Akt1 Using in situ Click Chemistry	Molecular Biophysics	Medical Pharmacology
Daniel Neuman	Targeted Photoactivated Nanoparticles for the Treatment of Ovarian Cancer	Chemistry	Pharmacology
Wounjhong Park	Nanoprobes and Integrated Nanodevices for Cancer Detection and Treatment	Physics	Medical Oncology

1.3 Nano Med School Tutorial Sessions and Nanotechnology Trainees Forum

In order to build upon the success of the premeeting Commercialization Forum held at the first annual investigators meeting, program staff coordinated tutorial training sessions aimed at nearly a third of meeting participants: graduate and postdoctoral students. Since Alliance investigators come from a wide range of backgrounds in physical, life, and clinical sciences, the NCI Alliance Nano Med School covered topics of basic cancer biology, animal models, biodistribution of nanoparticle platforms, and the materials science of nanotechnology. Local UNC Alliance investigators Dr. Channing Der, Dr. Terry Van Dyke, Dr. Leaf Huang, and Dr. Joseph DeSimone provided a half-day of insightful presentations that was kicked off by a presentation by Dr. Carolyn Compton from NCI. While the sessions were

initially intended for students, the tutorials drew more than 250 attendees who consisted of approximately 25% investigators, 60% postdoctoral fellows and graduate students, and 15% government/industry participants. All tutorial slide sets were made available to meeting participants via the Alliance Web site (http://nano.cancer.gov/meetings_events/nano_tutorials.asp).

Based on overwhelming attendance and positive feedback, the Nano Med School Tutorial Sessions are also part of the 3rd annual investigators meeting, with presentations made by Northwestern CCNE investigators Drs. Milan Mrksich and Vinayak Dravid to educate life science researchers on nano-basics and sensing platforms for biological applications. Conversely, Drs. Raymond Bergan and Vincent Cryns will insight on basic cancer biology for engineers and use of animal models for nanotherapeutic studies.

Finally, based on recommendations of the NCI Alliance's Communications and Integration Working Group (CIWG), a special session for trainees will also be held at the 3rd annual investigators meeting. The session aims to provide a forum for trainees to share and discuss relevant cross-cutting issues encountered in cancer nanotechnology research with the intent of reducing the cycles of learning. The session will be held in collaboration with representation from NCI's Center to Reduce Cancer Health Disparities and the NCI Clinical Proteomic Technologies for Cancer program.

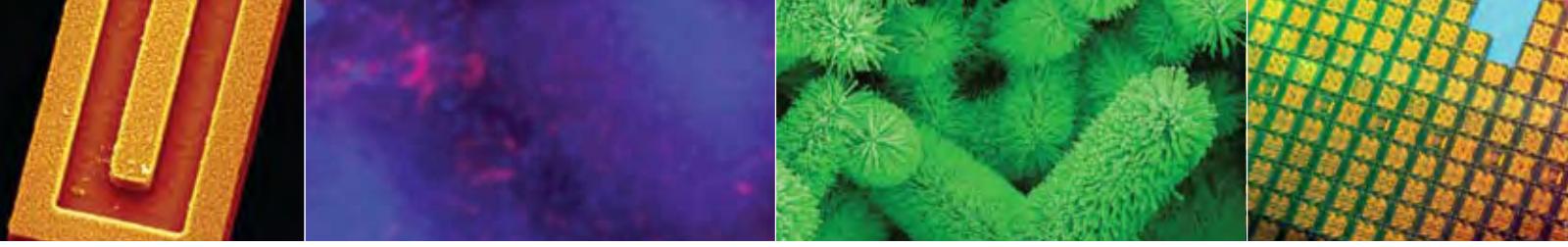
1.4 Alliance Investigators Training and Education Highlights

Centers of Cancer Nanotechnology Excellence

- The **Emory-Georgia Tech CCNE** has successfully convened the Frontiers of Cancer Nanotechnology Seminar Series to educate a multidisciplinary research community on new and novel nanotechnologies. Each presentation is broadcast live over the Internet and archived on the CCNE Web site for broadest possible access. The Center also runs a postdoctoral fellowship program and has developed new nanotechnology courses for a multidisciplinary audience. Emory-Georgia Tech Distinguished CCNE fellows are required to be assigned to at least two principal investigators. The program includes scientists with a wide range of backgrounds and skills, ranging from electrical engineering to molecular biology. Fellows within these fellowships work closely with CCNE investigators on nanoparticle platform development as well as clinical translation for both cancer therapy and imaging. The CCNE is aiming to expand the Distinguished CCNE Fellow program from four to six fellows, and envisions that fellows will stay for approximately three years.
- The **NanoTUMOR CCNE** at University of California, San Diego, has successfully developed and implemented four nanotechnology forums and two workshops and offered an extension course during the summer of 2007. The university also established a new Department of NanoEngineering within its Jacobs School of Engineering effective July 1 of this year. Two CCNE investigators: Sadik Esener (Department of Electrical and Computer Engineering) and Michael Heller (Department of Bioengineering) serve on the leadership team for this new department. Another example of active engagement in training is an exchange of students and postdoctoral fellows between University of California, San Diego, and MIT-Harvard CCNEs. The students in this program work on a joint collaboration project involving professors Bhata (MIT), Sailor (UCSD), and Ruoslahti (Burnham Institute).
- The **NanoSystems Biology Cancer Center at Caltech** has developed a strong interdisciplinary student exchange process as an integral part of carrying out its research, with students from pathology and immunology departments routinely working in nanofabrication laboratories. A pilot program has been developed for NSBCC graduate students and postdoctoral fellows to be coupled into a Caltech K-12 outreach program. This means that each month, 2 NSBCC students will be taking their science to public schools in Los Angeles to expose and educate younger students on cancer nanotechnology.

- The **MIT-Harvard CCNE** has focused postdoctoral, graduate, and undergraduate training efforts on the interface between nanotechnology and “wet-bench” cancer biology, particularly *in vivo* mouse model studies. Consistent joint scientific group meetings enable cross-disciplinary dissemination of research efforts and new knowledge. Angela Belcher’s laboratory (Project 5) has developed a Nanotechnology Teaching Module for elementary school students to provide hands-on experience with nanotechnology called “Seeing the Nanoscale.” The laboratory is working with approximately 50 students around the country on projects as part of the FIRST LEGO League (FLL). FLL presents science and technology concepts to children ages 9 through 14, using real-world context and hands-on experimentation. About 30 students visited the Belcher laboratory. Dr. Belcher also met with students in Berkeley, California, to design projects involving nanotechnology to seek out cancer cells. Sangeeta Bhatia’s lab continues to host middle school girls in the lab through the MIT KEYs program. KEYs is a motivational program that brings 11-13 year old girls together with MIT women students to participate in workshops held periodically throughout the year. The goal of KEYs is to empower young women by promoting their self-confidence, increasing their self-esteem, and unveiling opportunities for their potential career paths.
- Research and education at the graduate and postgraduate levels are tightly linked at the **Northwestern CCNE**. Over the past year, 34 graduate students and 20 postdoctoral fellows were actively engaged in Center research. Recognizing the unique opportunity to provide undergraduate research opportunities in hands-on translational medical nanotechnology research, the NU-CCNE directed efforts over the past year to research, develop, and launch a Research Experience for Undergraduates (REU). The program effectively leverages two existing programs at NU: the NSF-sponsored Research Experience for Undergraduates (REU) program at the International Institute for Nanotechnology and the NCI-funded Continuing Umbrella of Research Experience (CURE) Program at the Robert H. Lurie Comprehensive Cancer Center. The 9-week summer program included an intensive immersion in laboratory-based scientific research, which was augmented by research seminars, a field trip to Argonne National Laboratory (ANL), professional communication workshops, technical writing workshops, and access to and training on state-of-the-art instrumentation, social activities, a final symposium, and experience as a submitter and peer reviewer in *Nanoscape: The Journal of Undergraduate Research in Nanotechnology*.
- **Siteman CCNE** investigators have developed a nanotechnology course (Current Topics in Nanomedicine) and was taught in Fall, 2007 through the Division of Biology and Biomedical Sciences (DBBS) and was cross-listed in the School of Engineering and Applied Sciences (SEAS). This course will be taught again in Fall, 2008. The course masters are Drs. Sam Wickline, Michael Hughes, Patrick Winter and Irfan Ahmad. Siteman CCNE has successfully implemented a distance learning component for developed nanotechnology courses and students from the UC-Santa Barbara, UC-Berkeley, Emory and Georgia Tech have enrolled, where they have received credit through Washington University. The lectures are videotaped and archived using a freeware program called Moodle, allowing access to other CCNE investigators from WU and other sites in the country. Additionally, the Siteman CCNE convened a nanomedicine seminar series and the annual Nanotechnology and the Life Sciences Workshop in collaboration with the National Heart, Lung, and Blood Institute Program of Excellence in nanotechnology at Washington University in St. Louis.
- The **Carolina CCNE** successfully applied to the UNC Graduate School for establishment of a Graduate Certificate in Nanotechnology, which will supplement the training of students and postdoctoral fellows in an interdisciplinary fashion, including a specialized course, research rotation, and course selections designed to foster cross-disciplinary training between the physical and biological sciences.

- The **Stanford CCNE** for Therapeutic Response organized a nanomagnetic biosensor and MEMS symposium at the 2006 International Magnetics Conference. Center researchers also hosted a monthly seminar entitled “Integrated Cancer Biology Seminar,” which focused on biocomputational problems requiring analysis of high-throughput molecular data. Robert Sinclair, PI of the Stanford CCNE’s nanotechnology characterization core is working with the International Association for Nanotechnology (IANANO) in providing training for their “Training the Trainer” series of workshops to educate science teachers and practicing scientists and engineers in nanomaterials characterization.



Building Team Science

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NANOTECHNOLOGY-DERIVED POSITRON-EMITTING PROBES FOR MOLECULAR IMAGING

By Sebastian Olma¹, Kan Liu¹, Wei-Yu Lin¹,
Yi-Chun Chen¹, Kym F. Faull¹, Joseph
DeSimone², Anna Wu³, R. Michael
van Dam¹, Clifton K.-F. Shen¹, Hsian-Rong
Tseng¹, and Michael E. Phelps¹

Collaborating Centers:

¹NanoSystems Biology Cancer Center CCNE
(NSBCC-CCNE)

²Carolina Center of Cancer
Nanotechnology Excellence
(C-CCNE)

³Center for Cancer Nanotechnology
Excellence Focused on Therapy Response
(CCNE-TR)

Positron emission tomography (PET) is a sensitive non-invasive imaging technology for measuring biochemical processes at a whole body level in living subjects. As a result, PET imaging in cancer provides powerful means to (i) identify early

disease, (ii) differentiate benign from malignant lesions, (iii) examine all organs for metastases, (iv) stratify patients based on potential sensitivity to targeted therapies, and (v) provide an early readout of response to therapy. The major roadblock to increasing the applications of PET in preclinical and clinical research, aiding the drug discovery and molecular imaging diagnostics is a convenient and low-cost source of a diverse array of PET probes. New approaches are needed to enable biologists and clinicians to synthesize a wide range of PET probes. Integrated microfluidic technology, with intrinsic advantages of speed, chemical economy, flexibility, user-friendliness, safety, modularity and low cost, is a prime technology platform for producing radiolabeled PET probes. The goal of our project (NSBCC-CCNE Project 3, PI: Dr. Michael Phelps) is to develop new technology platforms that will accelerate the discovery and development processes of new PET probes and facilitate a broader use and value of PET imaging. Our joint team brings together the expertise of eight research

FIGURE 1. Optical micrographs of three generations of microfluidic chips for multi-step radiosynthesis of small-molecule PET imaging probes.

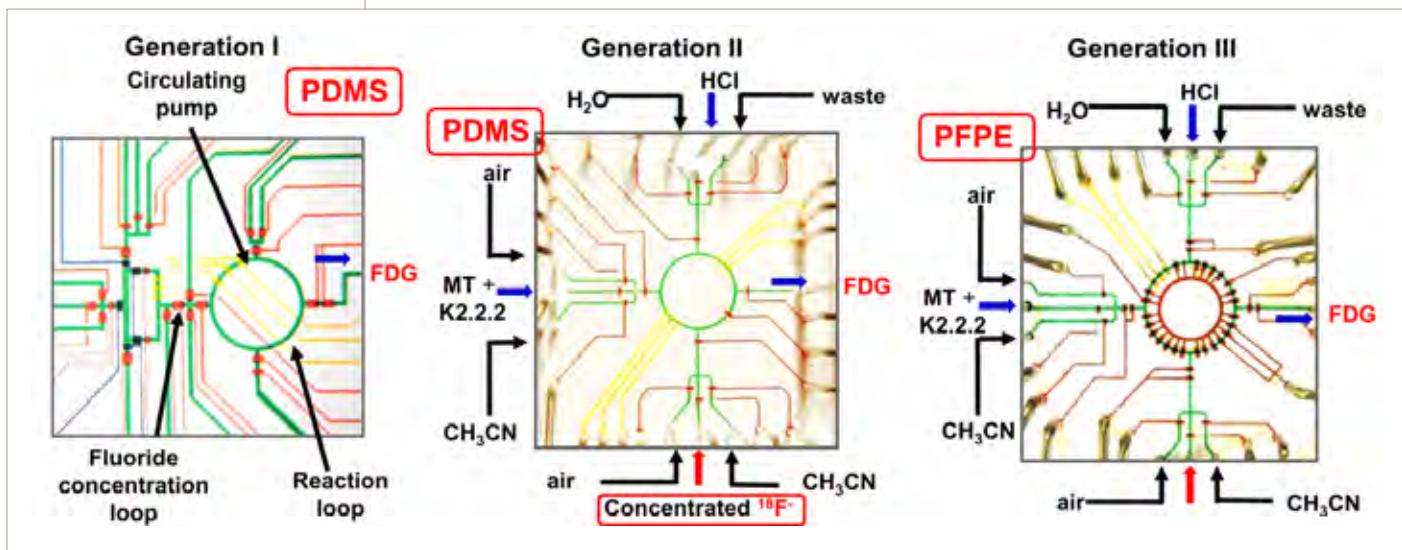
Channels have been loaded with colored food dye to visualize the different components of the chip (green: channels for fluids; red: pressurized control channels for valve actuation; yellow: triplets of pressurized control channels for peristaltic pumping). Each chip is roughly 20mm square.

groups covering the fields of radiochemistry, microfluidics, polymer materials, device prototyping, molecular imaging and antibody engineering.

Over the past three years our team has designed, fabricated and tested three generations of microfluidic devices for automated production of $[^{18}\text{F}]$ -labeled PET imaging probes (Figure 1). Compared to the conventional approach, accelerated synthesis of 2- $[^{18}\text{F}]$ fluoro-2-deoxy-D-glucose ($[^{18}\text{F}]$ FDG), the most commonly used PET tracer for imaging altered glucose metabolic states in cancer, was accomplished with improved radiochemical yield and purity using the Generation-I devices.^[1] Design modifications in Generation-II devices enhanced reliability and increased the generality of this radiochemical technology platform. The rapid synthesis of a different PET tracer, $[^{18}\text{F}]$ -3'-deoxy-3'-fluoro-L-thymidine ($[^{18}\text{F}]$ FLT), a PET imaging probe for DNA replication and cell proliferation,

has recently been demonstrated in the Generation-II devices. In collaboration with Dr. Joseph DeSimone at the C-CCNE and Liquidia Technologies, Inc., chemical and solvent resistant polyperfluoropolyether (PFPE) elastomers^[2] (developed at UNC and commercialized by Liquidia) are utilized to replace the original polydimethylsiloxane (PDMS) materials for the fabrication of the Generation III chips. Using the Generation III chips with improved chemical inertness and device robustness, we will be able to further expand the chip-based radiochemistry for syntheses of a wide range of PET probes.

We are also working with Dr. DeSimone's group to study *in vivo* biodistribution of the nanoparticles produced by their particle molding technology known as Particle Replication in Non-wetting Templates (PRINT).^[3] The PRINT process enables the production and harvesting of monodisperse, shape-specific nanoparticles



made from a variety of polymers. The PRINT nanoparticles decorated with 1,4,7,10-tetraazacyclo-dodecane-1,4,7,10-tetraacetic acid (DOTA) can be labeled with the radioisotope ^{64}Cu and sequentially imaged in small animals *via* microPET (Figure 2) to obtain their *in vivo* biodistribution properties. These PRINT particles are presently being designed to reach new understandings and therapies in cancer prevention, diagnosis and treatment.

Dr. Anna Wu, from the CCNE-TR, has accumulated extensive experience on exploring the potential of engineering antibody fragments^[4] as PET probes with improved specificity and well-controlled pharmacokinetics. Our team has been work with Dr. Wu's research group to test the feasibility of performing automated syntheses of $[^{18}\text{F}]$ -labeled antibody

fragments in a microfluidic setting. We have been developing a new generation of microfluidic devices, in which two sequential reactions — (i) radiosynthesis of N-succinimidyl-4-[^{18}F]fluorobenzoate ($[^{18}\text{F}]$ SFB) and (ii) labeling of small quantities of antibody fragments with the *in situ* prepared $[^{18}\text{F}]$ SFB — can be conducted in an automated fashion.

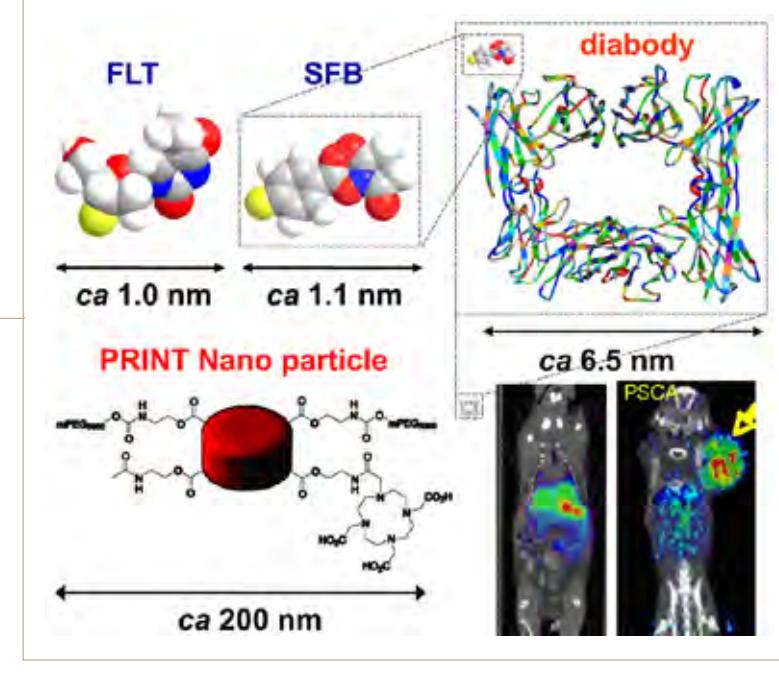
Such collaborative cross-disciplinary efforts significantly advance our goals and provide opportunities for our nanotechnologies and microfluidics platforms to impact molecular imaging and cancer-related research. We envision that a microfluidic-based platform along with the existing widespread commercial supply of $[^{18}\text{F}]$ fluoride will provide an enabling technology for routine probe production and for academic and commercial scientists to accelerate their

discovery and development of new tracers for PET in research, drug discovery and development, and molecular imaging diagnostics in patient care.

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FIGURE 2. Illustration of various categories of small molecules, biomolecules and synthetic nanoparticles which can be labeled with positron-emitting radionuclides (e.g. F-18) using our microfluidics. Micro-PET: PRINT nanoparticles (Cu-64 , left) and anti-PSCA (prostate stem cell antigen) minibody (I-124 , right).



Training Across the Alliance



Postdoc Fellow, Rong Fan, smiles for his happy experience in cancer research at the NanoSystems Biology Cancer Cancer (NSBCC-CCNE).



Single cell chip, developed by Rong Fan and colleagues, can record the secret conversation among individual cells.

INTERDISCIPLINARY EXPERIENCE FOR SUCCESS IN CANCER RESEARCH

*By Rong Fan, Ph.D. Postdoctoral Fellow
NSBCC-CCNE*

Dr. Leroy Hood, the co-director of NSBCC-CCNE, has a “growth curve” theory that states the path to lead one’s career from one success to another is to find a new growth point. This “theory” has guided Dr. Hood from his success in 1980’s for developing automated gene and peptide sequencing to now being a leading scientist in the area of systems biology. My postdoctoral training at Caltech shows that this theory also provides valuable advice on developing experience for success in clinical cancer research.

The first piece of scientific research I conducted dates back to 2000 at the University of Science and Technology of China where I studied the superconductors in the Department of Physics. The next year, I attended the Ph.D program in the Department of Chemistry at UC Berkeley to investigate the synthesis nanomaterials for energy conversion. However, despite my success in studying energy sciences, I was strongly attracted by the beauty of biological systems, and decided to look at biomedical problems after graduation.

In 2006, I was delighted to join the cancer biology research team in Professor Jim Heath’s laboratory. In the beginning, this bold move turned out to be really

a tough cross. Like most postdoc fellows, I was hoping to start my projects as soon as possible and keep myself in a pace of productiveness. I proposed several “quick” ideas in the first month. Professor Heath was always patient in answering my questions and arranged several meetings to discuss technical details of these ideas. However, what is most beneficial to me is his philosophical advice that says we need to let the biology teach us. Thanks to the unique environment of the NSBCC-CCNE, I was able to talk to experts from diverse areas within our center. These scientific communications made me learn a lot and inspired my deep and broad thinking in many cancer biology topics such as oncogenic signaling pathways, cancer heterogeneity, cancer stem cells, etc. Along with learning various hands-on techniques in detection techniques used in Heath lab, I read a lot of research articles in biology. One day after several months, I was excited by an interesting story about the paradoxical role of our immune system with cancer, and then I brought this idea to Professor Heath. The immune system of humans is able to fight many diseases, including cancer. But what a surprising paradox is that the immune response, especially inflammation evoked by tumor-infiltrating immune cells, creates a complicated microenvironment that may facilitate tumor promotion and progression. In this regard, tumors cells hijack the

immune system to assist their “criminal” counterparts that eventually leads to the malignant disease — cancer. The tumor microenvironment is comprised of a large number of different cell types, e.g. normal epithelial, tumor epithelial, macrophages, T-cells, etc. It is so heterogeneous at single cell level. Therefore, it is a grand challenge to perform a comprehensive characterization of tumor microenvironment at both cellular and molecular levels. To tackle this problem, I proposed a microfluidic device that can isolate different cell types from only a small quantity of tumor tissue (e.g. from needle biopsy) and then analyze the molecular network that dictates how these cells function, communicate and coordinate to create favorable tumor microenvironment. Understanding the tumor-immune interaction may help us find ways to prevent tumor progression by suppressing the immune system’s tumor promoting function. Advances in the biology of the tumor microenvironment and in particular, the clinical tool to diagnose the tumor microenvironment, allowing us to imagine a future in which cancer becomes a manageable, chronic, benign ailment one can live with for a whole life.

In the past year, I have made progress that may allow us to assess the impact of heterogeneous tumor micro-environment. First, I devised an integrated bar-code chip

to simultaneously detect multiple cell-cell signaling molecules from a single cell. These molecules include cytokines and chemokines that are the “language” used by immune cells to communicate. For example, the isolated cells or cell colonies of human macrophages, a key player in promoting inflammatory environment in tumor, had very different conversations in the individual chambers even though they are from the identical cell lines. Such single cell heterogeneity might have implications in the heterogenic nature of tumor microenvironment. The second approach is through a comprehensive blood test. As blood is re-circulated throughout body every minute, it brings back information from all organs and tissues. Working with my colleagues, I developed an integrated blood test chip that can measure a panel of plasma proteins (including inflammatory molecules present in tumor microenvironment) from a finger prick of blood. To evaluate its effectiveness in clinical cancer diagnoses, tens of serum samples from prostate or breast cancer patients were assayed. Despite the limit of sample size, an intriguing correlation of cancer and inflammation was observed. We are very excited by this discovery and the future study towards analyzing a large number of clinical samples is under the way.

Although a bold move to cross disciplines provides opportunities for new growth points, a favorable “growth medium” is absolutely a deterministic factor for the success in postdoc research. Our center, the NSBCC-CCNE, joins the forces from Caltech, UCLA medical school and the Institute for Systems Biology (ISB) in Seattle, providing a multidisciplinary stage for new researchers. In the past year, I drove to UCLA medical school every week to attend Professor Hong Wu’s group meetings. Through conversation with our medical school partners, I was able to find where the real challenges are in cancer research faced by biologists and clinicians, and then design solutions to tackle these specific problems. I also participated in the systems biology summer course organized by our NSBCC-CCNE member — ISB at Seattle. I found this training very useful.

The most valuable experience I have had at NSBCC-CCNE is how to find, understand the real problems and design solutions to tackle them in an interdisciplinary field such as clinical cancer research. The unique environment at NSBCC-CCNE provides great opportunities.

Alliance Young Investigator Spotlight



Hsian-Rong Tseng, Ph.D.

(Pharmacology/UCLA)

HSIAN-RONG TSENG, PH.D.

NSBCC-CCNE

Dr. Tseng participates in the NanoSystems Biology Cancer Center (NSBCC-CCNE) led by Drs. Jim Heath (Caltech), Mike Phelps (UCLA) and Lee Hood (ISB). Tseng was trained as an organic and physical chemist and has been an assistant professor at the Crump Institute for Molecular Imaging and Department of Molecular and Medical Pharmacology in the David Geffen School of Medicine at UCLA since 2003.

Tseng's research interests are to develop microfluidic technology platforms and to utilize these technology platforms for applications in the fields of chemistry, molecular imaging and cancer biology. In contrast to conventional bench-top setups, microfluidic devices can be used to manipulate chemical and biological processes on nanoliter (nL) to microliter (μL) scales with the profound advantages of sample economy, enhanced heat and mass transfer, and improved control over experimental conditions. During the past four years, the Tseng research group together with several collaborators at UCLA and Caltech initiated the joint efforts to develop a variety of PC-operated, integrated microfluidic devices for (i) sequential syntheses of nanogram-level molecular imaging probes for positron emission

tomography (PET) (*Science* 2005, 310, 1793), (ii) parallel screening of high-affinity inhibitors against proteins involved in malignant transformation (*Angew. Chem. Int. Ed.* 2006, 45, 5276), and (iii) systems-oriented profiling of signaling networks that drive the malignant transformation of cancers. These preliminary data validated the feasibility of performing complicated chemical reactions and biological operations in individual microchips and provide a solid foundation for Tseng's future research plans. Ultimately, Tseng's research team will produce further integrated microfluidic technology platforms for the broader space in chemistry, molecular imaging and cancer biology beyond the existing complexities. Many different existing functional microfluidic modules will be integrated to produce a number of game systems: "Let's Play _____", where the blank will hopefully be filled with:

1. Microfluidic reactors for development of *in vivo* imaging probes and therapeutics.
2. Quantitative systems-biology chips for cancer diagnosis and predictive therapy.

For more information about Hsian-Rong Tseng and his research group please visit the group's website at

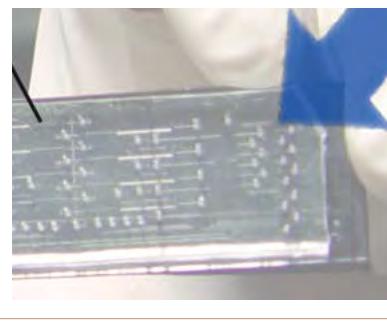
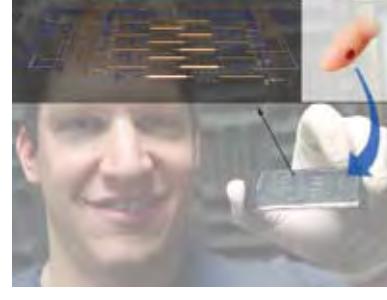
<http://labs.pharmacology.ucla.edu/tsenglab/>.

Nanotechnology Highlights



FIGURE 1. Integrated blood

Chip. M.D./Ph.D student, Ophir Vermesh, at NSBCC-CCNE is showing the integrated blood bar-code chip that can measure a panel of proteins plasma of a finger prick of blood within a few minutes.



INTEGRATED BLOOD BAR-CODE CHIPS MAKE CLINICAL DIAGNOSES CHEAP AND INFORMATIVE

By Rong Fan, Ph.D. (rfan@caltech.edu)
NSBCC-CCNE

The singular term “cancer” deceptively encompasses multiple diseases that are highly heterogeneous. This heterogeneity is manifested at all levels — from patient to patient and from cell to cell. This is because the molecular origins of cancer are varied. The terms such as Stage 1 or Stage 2, etc., that are utilized to describe the progression of cancer (and often used to guide treatment) are poor predictors of the response to therapy that an individual patient might have. The recent advent of cancer therapeutics targeted at certain specific molecular lesions that are involved in the transformation from health to disease has highlighted this inadequacy of traditional diagnostics. Some of these therapeutics only affect small subpopulations of patients with a given type of cancer (e.g. breast cancer). Patients that don't exhibit positive responses are instead just subject to the negative side effects of these therapies, which can be significant.

Thus, assigning the right drug to the right patient is a challenge. Once the right drug has been assigned, controlling dosage levels to maximize the efficacy while

minimizing the toxicity is important. It is likely that in the near future personalized cancer treatments will involve combination therapies, and this highlights the challenge even more. Clearly meeting this challenge means finding measurement methods that can accurately and comprehensively diagnose the cancer, monitor therapeutic efficacy, and detect recurrence.

State of the art research in cancer biology is beginning to yield clues regarding what needs to be measured to achieve a comprehensive cancer diagnosis. Network models of disease — that is, models of the interacting gene and protein networks that describe tissue function, and how those networks are perturbed by the onset and progression of disease — are beginning to reveal the differentially expressed or otherwise altered genes and proteins that can provide disease fingerprints¹. Furthermore, those networks can be data mined to identify proteins that are organ-specific (i.e. only expressed in the organ of interest) and secreted into the blood. The key is that each organ has its own unique blood molecular fingerprint, and if the levels of those blood proteins can be measured, then they can be correlated back to the health state of the organ. For example, a toxic response to a cancer therapeutic might be best monitored by measuring the liver-specific blood molecular fingerprint.

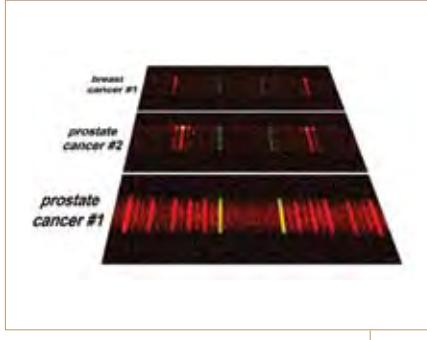
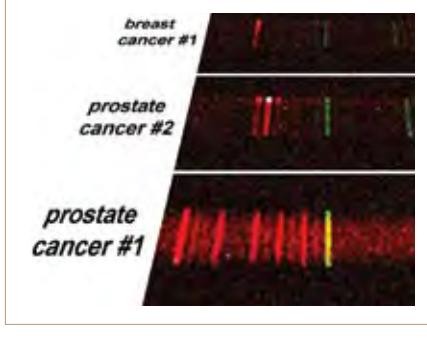


FIGURE 2. Distinct Blood Bar-Codes.

Using the integrated microchips, cancer patients can be clearly diagnosed through a rapid blood test. Moreover, by measuring a panel of biomarkers and cell-cell signaling molecules, these chips may be employed to identify the different cancer subtypes based on the unique "blood bar-codes" that aid doctors to give the right patient the right drug.



An inflammatory response might be monitored by assessing proteins from the white blood cells, which can be considered a circulating organ. The cancer itself may be monitored by measuring the blood protein levels that originate from the diseased organ. While this approach represents a huge opportunity for cancer diagnostics and treatment, it also represents a staggering technology challenge. It is meeting that challenge that constitutes the heart of our research within the NanoSystems Biology Cancer Center (NSBCC-CCNE).

The *in vitro* cancer diagnostics team in Heath lab at Caltech devised an integrated blood bar-code chip (IBBC) that can perform blood separation and *in situ* measurement of a panel of plasma proteins from a finger-prick of blood on a 10 minute time scale. The plasma separation was achieved using a simple hydrodynamic principle — the Zweifach-Jung effect. Plasma is skimmed into high-flow-resistance channels, termed plasma channels that are split off from this primary channel. As the resistance ratio between the plasma channels and the primary channel is increased, a critical streamline in the primary channel moves towards the plasma channel split point. Blood cells with a radius larger than the distance separating the critical streamline from the plasma channel are directed away from the primary channel. As a result, 10-15% of the plasma is collected into the downstream of plasma channels where a protein detection array was placed.

This blood separation module enables the rapid separation of a finger prick of blood within a few minutes. It allows the capture of plasma protein profile that closely resembles the patient's physiology; conventional blood collection methods are impaired by fast blood kinetics that can destroy proteins, coagulate blood, etc.

To meet the challenge in diagnosing cancer heterogeneity and understanding the dynamic evolution of disease networks, a large panel of protein markers is measured simultaneously from a small quantity of blood. The detection mechanism we take is the DNA-encoded antibody library (DEAL) method², a variant of surface-bound immuno-assay array developed in Heath lab. To increase the array density to meet the stringent requirement of assaying tiny amount of clinical samples, the chip is constructed using microscale flow-patterning to spatially encode unique ssDNAs in the likeness of a barcode at a density 10x higher than conventional gene chips. Subsequently, an integrated microfluidic assay device translates the DNA microarray into an antibody microarray through DEAL. Biomarkers can then be detected using surface-bound immuno-sandwich-assays. By taking advantage of high DNA loading and a microfluidic environment, we have shown that the barcode chip has excellent sensitivity (comparable to state-of-the-art ELISA assays), broad dynamic range (10^5 , three orders of magnitude larger than most

bioassays), and high throughput (tens of proteins are simultaneously detected from each of twelve specimens within half an hour).

The integrated blood bar-code chip has shown effectiveness in pre-clinical testing. A dozen cancer markers and inflammatory molecules were measured in a blood bar-code chip from just a few microliters of serum samples taken from twenty-four cancer patients. In this test, analysis of these protein barcodes unambiguously isolated all the prostate cancer patients from the original 24-patient pool and even differentiated several possible subtypes associated with immune/tumor interactions. For example, two categories of inflammatory signatures were observed: one which is TNF- α positive and another which is GM-CSF positive. TNF- α plays an important role in apoptosis, while GM-CSF is responsible for recruiting immune cells to a developing tumor microenvironment and inducing differentiation; this discovery may reflect different mechanisms of immune control in tumorigenesis. The integrated microfluidic bar-code chips can be extended to analyze other biospecimens, i.e. skinny-needle biopsied tissues, etc. We envision this versatile technology can help in searching for disease fingerprints.

An accurate, comprehensive and personalized diagnosis increasingly means

a multiparameter analysis enabled by systems biology. However, it is now extremely costly to perform multi-variant diagnosis using conventional technologies such as ELISA and mass spectrometry. The small amount of sample collected from a patient is often insufficient to complete all necessary assays. Therefore, a major challenge of extending multiparameter diagnostics to the clinic is to reduce the cost to a few pennies or less per measurement. The integrated blood bar-code chip is constructed from only plastic and glass, and we anticipate that it can serve as a very inexpensive and yet informative diagnostic tool. Moreover, its portability and assay speed mean that it can be used for real time diagnosis in the clinic and, eventually, in the home.

NSBCC-CCNE in vitro cancer diagnostics team personnel: the NSBCC-CCNE director Prof. James R. Heath; co-director Dr. Leroy Hood; postdocs Dr. Rong Fan, Dr. Lidong Qin, Dr. Alok Srivastava; graduate students Ophir Vermesh, Gabriel Kwong, and Habib Ahmad.

References

1. Heath, J.R. & Davis, M.E. Nanotechnology and cancer. *Annual Review of Medicines* 59, 405 (2008).
2. Bailey, R.C., Kwong, G.A., Radu, C.G., Witte, O.N. & Heath, J.R. DNA-encoded antibody libraries: A unified platform for multiplexed cell sorting and detection of genes and proteins. *Journal of the American Chemical Society* 129, 1959-1967 (2007).

Alliance Activities



NCI Nanotechnology Alliance Investigators Meeting
October 16-18, 2007

NCI ALLIANCE FOR NANOTECHNOLOGY IN CANCER 2ND ANNUAL INVESTIGATORS MEETING

On October 16-18, 2007, The Alliance for Nanotechnology in Cancer held its second annual Investigators Meeting in Chapel Hill, NC. Hosted by the Carolina Center of Cancer Nanotechnology Excellence and the University of North Carolina at Chapel Hill, the meeting was attended by over 280 Alliance investigators, students and postdoctoral fellows, a 40% increase in attendance compared to the 2006 Investigators Meeting. All eight Centers

for Cancer Nanotechnology Excellence (CCNEs) and 12 Cancer Nanotechnology Platform Partnerships were represented.

Some of the highlights of the meeting included:

- a day-long tutorial aimed at bringing up to speed those new to the multidisciplinary field of cancer nanotechnology
- eight scientific sessions featuring the latest research results from Alliance investigators

- an evening session on the pathway to clinical development, along with two featured talks by Alliance investigators who have experience bringing nanotechnology-enabled drugs through the clinical trials pathway.

- over 100 posters detailing additional work from Alliance-funded laboratories

EVENTS

MIT-Harvard CCNE

2008 MIT CCR Symposium

“Nanotechnology and Cancer:
The Power of Small Science”

June 27th, 2008

Cambridge, MA

Registration will be available at:

<http://web.mit.edu/CCR>

Northwestern University CCNE

All Scout Nano Day

March 8, 2008

Location: Pancoe-Evanston

Northwestern Healthcare

Life Sciences Pavilion,

Abbott Auditorium

2200 Campus Drive

Northwestern University,

Evanston Campus

The very popular annual All Scout Nano Day provides an exciting overview of nanotechnology including hands-activities that demonstrate nanoscale properties, the laser and microscope tour and demonstrations, poster session, careers in science and engineering interactive, juried poster session, and pizza party. Boy Scouts, Girl Scouts and Venturing Crews are welcomed. For more information contact Denise Dooley, Outreach Coordinator (d-dooley@northwestern.edu).

SYMPOSIA

Emory-GT CCNE

2008 Emory-GT Frontiers of Cancer

Nanotechnology Symposium

March 30-April 1, 2008

Callaway Gardens

Pine Mountain, GA

COURSES

CCNE-TR

Transmission Electron

Microscopy (TEM)

Laboratory Class at Stanford,

Spring Quarter 2008

The laboratory course on Transmission Electron Microscopy will be offered to Stanford students. This practical lab class discusses experimental applications of electron microscopy to typical materials science studies. Topics include microscope operation and alignment, diffraction modes and analysis, bright-field/dark-field analysis of defects, high resolution imaging, and analytical techniques for compositional analysis (EDAX).

MIT-Harvard CCNE

Access to all MIT undergraduate and graduate courses can be found at:

<http://mit.edu/ocw/>

SCCNE

Online CME Siteman CCNE Course:

Samuel Wickline, MD,

“Nanotechnology for Molecular Imaging and Therapy in Cancer”

Visit: <http://cme-online.wustl.edu/user/catalog.asp>

Click on Preview Course, Oncology and then the course title.

LECTURES

CCNE-TR

S. X. Wang, “Molecular diagnostics and nanomagnetic biosensors,” Invited Tutorial, American Physical Society March Meeting, New Orleans, March 9-14, 2008.

The University of Texas at Austin, Institute for Cellular & Molecular Biology

A weekly series of so-called “Systems Lunches,” emphasize the use of systems biology methods and nanotechnology for addressing issues in human disease, in particular in oncogenesis. As a result of these meetings, new collaborations with faculty members on the development of novel nanotechnologies (multimodal nanoparticles, with Dr. Kostia Sokolov) for the imaging and treatment of cancer, and have begun to define and address the gene and interactome networks involved in cancer metastasis (with Dr. Muhammad Zaman and Dr. Edward Marcotte) have occurred.

SEMINARS

C-CCNE

The Carolina Center of Cancer Nanotechnology Excellence announces its 2nd Annual Symposium, November 14, 2008 at the Rizzo Conference Center in Chapel Hill, NC. Details will be posted on our website as they are available, contact ccne@med.unc.edu for information.

CCNE-TR

Regularly scheduled Nanobiotechnology Seminar Series held 3rd Tuesdays of every month. Please visit http://mips.stanford.edu/public/nanobiotech_seminar.adp for all speakers and webcasts.

Emory-GT Frontiers of Cancer Nanotechnology Seminar Series

March 24, 2008
Hongjie Dai, Ph.D.
J.G. Jackson-C.J. Wood Professor
Dept. of Chemistry
Stanford University
“Carbon Nanomaterial for Biological Applications”

April 15, 2008
Chad Mirkin, Ph.D.
Professor of Chemistry
Dept. of Chemistry
Northwestern University
“The Polyvalent Oligonucleotide Nanoparticle Conjugate: A New Frontier in In Vitro Diagnostics and Intracellular Gene Regulation”

May 12, 2008

Vladimir Torchilin, Ph.D.
Distinguished Professor & Chair
Pharmaceutical Biotechnology & Nanomedicine
Northwestern University
“Multifunctional Pharmaceutical Nanocarriers for Cancer Diagnostics and Therapy”

July 7, 2008

Mostafa El-Sayed, Ph.D.
Julius Brown Chair & Regents Professor
Dept. of Chemistry
Georgia Institute of Technology
“Metallic Gold is More Precious on the Nanometer Size Scale: Some Properties & Applications of Gold Nanoparticles of Different Shapes in Nanophotonics, Nanomotors, Nanomedicine, & Nanobiology”

*Many seminars also webcast from www.wcigtcnne.org

May 8, 2008

Guest Speaker: Paul Weiss,
Pennsylvania State University
Title: TBD
Location: Pancoe-Evanston Northwestern Healthcare Life Sciences Pavilion, Abbott Auditorium
2200 Campus Drive
Northwestern University,
Evanston Campus

SCCNE partnership with Program of Excellence Nanotechnology (PEN) at Washington University

A list of past and upcoming SCCNE-PEN Seminars is available on the following website: <http://www.nhlbi-pen.net/default.php?pag=seminars>

Topics include:

- Special Topics in Organic Chemistry-Nanomedicine
- Current Topics in Nanomedicine
- Principles and Applications of Biological Imaging
- Contrast Agents for Biological Imaging

For an update on the upcoming seminars, and for an access to the videos of the above lectures along with the lecture slides, please contact Monica Shokeen at shokeenm@mir.wustl.edu.

Alliance Classifieds

Internships

CCNE-TR

Summer Internship Opportunities:
The National Nanofabrication
Infrastructure Network (NNIN)
invites applications from
undergraduates to participate
in the REU (“Research Experience
for Undergraduates”) summer internship
program. Participating students will
be hosted at one of the twelve NNIN
labs (which include the Stanford
Nanofabrication Facility) and mentored
in nanoscience and technology research
project over the course of 10 weeks. Housing
and stipend are provided. Application
are due Feb. 19, 2008. For more
information, visit the website at:
http://www.nnin.org/nnin_reu.html

NU-CCNE Frontiers in Nanotechnology Seminar Series

April 3, 2008

Guest Speaker: Sandra Rosenthal,
Vanderbilt University
Title: “Structure-Property Relationships
in Functional Quantum Dots: From
Biological Imaging to White Light
Solid State Lighting”
Location: Pancoe-Evanston Northwestern
Healthcare Life Sciences Pavilion,
Abbott Auditorium
2200 Campus Drive
Northwestern University,
Evanston Campus

Job Postings

C-CCNE

Liquidia Technologies Internship Position:

Cell/Molecular
Biology Technician
Research Area: Cellular Biology
Description: Liquidia Technologies (www.liquidia.com) is a privately-held nanotechnology company that designs, develops, and manufactures precisely engineered particles and films for a wide variety of life and materials science applications. We are currently looking for a Cell/Molecular Biology Intern to play a critical role in execution of key experiments and analysis of nanoparticle engineered drug therapies. The intern will assist the biological team with in vitro and in vivo studies to analyze nanoparticle binding, uptake, internalization, and toxicity. Additional information and job opportunities are available at: www.liquidia.com/careers.html. Requirements: Masters or B.S. in cellular biology, molecular biology, biochemistry, pharmacology or related field. Several years of academic or industry laboratory experience is required. Internship or full-time experience in the biotechnology or pharmaceutical industry is highly preferred. Please send resumes to: careers@liquidia.com; Refer to job code Cell Bio Intern in the subject line when corresponding about this position.

CCNE-TR

Scientific Program Manager

The Molecular Imaging Program at Stanford (CCNE-TR) is searching for a Scientific Program Manager to help manage its NIH funded Center for Cancer Nanotechnology Excellence (CCNE) U54 Grant. The candidate will assist faculty and postdocs with the preparation of manuscripts and writing some portions of grants. Will work with Lab Project, Core Leaders and Investigators to establish a working relationship with a diverse group of scientists and NIH officials from various companies to further enhance the CCNE program. The candidate will supervise the nanobiotechnology lab experiments; coordinate projects between various labs, and assist with scientific issues that come across the various labs within the center (CCNE-TR). Occasionally, some wet-lab research in nanotechnology will be required.
Qualifications: The ideal candidate will have a Ph.D. in materials science, chemistry, or in a relevant field. Must have 1-2 to years experience with nanotechnology and ideally the use of nanotechnology in biological applications such as cancer. Preferably, the candidate will have a background in engineering or biology in a bionanotechnology environment. Excellent verbal and written communication skills are critical. Ability to interact with a diverse group of scientists and a proven track record in scientific management is highly desirable.

Interested applicants may submit their CV to: http://jobs.stanford.edu/find_a_job.html

Research Post Doctoral Position

The Louis Warschaw Prostate Cancer Preclinical Research Laboratory at the Cedars-Sinai Medical Center is focused on translational therapeutics development. The laboratory is part of NCI Center for Cancer Nanotechnology Excellence Program focused on Therapeutic Response. There is currently an opening for a highly motivated and talented protein biochemist to work on a project related to EGFR-TKI resistance mechanisms in solid tumors. The overall goal of the project is to identify and isolate protein biomarkers that can be subsequently utilized in nanodelivery studies to target resistant cancer cells. Project will involve lipid raft purifications and mass spectrometric analysis. A basic biology background is required. Experience with mass spectrometry, proteomics studies, and associated data analysis required. The ideal candidate will have excellent writing and communication skills. Recent Ph.D.'s are welcome. A publications record is necessary. Education/Experience: Ph.D in a related field; 5+ years of related research experience. Interested and qualified individuals may send their CV with three references to: jaina@cshs.org

Research Post Doctoral Position

The Louis Warschaw Prostate Cancer Preclinical Research Laboratory at the Cedars-Sinai Medical Center is focused on translational therapeutics development. The laboratory is part of NCI Center

for Cancer Nanotechnology Excellence Program focused on Therapeutic Response. There are currently several openings for highly motivated individuals interested in kinase signaling pathway interactions and novel targeted therapeutic mechanisms of response and resistance in solid tumor mouse models. Most projects translate directly into a clinical setting. The ideal candidate will be skilled in molecular and cellular biology techniques with some experience in small animal handling. Candidates should also have excellent writing and communication skills. Recent Ph.D.s are welcome. Publications in premier journals is required. Education/Experience: Ph.D in a related field; 5+ years of related research experience. Interested and qualified candidates may send their CV with three references to: jaina@cshs.org For more information on employment at CCNE-TR, please visit <http://mips.stanford.edu/public/grants/ccne/employment.tcl>

Emory-GT CCNE

Post-Doc Fellow (Biomedical Engineering)
The Emory-Georgia Tech Center of Cancer Nanotechnology Excellence (CCNE) and the Bioengineering Research Partnership (BRP) invite applications for postdoctoral research associates in biomedical engineering, nanotechnology, medicinal chemistry and bioinformatics. Specific research topics include:
(1) nanoparticles for gene and siRNA delivery; (2) nanotechnology for molecular

analysis and detection of atherosclerosis plaques; (3) nanoparticle reagents for sensitive imaging of Alzheimer's and other neurodegenerative diseases; (4) nanoparticle organ uptake, distribution, and toxicology; (5) biomedical applications of Raman and surface-enhanced Raman spectroscopy; (6) cellular image processing and 3-D reconstruction; (7) synthesis of biocompatible and biodegradable polymers for targeted delivery of imaging and therapeutic agents; and (8) molecular histopathology and correlation of biomarkers with clinical outcome. The minimum requirements include a PhD or MD degree in engineering, chemistry, biology or medicine, at least two first-author papers in high-quality journals (impact factor > 5.0), and an interest in collaborative work at the interface of science, engineering, and medicine. Exceptional candidates will be considered for the prestigious CCNE fellowship at Emory University and the Georgia Institute of Technology. We offer competitive salaries plus fringe benefits. To apply, send a cover letter, an updated CV, and names of 3-5 references to Mr. Ryan Jowers, Cancer Nanotechnology Center Manager, Department of Biomedical Engineering, Emory University, 101 Woodruff Circle Suite 2007, Atlanta, GA 30322. Electronic applications are encouraged and should be addressed to Mr. Ryan Jowers at ryan.jowers@bme.emory.edu. For further information, see www.nielab.org and www.wcigtcne.org. All positions are open until filled.

MIT-Harvard CCNE

MIT is an equal opportunity/affirmative action employer. Applications from women, minorities, veterans, older workers, and individuals with disabilities are strongly encouraged. For current employment opportunities, please visit: <http://hrweb.mit.edu/staffing/>

NU-CCNE

NU-CCNE Research Experience for Undergraduates

June 23-August 22, 2008

\$4,000 stipend (plus funding for dormitory housing and travel)

Northwestern University

9-week Summer Program, includes an intensive immersion in laboratory-based scientific research, which is augmented by research seminars, a field trip to Argonne National Laboratory (ANL), professional communication workshops, technical writing workshops, and access to and training on state-of-the-art instrumentation, social activities, a final symposium, and experience as a submitter and peer reviewer in Nanoscape: The Journal of Undergraduate Research in Nanotechnology. For more information contact Denise Dooley, Outreach Coordinator (d-dooley@northwestern.edu).

Funding Opportunities

CCNE-TR

New User Grants:

The Stanford Nanofabrication Facility invites applications from researchers in medicine and biology for New User Grants. Applicants should be a faculty member at a US university, other than Stanford University, and must be new to the Facility. There is no application deadline as awards are made on an ongoing basis. SNF is a shared-equipment, open-use facility serving researchers from a wide variety of disciplines. As part of the National Nanofabrication Infrastructure Network (NNIN), SNF is especially committed to encouraging use of micro- and nano-fabrication technologies in non-traditional research areas of biology and medicine. For more information about SNF, please visit our website (<http://snf.stanford.edu>) and contact one of our technical liaisons to learn about micro- and nano- fabrication technologies in biomedicine.

Technology Opportunities

CCNE-TR

In the Lab:

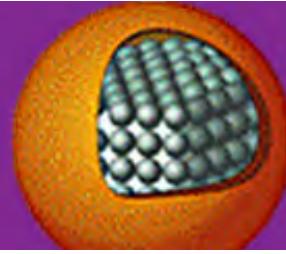
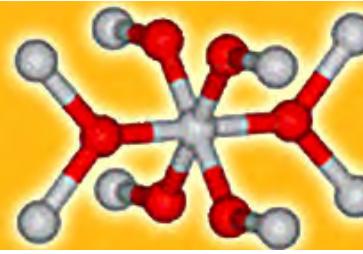
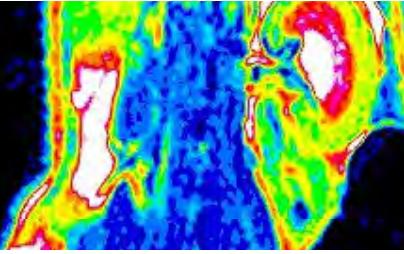
Multiple high-throughput methodologies are maintained in the Center for Systems and Synthetic Biology at the University of Texas at Austin that have proven useful in the development of reagents and systems methods for nanotechnological innovations in cancer diagnostics and therapeutics. These include high-throughput fluorescence microscopy, high-throughput siRNA knockout methods, computational assistance in network analysis, and an automated facility for the selection of aptamers and antibodies. This latter facility will be on display at a NCI co-sponsored (along with the Human Proteome Resource and Structural Genome Consortium) conference in Stockholm where the target problem (how to generate multiple protein targets for the development of useful affinity reagents) will be explored.

The NCI Alliance Nanotechnology in Cancer Bulletin is a collaborative effort developed and facilitated by the Communications and Integration Working Group (CIWG) of the Alliance program. The group is currently led by Alliance co-chairs, Ryan Jowers (Emory-GT CCNE) and Kathleen Cook (NU-CCNE), with coordination from NCI co-chairs, Travis Earles and Jerry Lee, Ph.D.

The CIWG's mission is to catalyze effective Alliance-wide and external communications, facilitate Alliance team science integration, create education outreach opportunities, and leverage best practices.

For comments or article ideas, please contact your Alliance CIWG Primary Contact(s):

CCNEs		
C-CCNE, Chapel Hill, NC Susan Sunnarborg, Ph.D. susansunnarborg@med.unc.edu	NSBCC-CCNE, Pasadena, CA Diane Clark Robinson dianer@caltech.edu	SUNY/Buffalo-CNPP, Buffalo, NY Indrajit Roy, Ph.D. iroy@buffalo.edu
CCNE-TR, Stanford, CA Billie Robles brobles@stanford.edu	S-CCNE, St. Louis, MO Angela Benassi benassia@ccadmin.wustl.edu	UWash-CNPP, Seattle, WA Omid Veiseh omid@u.washington.edu
NANO-TUMOR CCNE, San Diego, CA Adriana Vela adriana_wp@yahoo.com	UCSF-CNPP, San Francisco, CA Jessica Pahler jpahler@diabetes.ucsf.edu	SKCC-CNPP, San Diego, CA Jan Schnitzer, MD jschnitzer@skcc.org
Emory-GT CCNE, Atlanta, GA Ryan Jowers ryan.jowers@bme.emory.edu	UMich-CNPP, Ann Arbor, MI Jola KuKowska-Latallo	Northeastern-CNPP, Boston, MA Renata Nyul r.nyul@neu.edu
MIT-Harvard CCNE, Boston, MA Shannon Cozzo scozzo@mit.edu	UMiss-CNPP, Columbia, MO Jeanne Muse musej@health.missouri.edu	MD Anderson-CNPP, Houston, TX Chun Li, Ph.D. cli@di.mdacc.tmc.edu
NU-CCNE, Evanston, IL Kathleen Cook k-cook@northwestern.edu Mary Drzewiecki m-drzewiecki@northwestern.edu	MIT-CNPP, Boston, MA pdextras@mit.edu	RPCI-CNPP, Buffalo, NY Deborah Pettibone Deborah.pettibone@roswellpark.org
	VCU-CNPP, Richmond, VA Harry Dorn, Ph.D. hdorn@vt.edu	MGH-CNPP, Boston, MA Sung Chang skchang@partners.org



Building Team Science

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TACKLING METASTASIS THROUGH TEAM SCIENCE: CANCER BIOLOGISTS LEAD THE CHARGE SYNERGIZING THEIR DISCOVERIES BEHIND COMMON NANOTECHNOLOGY PLATFORMS

By Leland W. K. Chung¹, Jianjun Cheng²,
Douglas Hanahan³ and Kattesh V. Katti⁴

¹Emory/Georgia Tech CCNE, Atlanta, GA

²University of Illinois at Urbana-Champaign,
Siteman CCNE, St. Louis, MO

³University of California at San Francisco
CNPP, San Francisco, CA

⁴University of Missouri CNPP,
Columbia, MO

Cancer mortality and morbidity remain a challenge, considering that only 2.1% of the patients who underwent curative and adjuvant cytotoxic chemotherapy had a 5-year survival in the United States. The root of this problem is cancer metastasis. Metastatic cancer is lethal and disseminating

cancer cells are extremely difficult to tame. This problem can only be resolved by pursing an increased understanding of cancer biology, new technology for early cancer detection and novel therapy for the management of advanced cancer metastases even after cancer has spread to vital organs. Alliance CCNE/CNPP scientists, Dr. Douglas Hanahan from the University of California at San Francisco, Dr. Jianjun Cheng from the University of Illinois at Urbana-Champaign, Dr. Kattesh Katti from the University of Missouri at Columbia and Dr. Leland Chung from Emory University in Atlanta have worked together in a way that would not have been possible without CCNE Nanotechnology Platforms. These team scientists have recently formed an interdisciplinary group to begin tackling this problem. We met at various Alliance meetings/events and followed up with emails and teleconferences. Unlike other "traditional" team science projects, our team scientists did not know each other when we began our efforts, had no prior joint publications, and were not likely to meet

FIGURE 1. Imaging pancreatic tumors grown subcutaneously and prostate tumor grown in bone of immune compromised mice. A pancreatic tumor cell line, PDAC3.3, and a bone metastatic prostate tumor cell line, C4-2, were implanted respectively at subcutaneous and intratibial site of nude mice. Tumor growth can be clearly imaged without interference background (left panels). The presence of the tumors was confirmed by histopathology (right panels).

each other because of disparate scientific disciplines. Yet remarkably, because of our common passion to defeat cancer metastasis, and the collaborative network generated by the NCI Alliance program, we have come together over the past few months, sharing ideas, chemical reagents, cell lines, and laboratory models. We are happy to report that in our short time together, the exciting results have already shown that by working together on cancer biology, early detection and innovative treatment of cancer metastasis without prior conditions and in the spirit of cooperation, we can accelerate the pace of scientific discovery.

For over a decade, Dr. Douglas Hanahan's laboratory has worked on understanding the molecular events underlying multi-step carcinogenesis, cell proliferation and angiogenesis (1). They created a transgenic pancreatic cancer progression model that recapitulated the histopathology and behavior of human disease (2). Dr. Jianjun Cheng is a polymer and material scientist with strong commitment to translational

research. He holds numerous patents on the design and synthesis of novel drug-nanoparticle for cancer drug delivery (3). Dr. Kattesh Katti's laboratory has synthesized gold and silver nanoparticles for improved cancer diagnosis and therapy (4). His laboratory discovered bombesin, an effective targeting ligand for the delivery of these metallic nanoparticles tagged with radioactivity to human cancer epithelial cells (5). Dr. Leland Chung is a cancer biologist with a special interest in prostate cancer bone metastasis. His laboratory established a number of cancer metastasis models closely resembling human androgen-independent and lethal bone-metastatic prostate cancer (6). Recently, Dr. Chung's laboratory, in collaboration with Dr. Lucjan Strelkowski's laboratory at Georgia State University, discovered a class of near infrared (NIR) heptamethine cyanine dyes that have the unique ability to be taken up by human and mouse cancer cells but not normal cells.

Since pancreatic cancer and hormone-refractory bone-homing prostate cancers are considered the most aggressive and lethal forms of human cancers, Drs. Hanahan and Chung collaborated to demonstrate that one of the heptamethine cyanine dyes, IR-783 (Sigma-Aldrich), can be readily taken up by several pancreatic and prostate cancer cell lines and pancreatic and prostate tumor xenografts in mice (Figure 1). Although this NIR dye can be photosensitized by light to yield tumoricidal derivatives, it requires high concentrations difficult to achieve in live animals. This problem attracted the attention of Dr. Cheng, who then worked with his graduate student, Rong Tong and

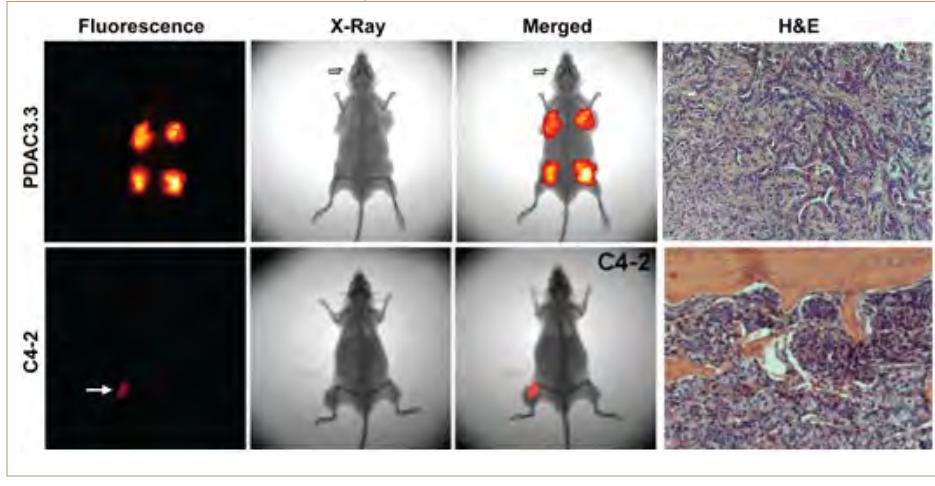
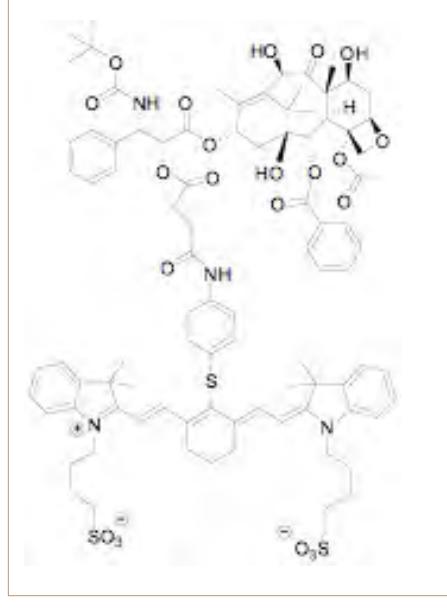


FIGURE 2. Chemical structure of IR-MUT-1. IR-MUT-1, a dye docetaxel conjugate, was synthesized and tested in human prostate and pancreatic tumor models.



Dr. Chung's student Dr. Xiaojin Yang, to develop a family of novel IR-783-taxol and -taxotere (or IR-MUT-1, see Figure 2) conjugates. They evaluated the cytotoxicity and biodistribution of these organic dye-drug conjugates and demonstrated that these conjugates could accumulate in cancerous but not in normal tissues for a prolonged period of time (over 4 days, see Figure 3). The attractive and promising properties of the dye-drug conjugates in pancreatic and prostate tumor models will soon be expanded into large scale studies of efficacy and safety with the hope that these designed drugs can be applied in human cancers as a new class of highly effective targeted therapeutics with minimal toxicity to normal tissues and cells.

Dr. Katti's laboratory has completed a series of basic studies documenting the effectiveness of bombesin as a cancer cell-surface-specific ligand that can guide gold nanoparticles to cancer cells without accumulating in normal cells. In collaboration with Dr. Chung's laboratory, they demonstrated that bombesin-guided gold nanoparticles can be delivered systemically to cancer cells. These new guided nanoparticles offer promise for cancer detection and also can be activated by external energy to induce focal hyperthermia to specifically kill cancer cells, which has the potential to improve cancer metastasis therapies.

In sum, the Alliance research network provides unprecedented opportunities for research collaborations between biologists, material scientists and polymeric and

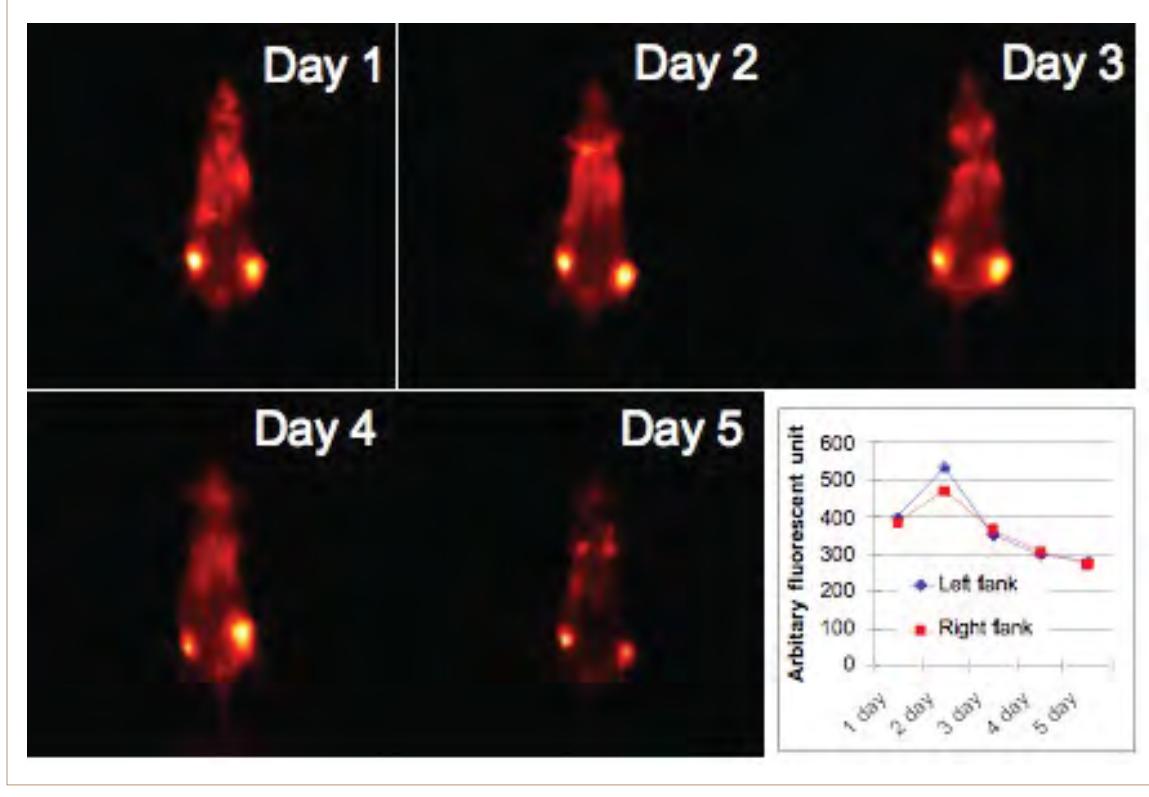
synthetic chemists who share a common research interest in defeating cancer metastasis. A meaningful synergy has already been achieved among CCNE and CNPP investigators through open communication and collaboration without preconditions. The group has already discovered a new class of cancer homing NIR-drug conjugates that offer hope for both imaging and targeting metastatic pancreatic and prostate cancers. Their collaboration was made possible by support and encouragement from the NCI administrative staff of the Alliance program, who assisted with communication and provided budgetary, personnel and administrative flexibility allowing collaborative efforts by the team scientists to flourish. The Alliance represents a new model of effective management of team science and resources which hopefully can be expanded within the National Cancer Institute extramural support portfolio to accelerate discovery and the rapid translation of bench science to the clinic.

References:

1. Du YC, Lewis BC, Hanahan D, Varmus H. Assessing tumor progression factors by somatic gene transfer into a mouse model: Bcl-xL promotes islet tumor cell invasion. PLoS biology 2007;5(10):2255-69.
2. Hager JH, Hodgson JG, Fridlyand J, Hariono S, Gray JW, Hanahan D. Oncogene expression and genetic background influence the frequency of DNA copy number abnormalities in mouse pancreatic islet cell carcinomas. Cancer research 2004;64(7):2406-10.
3. Cheng J, Teply BA, Sherifi I, et al. Formulation of functionalized PLGA-PEG nanoparticles for in vivo targeted drug delivery. Biomaterials 2007;28(5):869-76.

FIGURE 3. Prolonged retention of IR-MUT-1 in tumor tissues for days. Unlike small molecule drugs are typically cleared from body within minutes or a few hrs, IR-MUT1 retained in tumor tissues for several days and induced apoptosis in tumors without affecting the normal tissues.

4. Kannan R, Rahing V, Cutler C, et al. Nanocompatible chemistry toward fabrication of target-specific gold nanoparticles. *Journal of the American Chemical Society* 2006;128(35):11342-3.
5. Karra SR, Schibli R, Gali H, et al. 99m Tc-labeling and *in vivo* studies of a bombesin analogue with a novel water-soluble dithiadiphosphine-based bifunctional chelating agent. *Bioconjugate chemistry* 1999;10(2):254-60.
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Young Investigator Highlight



Scott Manalis, Ph.D.
MIT CNPP, Boston, MA

COLLABORATING ACROSS THE ALLIANCE

Scott Manalis, Ph.D.
MIT CNPP, Boston, MA

Dr. Manalis is the co-PI for the NCI Cancer Nanotechnology Platform Partnership (CNPP) entitled *Integrated System for Cancer Biomarker Detection*. He was trained in Applied Physics at Stanford University and is currently an associate professor in biological and mechanical engineering at MIT.

Manalis is interested in exploiting the unique physical properties associated with micro- and nanoscale dimensions to develop precision measurement methods for single cells and biomolecular interactions. His lab has recently developed a technology that enables mass to be measured in the aqueous environment with a resolution that is a million-fold better than existing methods. Their technology, known as the suspended microchannel resonator (SMR), places the fluid inside of the resonator instead of immersing the resonator in the fluid and thereby solves the long-standing problem of signal degradation from viscous drag. This has enabled single cells, nanoparticles

and biomolecules to be weighed in solution with femtogram resolution. (*Nature* 2007, 441 1066). The Manalis lab is also developing high performance fluidic interfaces to micro- and nanofluidic sensors such as the SMR. These interfaces utilize novel Teflon valves and pumps that are resistant to virtually all chemicals. (*Lab on a Chip* 2008, 7 347). They are currently developing a microfluidic Autosampler Chip that will be capable of automating all fluidic manipulations necessary for performing precision measurements with the SMR sensor.

Within the NCI CNPP, Manalis together with Jongyoon Han (MIT) and Bruce Zetter (Harvard Medical School) are developing a general approach for improving the performance of ligand — receptor assays. While immunoassays such as ELISA are well established for antigen-based biomarker detection, the fidelity of the assay is governed by the disassociation constant, K_d , of the antibody-antigen complex. If the antigen concentration is significantly below K_d , then the binding kinetics are slow and readout precision of the antigen-antibody complex can be degraded by noise. Their approach is based on a nanofluidic

Within the NCI CNPP, Manalis together with Jongyoon Han (MIT) and Bruce Zetter (Harvard Medical School) are developing a general approach for improving the performance of ligand — receptor assays.

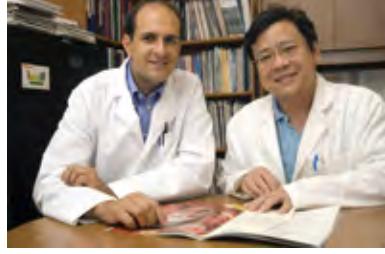
device that controllably concentrates a dilute sample and an ultra-sensitive SMR mass sensor that detects specific biomarkers within the concentrate. Since the amplification (or gain) of the concentrator is adjustable, the dynamic range and detection limit of the immunoassay can be governed by the properties of the concentrator and not K_d . The devices are batch fabricated by conventional foundry-level processing techniques, and the cost per device could potentially be suitable for routine use in a clinical setting.

The environment fostered by the NCI Alliance has led to several productive collaborations for the Manalis laboratory. For example, he is working with Dr. Parag Mallick and other investigators within the Stanford CCNE on a project to determine if the response of cancer cells to pathway-directed therapeutics can be classified according to subtle changes in growth. The project leverages the Stanford CCNE's discovery of numerous cell-surface protein biomarkers indicative of therapeutic response and an ultrasensitive mass sensor that has been advanced within his CNPP. In the future, Manalis and colleagues plan to

use the SMR's ability to resolve mammalian cell mass with a precision near ~0.01% to investigate how cell growth relates to progression through the division cycle, and if the response of cancer cells to pathway-directed therapeutics can be classified according to subtle changes in growth. He is also working with Dr. Sangeeta Bhatia (Harvard/MIT CCNE) and Dr. Katti Kattesh (University of Missouri CNPP) on the development of gold nanoparticles for ultrasensitive mass-based detection of cancer biomarkers. Finally, he is participating within a consortium (which includes Dr. Jim Heath, Caltech CCNE and Dr. Grzybowski, Northwestern CCNE) to integrate super-low fouling poly(carboxybetaine) surfaces that are currently being developed by Shaoyi Jiang (University of Washington) with various nano- and microscale detection platforms that are suitable for routine use in a clinical setting.

For more information about Scott Manalis and his research group please visit the group's website at: <http://www.media.mit.edu/nanoscale/index.html>.

Training Across the Alliance



*On the left:
Aaron Mohs, Ph.D.,
Emory CCNE
Distinguished Fellow*

*On the right:
Shuming Nie, Ph.D.,
Director for Nanotechnology
and Bioengineering, Winship
Cancer Institute*

CONNECTING ACROSS DISCIPLINES — EMORY/GT CCNE'S DISTINGUISHED FELLOWS PROGRAM

*By Quinn Eastman, Ph.D.
Science Writer, Emory University*

An organic chemist dons scrubs to work side by side with a thoracic surgeon and test a new tumor imaging probe in animals. An electrical engineer is enlisted to make sense of the huge amounts of data new biophysical techniques produce.

These examples of collaboration at Emory and Georgia Tech's Center for Cancer Nanotechnology Excellence show how the field of cancer nanotechnology touches several disciplines. They also illustrate how participants in an innovative postdoctoral fellow program at Emory/Georgia Tech are connecting those disciplines.

"Our goals are to attract the best people possible and form bridges between the research programs of various faculty," says CCNE director Shuming Nie.

Emory-Georgia Tech Distinguished CCNE fellows are required to be assigned to at least two principal investigators. The program includes scientists with a wide range of backgrounds and skills, ranging from electrical engineering to molecular biology.

For medicinal chemist Debatosh Majumdar, "nanotechnology offers a little bit of everything. The chemistry can be relatively simple, but after that the challenge is biology."

As a Distinguished CCNE Fellow, "the demands and expectations are higher, because there will be more things on your plate," says Aaron Mohs, the first fellow to begin work in 2006.

For his graduate work, Mohs explored how to create biodegradable contrast agents for MRI (magnetic resonance imaging). Now, he is evaluating the potential toxicity of nanoparticles as vehicles for tumor imaging and treatment. His work spans several types of nanoparticles studied by CCNE investigators, including those made of gold, iron oxide, polymers and semiconductor quantum dots.

"Part of the challenge comes because we don't know whether some nanoparticles' toxicity will come from their chemical composition or from physical characteristics like size and shape," Mohs says. He is beginning to explore how effectively nanoparticles might cross intestinal barriers if they enter the body orally.

His "pre-pre-clinical" work harmonizes with the NCI's Nanotechnology Characterization Laboratory, he says: "They provide a structure and we apply it to the unique technologies we're developing here."

Although most of his work is on cultured cells, Mohs has teamed up with a new Emory surgery faculty member, Sunil Singhal. In a new "intraoperative suite" they designed, their team demonstrated the ability of fluorescent probes to visualize tumors within the lungs of pigs during surgery.

To provide the targeting power to the nanoparticles Mohs is testing, his colleague Hari Sajja is involved in producing, purifying and conjugating proteins such as ATF-plasminogen, which binds to a receptor overexpressed in many cancers. An experienced chemical engineer, Sajja previously worked on selecting RNA molecules that specifically bind various compounds.

He became interested in targeting treatment to a tumor because it offers the possibility of avoiding the side effects of traditional chemotherapy, and says that what he likes the most in the lab is imaging using animals.

“That is the acid test — when you find out whether the preparation you have made really works,” Sajja says.

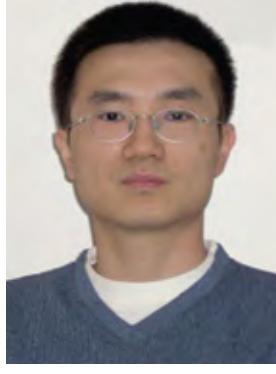
Mitch Parry, a computer science PhD with expertise in signal processing, is building computing infrastructure for the CCNE group. Working with Georgia Tech bioinformatics professor May Wang, Parry is also developing computing tools for tissue mass spectrometry.

With a minimum of processing, tissue mass spectrometry could be used to rapidly evaluate biopsy samples, but it presents a challenge in sorting through immense amounts of raw data and making sense of it.

Director Nie is aiming for an expansion of the Distinguished CCNE Fellow program from four to six fellows, and envisions that they will stay for around three years. The fellows lunch with the CCNE’s monthly visiting speakers and have access to reserved travel funds.

“Our goals are to attract the best people possible and form bridges between the research programs of various faculty,” says Emory/GT CCNE director Shuming Nie.

Training Across the Alliance



*Ken-Tye Yong, Ph.D.,
Postdoctoral Fellow
State University of
New York at Buffalo CNPP,
Buffalo, NY*

INTERDISCIPLINARY EXPERIENCE FOR SUCCESS IN CANCER RESEARCH

*By Ken-Tye Yong, Ph.D.,
Postdoctoral Fellow
State University of New York
at Buffalo CNPP, Buffalo, NY*

During my PhD years, my research has focused on the synthesis, functionalization, and application of nanomaterials. These materials have various applications in fields ranging from electronics to biology due to their unique properties. After graduation in 2006, I joined Dr. Paras N. Prasad's group as a postdoc in the Institute for Lasers, Photonics and Biophotonics at State University of New York at Buffalo. At that time, I was given the freedom to choose my own research career path either in biomedical or solar energy field, which are among the best programs available in the Institute.

I have a series of discussions with my advisors, Dr. Paras N. Prasad, Dr. Earl J. Bergey and Dr. Anirban Maitra. They inspired me to apply background in nanomaterials to biomedical research. Because of the support from the SUNY/Buffalo CNPP (Cancer Nanotechnology Platform Partnership), I am able to work with colleagues from different disciplines

(e.g. physicians, engineers, chemists, and physicists) and dedicate myself to pancreatic cancer research. Because pancreatic cancer often evolves without early symptoms and the majority of patients are diagnosed at an advanced, and hence incurable, stage, we note that it is of vast importance to develop ultrasensitive imaging probes for diagnosing pancreatic cancer at an early stage in order to potentially improve the survival rate of pancreatic cancer patients.

One promising nanomaterial which could serve as an imaging probe for early detection of pancreatic cancer is quantum dots (QDs). Quantum dots are inorganic luminescent semiconductor nanoparticles which allow control of their electronic and optical properties by varying particle sizes. Though I was able to use chemical approaches to reproducibly provide precise control of composition, size, and shape of the QDs formed, there remain challenges in making them compatible with biological systems. My colleagues and I have developed methods to make these particles more biocompatible and at the same time locate the cancerous area. After treating QDs with several coatings, they can serve as glowing markers that clearly identify several types of pancreatic cancer cells. These encouraging results justify further investigation of the use of quantum dots as imaging agents for pancreatic cancers.

This bioimaging of pancreatic cancer cells relied on QDs mainly concentrates on the *in vitro*, experiments done outside of a living body in a controlled environment. Throughout the process, I have observed QDs lack some critical features for *in vivo* study and they can be improved by adding other functions. During that time, I noticed American Association for Cancer Research-PanCAN has actively engaged in funding young scientists to conduct research in pancreatic cancer treatment and detection. Because I was familiar with the limitations and difficulties of using QDs in experiments conducted in the living body, I generated ideas to enhance their capabilities as diagnostic tools and wrote a proposal about these plans. My advisors

were very supportive and encouraged me to apply for the funding sponsored by AACR-PanCAN. I am very fortunate and honored to have been selected as the recipient for the AACR-PanCAN Fellowship Award this year. I am proud to participate in SUNY/Buffalo CNPP program, in which I have learned how to fuse my research experience in nanomaterials to a multidisciplinary field and interact and cooperate with scientists from all over the world. The training not only allows me to realize the challenges faced by current cancer research but also helps me initiate and formulate independent ideas based on the findings and discoveries in the project. I am really grateful to be part of it.

One promising nanomaterial which could serve as an imaging probe for early detection of pancreatic cancer is quantum dots (QDs).

Training Across the Alliance



*Aaron M. Mohs, Ph.D.
Emory — Georgia Tech
CCNE Distinguished Fellow
Emory/GT CCNE,
Atlanta, GA*

DISTINGUISHED FELLOWSHIP HONOR LEADS TO GREAT OPPORTUNITIES

*By Aaron M. Mohs, Ph.D.
Emory — Georgia Tech CCNE
Distinguished Fellow
Emory/GT CCNE, Atlanta, GA*

Receiving the Emory-GT CCNE Distinguished Fellowship has been a great honor and also an excellent opportunity to explore several of the new technologies developed at our center. One of the primary responsibilities of being a CCNE Fellow is to interact with multiple investigators within our CCNE and to serve as a bridge between projects or groups to increase collaboration. To highlight the opportunities provided by my Fellowship, one project that I am involved with focuses on developing nanoparticles and instrumentation for intraoperative imaging to dramatically improve patient outcome following cancer surgery. My role in this project is to interface novel technologies in nanoparticle imaging probes and imaging devices with clinical need by closely working with faculty in the Department of Surgery at Emory. This interdisciplinary interaction compels scientists to design technology for immediate patient impact and exposes clinicians to the benefit of bringing the latest technology into the hospital. Another area of my research focuses on the toxicology of nanomaterials, or nanotoxicology. Evaluating the safety of nanomaterials, both *in vitro* and *in vivo*, is a decisive point in the development of any nanomaterial designed for use in a living organism, regardless of

the platform used, e.g. polymeric, gold, iron oxide, or semiconductor nanoparticles. Therefore, understanding the interaction between each of these technologies being developed within our CCNE and the biological environment puts this project in a unique position to evaluate potential lead candidates of nanotechnology for further development and identify potential roadblocks or requirements for the next generation of nanomaterials. Traditional postdoctoral research projects may not always provide these opportunities for multidisciplinary research and collaboration at the interface of engineering, science, and medicine, but by being a CCNE Fellow, these highly collaborative interactions are my primary focus.

Aside from research responsibilities, my CCNE Fellowship has provided me with many opportunities to build networks within the scientific community. My fellowship put me in a position where I can actively contribute to NCI Alliance for Nanotechnology in Cancer working groups, such as the Nanoinformatics and the Diagnostic, Imaging, and Sensing Working Groups. Within our CCNE, I have been able to interact with many research and clinical faculty and meet with outside professors and clinicians in our Distinguished Seminar series. Because of the scientific and clinical components of my research and the excellent opportunity to network with the scientific community both internally and externally, the Emory-GT Distinguished Fellowship has provided me with an extraordinary opportunity to build my scientific career at the forefront of biomedical research.

Accelerating Translation

Commercialization of Nanotechnology

By Deborah Halber

Once the domain of high-tech startups, the area surrounding the Massachusetts Institute of Technology (MIT) in Cambridge, Mass., is attracting a growing cluster of biotech and drug companies. Two of the newest are spinning off technologies from the laboratories of MIT's David H. Koch Institute for Integrative Cancer Research and Massachusetts General Hospital (MGH)/Harvard University.

BIND Biosciences, Inc. and T2 Biosystems Inc. seek to revolutionize the detection, diagnosis and treatment of cancer and other life-threatening diseases. They are both commercializing cutting-edge research supported by the MIT-Harvard Center for Cancer Nanotechnology Excellence, part of the National Cancer Institute's \$144M commitment to nanotechnology.

Dr. Omid C. Farokhzad, assistant professor of anesthesia at Harvard Medical School, co-founded BIND Biosciences in 2006 with \$2.5 million in funding from Polaris Venture Partners and Flagship Ventures of Cambridge. The company, which raised an additional \$16 million in 2007, develops therapeutic targeted nanoparticles that deliver drugs directly to diseased cells while minimizing systemic exposure, thereby increasing efficacy and reducing side effects.

"Taking biomedical advances associated with cancer treatment and diagnosis from the bench to the market requires partnering

with many different groups as exemplified in these two cases out of the NCI-funded Centers for Cancer Nanotechnology Excellence," said Thomas M. Stackhouse, assistant director of the NCI's Technology Transfer Center (<http://ttc.nci.nih.gov>).

"Through a complete range of services including day-to-day transactional agreements, the NCI's Technology Transfer Center is able to help create and advance partnerships with the NCI to bring the benefit of new technologies to the patients."

BIND Biosciences' initial efforts are in cardiovascular and inflammatory disease and cancer — a clinical test for cancer treatment is slated for 2009 — while ongoing research at MIT and Harvard-affiliated Brigham and Women's Hospital is pioneering the technology to a myriad of clinical and research applications, including RNA interference.

"Our goal is to develop and invent technologies with near-term and long-term impact that will change the face of how medicine is practiced," Farokhzad said.

T2 Biosystems is creating a new generation of small, affordable lab-quality diagnostic tools for use in the emergency room, the ambulance, the physician's office, the home and the field. By exploiting the physics underlying the interaction of magnetic nanoparticles with biological substances and detecting the results with miniaturized magnetic resonance systems, the company is seeking FDA approval for its innovative new approach to medical diagnostics.

T2 Biosystems' six co-founders at MGH and MIT raised \$5.5M in 2006 and 10M in 2008. CEO John McDonough joined in 2007, after helping launch startups in medical and Internet applications.

T2 Biosystems' prototype portable device will test blood, urine, saliva or any other water-based biofluid within minutes for a wide variety of targets, including viruses, cells, proteins, enzymes, nucleic acids and small molecules, McDonough said.

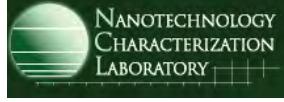
Because there is no visual analysis involved, the test is more accurate and faster than traditional methods. "Because of the work involved in taking a technology from the lab to the marketplace, it helps to determine where there is an immediate need for the technology," McDonough said. "Where does it save someone's life and take costs out of the health care system? For us, the answer is our ability to provide a rapid diagnostic test."

It doesn't hurt that MIT engineering powerhouse Robert S. Langer, whose ideas have spawned a string of biotech

startups and who holds over 600 issued or pending patents, helped found both BIND Biosciences and T2 Biosystems. But McDonough and Farokhzad agree that other factors are critical for success. "My recommendation for people who do not have folks like Bob as a collaborator would be to seek out mentors and advisors who have experience in taking great science from the university into a commercial setting," McDonough said. "Advisors can include people from the universities, angel and venture investors along with people who have experience and may currently be working in a commercial setting."

Farokhzad agreed. "Reach out to mentors who will help you avoid some key mistakes," he said. He also urged young researchers to file patents for their innovative new work. "The one way you make sure your technology goes nowhere is if you don't patent it," he said. "Companies will develop your technology only if they are secure that if they spend tens of millions on it, nobody is going to scoop them."

Nanotechnology Highlights



THE NANOTECHNOLOGY CHARACTERIZATION LABORATORY

By: Jennifer Hall, Ph.D.

Data Coordinator/Scientific Writer
Nanotechnology Characterization Lab
NCI-SAIC Frederick, Frederick, MD

The Nanotechnology Characterization Laboratory (NCL) provides infrastructure support to the National Cancer Institute (NCI)'s Alliance for Nanotechnology in Cancer program — including the CCNEs and CNPPs, as well as the larger nanotechnology and cancer research communities. NCL's primary mission is to accelerate the translation of promising and safe nanotechnology-derived cancer therapeutics and diagnostics from the advanced discovery-phase towards clinical trials. Towards this goal, NCL conducts thorough preclinical characterization of nanomaterials intended for cancer applications. NCL characterization services are available by application to developers and researchers from academia, industry, and government. NCL characterization is offered at no cost to the developer.

The NCL was conceived on paper at NCI in 2003 in response to the growing number of promising proof-of-concept studies involving nanotech cancer therapies. At that time, this exciting work had not yet translated into clinically used cancer drugs and diagnostics. NCI recognized that this issue couldn't effectively be addressed

without interagency collaboration and the involvement of the public, private, and academic sectors. Within a year, relationships were established with the National Institute of Standards and Technology (NIST) and the US Food and Drug Administration (FDA) and the NCL was founded at NCI's Federally Funded Research & Development Center at SAIC/NCI-Frederick.

The first objective of the newly-founded laboratory was to work with NIST and the FDA to develop a set of standardized methods for safety and efficacy testing of nanomaterials (i.e. the NCL assay cascade). By the beginning of 2006, the NCL fully operational with a working set of characterization assays specifically designed to help nanotech cancer therapies and diagnostics meet regulatory requirements.

Once its assay cascade was established, the NCL began actively soliciting collaborations with developers of promising nanotech cancer therapies and began several translational projects. Among these are projects from several Alliance for Nanotechnology in Cancer CCNEs and past and present grantees. The NCL produced its first client report for Dendritic Nanotechnologies, Inc. (DNT) in late 2006. The data in this report helped DNT obtain equity in its operation, resulting in its acquisition by a larger pharmaceutical development firm.

In 2007, the NCL almost doubled the number of its collaborations with academia, industry, and government. The NCL now has over 30 such collaborations aimed at bringing particular nanotech products to clinics. This encompasses over 100 unique nanoparticle constructs undergoing NCL characterization. In 2007, NCL also began contributing to the progression of nanotech candidate drugs through clinical trials. One NCL submission is scheduled for an IND submission in 2008 and another has completed Phase I and will enter Phase II in 2008. In 2007 the NCL also produced four client reports, five peer-reviewed articles in prestigious scientific journals, and had three of its protocols accepted in final ballots as American Society for Testing and Materials (ASTM International) standards. These represent the first internationally recognized formal standards for biocompatibility-testing of nanomaterials intended for medical applications.

The NCL's primary focus is to work with the developers of nanotech cancer drugs and diagnostics to help move their products towards clinical trials. The NCL also collaborates with scientists who have not yet selected their lead compound, but need assistance with physicochemical, safety or efficacy studies. NCL is comprised of staff from the fields of chemistry, physics, immunology, cell biology and

toxicology — and now has experience with the majority of nanoparticle types intended for medical applications, including liposomes, nanoshells, nanorods, metal colloids, functionalized gold, titanium dioxide, derivatized fullerenes, dendrimers, quantum dots, nanoemulsions, nanocrystals, iron oxides, and polymer-based nanomaterials.

As those experienced with nanotechnology understand, multifunctional nanoparticles are intricate, often delicate systems, and their characterization is challenging. Nanoparticles have to be characterized quite rigorously, as there are multiple components that must work in concert to achieve functionality. Meaningful physicochemical characterization of a multifunctional entity like a nanoparticle includes assessment of the individual parts, the stoichiometry and connections between the parts, and the chemical stability of those associations (e.g., covalent and van der Waal bonds).

Nanoparticle biological characterization is also challenging. For instance, nanoparticles often absorb light and interfere with *in vitro* methods used to evaluate their physicochemical or immunological properties. Many nanoparticles have catalytic properties and can enhance assays that rely on enzymatic reactions, generating false-positive results. Assays routine to the preclinical characterization of conventional

pharmaceuticals, such as the Limulus amebocyte lysate (LAL) test for endotoxin contamination detection may yield spurious results when applied to nanoparticle samples.

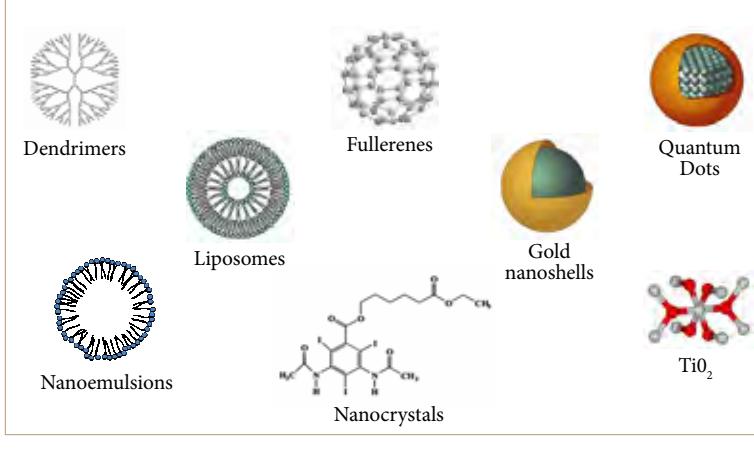
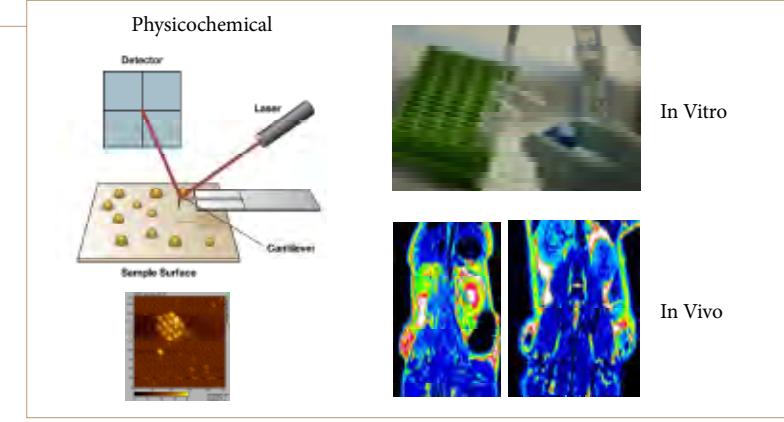
A plethora of data now exists in the scientific literature, as well as characterization data generated by NCL on proprietary formulations, demonstrating that each nanoparticle is unique. Slight changes to a nanoparticle's size or surface chemistry, for instance, can dramatically influence a physiological response. A thorough characterization of a nanoparticle-based therapeutic includes evaluation of physicochemical properties, sterility and pyrogenicity assessment, biodistribution (ADME or absorption, distribution, metabolism and excretion) and toxicity characterization — which includes both *in vitro* tests and *in vivo* animal studies. The NCL has experience in each of these tiers of a rational characterization cascade and has validated its assays on a wide variety of nanomaterials.

The NCL is currently accepting applications for characterization services. NCL characterization (including physicochemical, *in vitro*, and *in vivo* experiments) is offered at no cost to the developer. Please visit our website <http://ncl.cancer.gov> for more information.



Characterizing Nanoparticles in the NCL Assay Cascade.
Nanotechnology strategies submitted to NCL are characterized in a standardized assay cascade developed in collaboration with the National Institute of Standards and Technology and the Food and Drug Administration. This three-tiered system for nanoparticle characterization consists of physicochemical, in vitro, and in vivo testing. NCL characterization services are offered at no costs to our collaborators.

NCL Extramural Collaborators (2004-2008).
New collaborations in 2007 include (from top left): Alnis BioSciences, Dr. James R. Connor of Pennsylvania State University, CytImmune Sciences, Dr. Julia Y. Ljubimova of Cedars-Sinai Medical Center, Dr. Esther H. Chang of the Lombardi Comprehensive Cancer Center at Georgetown University, Carigent Therapeutics, Dr. Andrew Miller of Imperial College London, Dr. Vladimir P. Torchilin of Northeastern University, Dr. William Zamboni of the University of Pittsburgh, Dr. Kattesh V. Katti of the University of Missouri-Columbia, Avidimer Therapeutics, and Dr. Alex Wei of Purdue University.
New in 2008 include Luna Innovations and GE's Chemical Nanotechnology Laboratory.



Portfolio of NCL Nanoparticles. NCL has characterized many different types of nanomaterials, including liposomes, dendrimers, gold nanoshells, quantum dots, colloidal gold, nanoemulsions, fullerenes, TiO₂ nanocrystals, iron oxides, and polymers. The majority of the nanoparticles submitted to NCL are functionalized with drugs and targeting agents. In June of 2008, there were a total of 122 unique nanoparticles undergoing NCL characterization.

Alliance Activities

SYMPOSIA

Courses *Symposiums*
C-CCNE, Chapel Hill, NC
Annual Cancer Nanotechnology Symposium
Friday, November 14, 2008
Location: Carolina Club at UNC Chapel Hill
For more information, contact Susan Wohler Sunnarborg at susan_sunnarborg@med.unc.edu.

COURSES

Lectures
MIT-Harvard CCNE, Boston, MA
Access to all MIT undergraduate and graduate courses can be found at: <http://mit.edu/ocw/>

Seminars
Siteman CCNE at Washington University, St. Louis, MO
Biomedical Applications of Nanotechnology

This course is intended to survey the field of nanobiomedicine in a lecture format given by invited experts. Topics will range from multimodality imaging to targeted therapeutics to molecular diagnostics. Benefits and toxicities will be presented and the translational aspects of commercialization of nanosystems for medical use will be covered.

For an outline of course lectures and additional information about the course , please contact Lynn Coulter at lcoulter@cmrl.wustl.edu

LECTURES

Nano-Tumor CCNE, San Diego, CA
UCSD/Invitrogen Lecture Series
Thursday, October 23, 2008
Location: UCSD's Goldberg Auditorium at Moores UCSD Cancer Center
Scheduled speaker: Stephen Quake
Microfluidic Large Scale Integration (LSI), a technology that is helping to pave the way for large scale automation of biology at the nanoliter scale, and how this team has been exploring applications of "lab on a chip" technology in functional genomics, genetic analysis, and protein design.

For more information, contact adriana@nanobionexus.org

SEMINARS

CCNE-TR, Stanford, CA
2008 Nanobiotechnology Seminar Series
Dates and invited speakers:
September 16, 2008 — Jonathan Simons, M.D.
Nanotechnologies for Personalized and Predictive Prostate Cancer Care
October 14, 2008 — Charles Lieber, Ph.D.
Nanoelectronic-Biology Interfaces: From Ultrasensitive Detection to New Biomaterials
November 13, 2008 — Chad Mirkin, Ph.D.
Nanostructures in Biodiagnostics and Gene Therapy
Visit http://mips.stanford.edu/public/nanobiotech_seminar.adp for more information and to view archived webcasts of seminars.

Emory-GT CCNE, Atlanta, GA

2008 Emory-GT CCNE Frontiers of Cancer Nanotechnology Seminar Series
Location: Winship Cancer Institute, Atlanta GA, Room C501
Time: 3:00 p.m.
September 11, 2008 - Richard J. Cote M.D., FRCPath
New Approaches to Cell Capture, Analysis and Molecular Biosensing Using Novel Nanotechnology Platforms
October 13, 2008 – Dennis Liotta, Ph.D. Novel Cancer Therapeutics
November 10, 2008 – Joseph DeSimone, Ph.D.
Monodisperse, Shape-Specific Nano-biomaterials for Cancer Therapeutics and Imaging Agents
December 8, 2008 — Charles Lieber, Ph.D. Nanoelectronic-Biology Interfaces: From Ultrasensitive Detection to New Biomaterials

Nano-Tumor CCNE, San Diego, CA

Qdot® Nanocrystals for Biological Applications
Wednesday, October 29, 2008
Location: UCSD's Goldberg Auditorium at Moores UCSD Cancer Center
Schedule speaker: Eric Tulsky, Invitrogen, Inc.
For more information, please contact adriana@nanobionexus.org.

Alliance Classifieds

Job Postings

Emory-GT CCNE, Atlanta, GA

Post-Doc Fellow (Biomedical Engineering)

The Emory-Georgia Tech Center of Cancer Nanotechnology Excellence (CC NE) and the Bioengineering Research Partnership (BR P) invite applications for postdoctoral research associates in biomedical engineering, nanotechnology, medicinal chemistry and bioinformatics. Specific research topics include: (1) nanoparticles for gene and siRNA delivery; (2) nanotechnology for molecular analysis and detection of atherosclerosis plaques; (3) nanoparticle reagents for sensitive imaging of Alzheimer's and other neurodegenerative diseases; (4) nanoparticle organ uptake, distribution, and toxicology; (5) biomedical applications of Raman and surface-enhanced Raman spectroscopy; (6) cellular image processing and 3-D reconstruction; (7) synthesis of biocompatible and biodegradable polymers for targeted delivery of imaging and therapeutic agents; and (8) molecular histopathology and correlation of biomarkers with clinical outcome. The minimum requirements include a PhD or MD degree in engineering, chemistry, biology or medicine, at least two first-author papers in high-quality journals (impact factor > 5.0), and an interest in collaborative work at the interface of science, engineering, and medicine.

Exceptional candidates will be considered for the prestigious CC NE fellowship at Emory University and the Georgia Institute of Technology. We offer competitive salaries plus fringe benefits. To apply, send a cover letter, an updated CV, and names of 3-5 references to Mr. Ryan Jowers, Cancer Nanotechnology Center Manager, Department of Biomedical Engineering, Emory University, 101 Woodruff Circle Suite 2007, Atlanta, GA 30322. Electronic applications are encouraged and should be addressed to Mr. Ryan Jowers at ryan.jowers@bme.emory.edu. For further information, see www.nielab.org and www.wcigtnccne.org. All positions are open until filled.

MIT-Harvard CCNE, Cambridge, MA

MIT is an equal opportunity/affirmative action employer. Applications from women, minorities, veterans, older workers, and individuals with disabilities are strongly encouraged. For current employment opportunities, please visit: <http://hrweb.mit.edu/staffing/>.

The NCI Alliance Nanotechnology in Cancer Bulletin is a collaborative effort developed and facilitated by the Communications and Integration Working Group (CIWG) of the Alliance program. The group is currently led by Alliance co-chairs, Ryan Jowers (Emory-GT CCNE) and Kathleen Cook (NU-CCNE), with coordination from NCI co-chair, Jerry Lee, Ph.D.

The CIWG's mission is to catalyze effective Alliance-wide and external communications, facilitate Alliance team science integration, create education outreach opportunities, and leverage best practices.

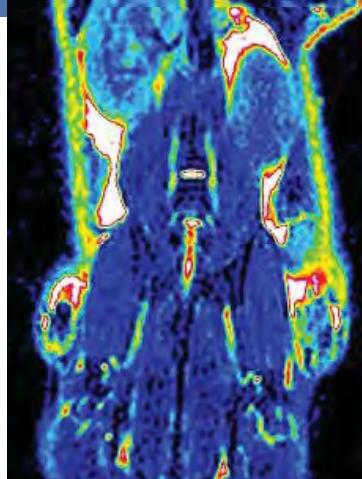
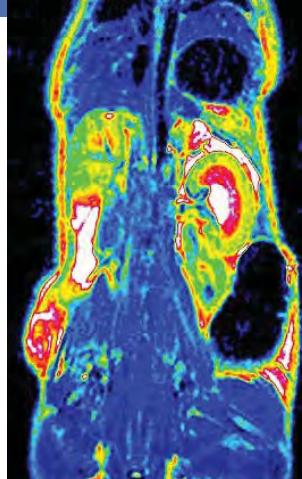
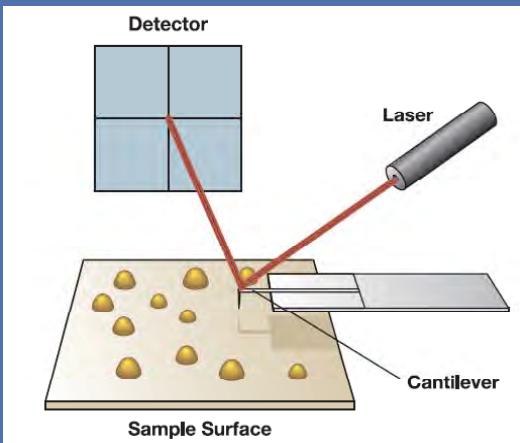
For comments or article ideas, please contact your Alliance CIWG Primary Contact(s):

CCNEs		
C-CCNE, Chapel Hill, NC Susan Sunnarborg, Ph.D. susansunnarborg@med.unc.edu	NSBCC-CCNE, Pasadena, CA Diane Clark Robinson dianer@caltech.edu	SUNY/Buffalo-CNPP, Buffalo, NY Indrajit Roy, Ph.D. iroy@buffalo.edu
CCNE-TR, Stanford, CA Billie Robles brobles@stanford.edu	S-CCNE, St. Louis, MO Angela Benassi benassia@ccadmin.wustl.edu	UWash-CNPP, Seattle, WA Omid Veiseh omid@u.washington.edu
NANO-TUMOR CCNE, San Diego, CA Davorka Messmer, Ph.D. dmessmer@ucsd.edu Adriana Vela adriana_wp@yahoo.com	UCSF-CNPP, San Francisco, CA Jessica Pahler jpahler@diabetes.ucsf.edu	SKCC-CNPP, San Diego, CA Jan Schnitzer, MD jschnitzer@skcc.org
Emory-GT CCNE, Atlanta, GA Ryan Jowers ryan.jowers@bme.emory.edu	UMich-CNPP, Ann Arbor, MI Jola KuKowska-Latallo	Northeastern-CNPP, Boston, MA Renata Nyul r.nyul@neu.edu
MIT-Harvard CCNE, Boston, MA Shannon Cozzo scozzo@mit.edu	UMiss-CNPP, Columbia, MO Jeanne Muse musej@health.missouri.edu	MD Anderson-CNPP, Houston, TX Chun Li, Ph.D. cli@di.mdacc.tmc.edu
NU-CCNE, Evanston, IL Kathleen Cook k-cook@northwestern.edu Mary Drzewiecki m-drzewiecki@northwestern.edu	MIT-CNPP, Boston, MA pdextras@mit.edu	RPCI-CNPP, Buffalo, NY Deborah Pettibone Deborah.pettibone@roswellpark.org
	VCU-CNPP, Richmond, VA Harry Dorn, Ph.D. hdorn@vt.edu	MGH-CNPP, Boston, MA Sung Chang skchang@partners.org



NANOTECHNOLOGY
CHARACTERIZATION
LABORATORY

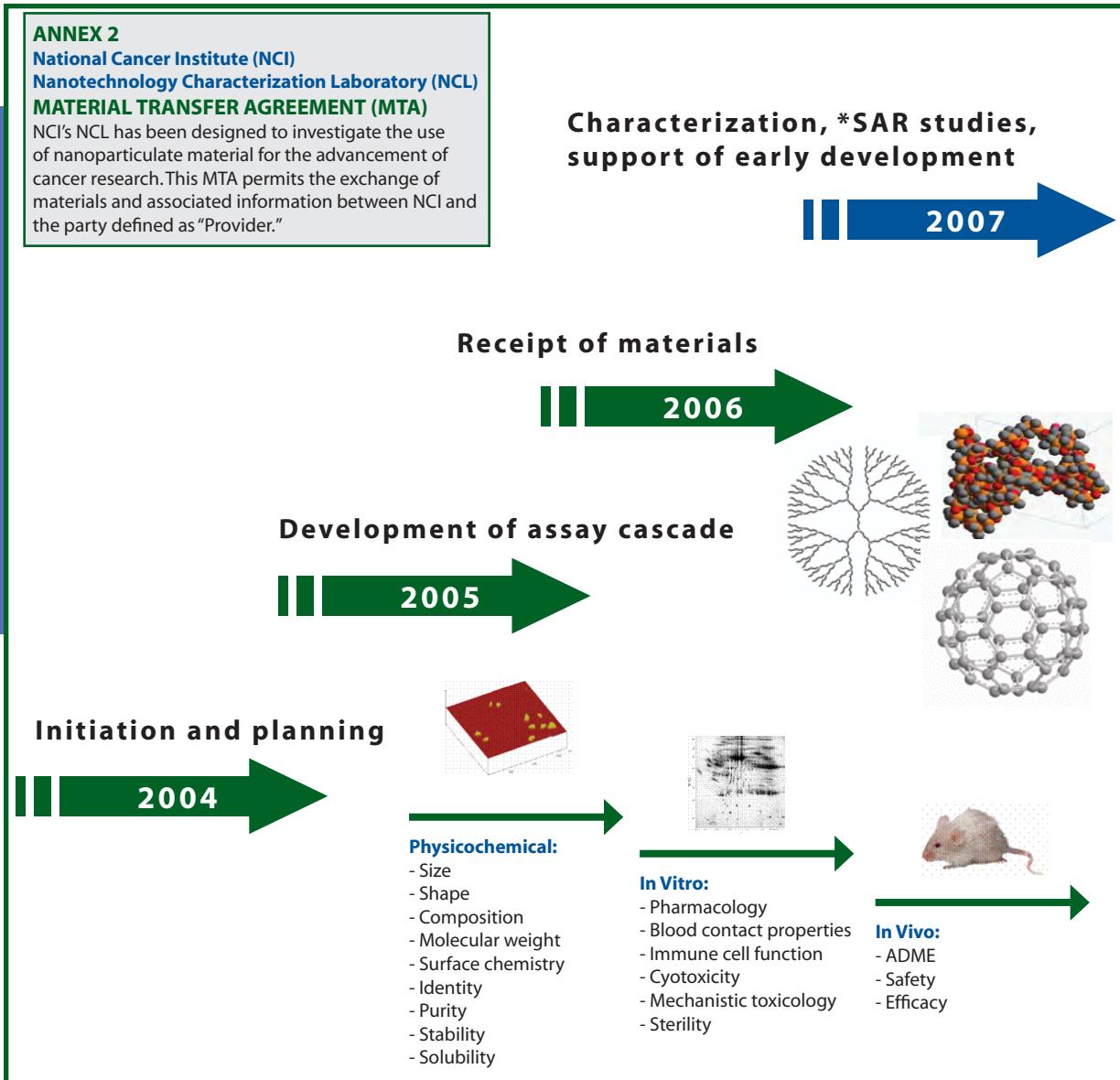
Accelerating Translational Research
NCL 2007 Annual Report



Characterizing Nanoparticles in the NCL Assay Cascade. Nanotechnology strategies submitted to NCL are characterized in a standardized assay cascade developed in collaboration with the National Institute of Standards and Technology and the Food and Drug Administration. This three-tiered system for nanoparticle characterization consists of physicochemical, *in vitro*, and *in vivo* testing.

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NCL Timeline: History of NCL. In 2004 NCL established working collaborations with the National Institute of Standards and Technology (NIST) and the Food and Drug Administration (FDA) and recruited its key personnel. In 2005 NCL developed a characterization assay cascade for preclinical assessment of nanomaterials and equipped its laboratories. In 2006 NCL began characterization of several promising nanoparticles intended for cancer applications, including therapeutics, imaging agents, and diagnostics. NCL's Scientific Oversight Committee, comprising representatives from NCI, NIST, and FDA, meets biannually to evaluate NCL's scientific data, program function, and progress toward accomplishing its objectives.

*SAR = structure-activity relationship.

EXECUTIVE SUMMARY

The Nanotechnology Characterization Laboratory (NCL) provides infrastructure support to the National Cancer Institute's (NCI) Alliance for Nanotechnology in Cancer and is entirely staffed through NCI's federally funded Research and Development Center at Science Applications International Corporation/NCI-Frederick. NCL's primary mission is to accelerate the translation of promising and safe nanotechnology-derived cancer therapeutics and diagnostics from the advanced discovery phase to clinical trials. Toward this goal, NCL conducts thorough preclinical characterization of nanomaterials intended for cancer applications.

NCL's objectives are to:

- Characterize nanoparticles using standardized methods
- Conduct structure-activity relationship studies
- Facilitate regulatory review of nanotechnology constructs
- Identify and characterize critical parameters related to nanomaterial ADME/tox
- Engage in educational and knowledge sharing efforts

In 2007 NCL made significant progress toward accomplishing these goals. The following are highlights:

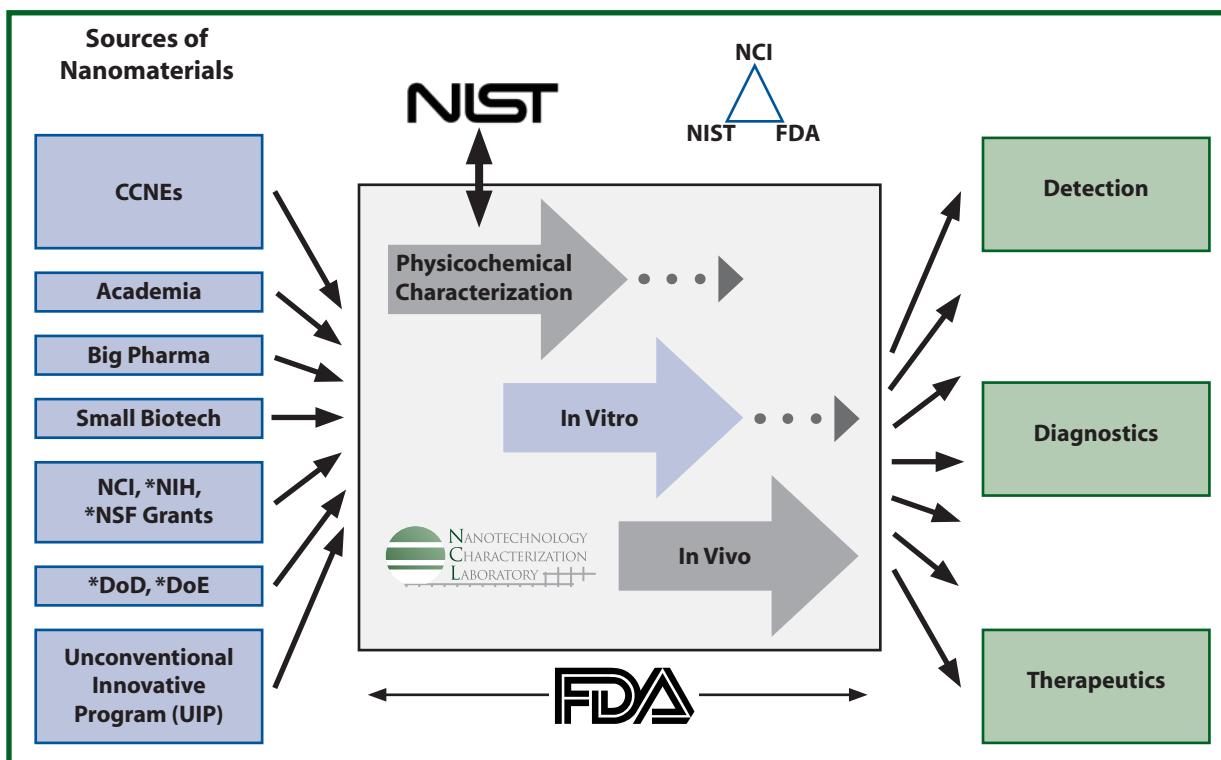
- The number of NCL submissions has greatly increased. NCL currently has more than 30 collaborations with developers of promising nanotechnology cancer therapeutics and diagnostics.
- NCL is advancing nanotechnology cancer therapies into and through the regulatory process. NCL is assisting one developer in moving from Phase I to Phase II clinical trials and is collaborating with another developer on an investigational new drug (IND) submission in 2008.
- More than 100 different nanomaterials are currently undergoing NCL characterization.
- In 2007 NCL continued to initiate new collaborations; 11 new MTAs and 5 Confidential Disclosure Agreements (CDAs) were signed.
- NCL engaged multiple Centers of Cancer Nanotechnology Excellence (CCNEs) and Cancer Nanotechnology Platform Partners (CNPPs) within NCI's Alliance for Nanotechnology in Cancer. Four of these interactions developed into submissions to NCL.
- NCL continued its assay development efforts. The NCL assay cascade now contains more than 30 protocols, 20 of which are publicly available (the others are still undergoing validation). Three of these protocols have passed the final ballot stage and are becoming American Society for Testing and Materials (ASTM) International standards.
- In collaboration with NIST, three colloidal gold nanoparticle reference materials (RMs) were developed. These RMs are available for purchase through NIST.
- NCL scientists published 5 peer-reviewed articles and presented at more than 20 national and international nanotechnology meetings.

- NCL presented its sponsors with four technical reports and hosted two formal meetings of its Scientific Oversight Committee.
- NCL continued to assist in the development of the cancer Nanotechnology Laboratory Analysis Bench (caNanoLab) database of nanomaterial properties.

Through all these activities, NCL is emerging as a recognized national and international leader in nanotechnology for biomedical applications.



NCI Alliance for Nanotechnology in Cancer



NCL Concept of Operations. NCL is a formal collaboration among NCI, NIST, and FDA. NIST possesses state-of-the-art instrumentation, and FDA has a commitment to developing mechanisms for facilitated review of new medical technologies. NCL characterizes nanomaterials intended for cancer applications from within the NCI Alliance for Nanotechnology in Cancer (CCNEs and UIP) and from academia, industry, and other Federal Government agencies. These nanomaterials eventually benefit cancer patients as commercially available imaging agents, diagnostics, and therapeutics.

*NIH = National Institutes of Health; NSF = National Science Foundation; DoD = U.S. Department of Defense; DoE = U.S. Department of Energy.

BACKGROUND

NCL was conceived on paper at NCI in 2003. In 2004 NCL completed the initiation and planning phase by establishing a laboratory at NCI-Frederick. In 2005 NCL initiated relationships with NIST and FDA and recruited key scientists and staff members. Also in 2005 NCL collaborated with NIST and FDA to develop a working set of standardized methods for safety and efficacy testing of nanomaterials (i.e., the NCL assay cascade). By the beginning of 2006 NCL was a fully operational interagency collaboration among NCI, NIST, and FDA was making progress toward fulfilling its objectives.

During 2006 NCL increased its emphasis on involvement in standards development organizations such as ASTM International, the American National Standards Institute (ANSI), and the International Standards Organization (ISO). NCL also began actively soliciting collaborations with developers of promising nanotechnology cancer therapies and began several translational projects. NCL published its first client report to Dendritic Nanotechnologies, Inc., in late 2006. The data in this report helped the company encourage investment in its operation, resulting in its acquisition by a larger pharmaceutical development firm.

In 2007 NCL made significant progress toward accomplishing its mission, almost doubling the number of extramural collaborations since its inception. NCL now has more than 30 such collaborations aimed at bringing particular nanotechnology concepts to clinics. This effort encompasses more than 100 unique nanoparticle constructs undergoing NCL characterization. In 2007 NCL also began contributing to the progression of nanotechnology candidate drugs through clinical trials. One NCL submission is scheduled for an IND submission in 2008, and another has completed Phase I and will enter Phase II in 2008. In 2007 NCL also produced four client reports and five peer-reviewed articles in prestigious scientific journals, and three of its protocols were accepted in final ballots as ASTM International standards. These represent the first internationally recognized formal standards for biocompatibility testing of nanomaterials intended for medical applications.

Interagency Agreement

To help meet the goal of reducing cancer's burden, NCI's Alliance for Nanotechnology in Cancer engages in efforts to harness the power of nanotechnology to radically change the way we diagnose, treat, and prevent cancer. NCL is one of four major program components of the Alliance. The other 3 are the 8 CCNEs, the 12 CNPPs, and the Multidisciplinary Research Training and Team Development Programs. Success in NCL's mission requires expertise across multiple scientific disciplines and concerted efforts from the public and private sectors. To meet this challenge, NCI executed a memorandum of understanding, followed by an interagency agreement, with NIST and FDA.

NIST and FDA each bring unique expertise to the NCL partnership. NIST possesses state-of-the-art instrumentation, and NIST scientists aid NCL in identifying the best measurement tools, protocols, and analysis algorithms for physical characterization of nanoparticles. Through its collaboration with NCL, in 2007 NIST released its first nanoscale RMs for biomedical applications in the form of 10-, 30-, and 60-nm nominal-size gold colloid. This material will be used for interlaboratory testing to compare characterization techniques and instrumentation from laboratories across the country. FDA provides input to NCL on the type of testing needed to evaluate nanomaterials for regulatory review, and data generated at NCL inform FDA on which nanoparticle properties contribute most to safety and toxicity. Both NIST and FDA support NCL's activities to accelerate the development of nanotechnology-based products to benefit cancer patients.

Senior NIST and FDA personnel participate on NCL's Scientific Oversight Committee to review NCL-generated data. The NCL director interfaces with FDA policymakers through the NCI-FDA Interagency Oncology Task Force and national-level committees such as those sponsored by the National Nanotechnology Initiative. Finally, NCL staff members actively collaborate and communicate with NIST and FDA scientists and reviewers to address specific challenges in nanomedicine, such as alternative methods of characterization of nanomaterials in biological matrices and in *in vivo* studies. In July 2007 NCL hosted FDA at the NCL-FDA Data Review on Nanotechnology-Based Therapeutics at the NCI-Frederick campus.

The grid contains the following logos:

- Dendritic Nanotechnologies, Inc.**: A Starpharma Holdings Limited Company
- CYT IMMUNE SCIENCES INC.**
- carigent therapeutics**
- ALNIS BIOSCIENCES, INC.**
- CEDARS-SINAI MEDICAL CENTER**
- Imperial College London**
- PENNSTATE College of Medicine**
- Lombardi COMPREHENSIVE CANCER CENTER at GEORGETOWN UNIVERSITY**
- USF UNIVERSITY OF SOUTH FLORIDA Department of Chemistry**
- Nanospectra**
- Arrowhead Research CORPORATION**
- ATM**
- NANOTECHNOLOGY CHARACTERIZATION LABORATORY**
- Northeastern UNIVERSITY BOUVÉ COLLEGE OF HEALTH SCIENCES**
- CNI CARBON NANOTECHNOLOGIES INCORPORATED**
- NanoScan Imaging**
- Tego BIO SCIENCES**
- Avidimer therapeutics**
- evident TECHNOLOGIES**
- Mizzou University of Missouri-Columbia**
- UCLA Department of Chemistry & Biochemistry**
- PURDUE UNIVERSITY**
- University of Pittsburgh**
- NANOPARTICLE BIOCHEM, INC.**

NCL Extramural Collaborators (2004-2008). New collaborations in 2007 include (from top left): Alnis BioSciences, Dr. James R. Connor of Pennsylvania State University, CytImmune Sciences, Dr. Julia Y. Ljubimova of Cedars-Sinai Medical Center, Dr. Esther H. Chang of the Lombardi Comprehensive Cancer Center at Georgetown University, Carigent Therapeutics, Dr. Andrew Miller of Imperial College London, Dr. Vladimir P. Torchilin of Northeastern University, Dr. William Zamboni of the University of Pittsburgh, Dr. Kattesh V. Katti of the University of Missouri-Columbia, Avidimer Therapeutics, and Dr. Alex Wei of Purdue University.

CHARACTERIZE NANOPARTICLES USING STANDARDIZED METHODS

NCL services are available by application to anyone developing a nanotechnology cancer drug or diagnostic at no fee to the developer (NCL is federally funded through NCI's Alliance for Nanotechnology in Cancer). Through active solicitation of promising nanostrategies on the NCL Web site, face-to-face interactions at conferences and scientific meetings, and direct contact with investigators and companies, NCL has attracted more than 30 top-quality clients from academia, industry, and Government. Many of these researchers are well established in the fields of bionanotechnology and/or cancer research, and others are emerging and making significant contributions to nanomedicine.

Almost half of these client collaborations were initiated in the last part of 2006 or in 2007. NCL signed 11 MTAs and 5 new CDAs with new clients in 2007. NCL scientists reviewed 14 white paper applications for new nanotechnology strategies, requested followup (Phase II) proposals for 11 of these, and eventually accepted 10 proposals as characterization projects.

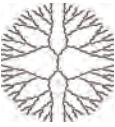
NCL has evaluated nanomaterials from the majority of types intended for medical applications, including liposomes, nanoshells, nanorods, metal colloids, functionalized gold, titanium dioxide, derivatized fullerenes, dendrimers, quantum dots, nanoemulsions, nanocrystals, iron oxides, and polymer-based nanomaterials. In 2007 NCL nearly doubled the number of nanoparticle samples undergoing characterization, receiving 85 new submissions. Thirty-five of these represented new nanoparticles (the remainder were improved formulations of prior submissions), resulting in a total of 108 unique nanoparticles undergoing NCL characterization.

Intramural and Extramural Collaborations

NCL supports nanotechnology drug development within NCI's Alliance for Nanotechnology in Cancer and within NCI-Frederick. NCL has interacted with several Alliance groups and is actively engaged in the characterization of nanostrategies from four of these sources. NCL collaborates

Portfolio of Collaborations To Fight Cancer. NCL collaborators are developing a variety of nanoparticle-based therapeutics and diagnostics. A few of NCL's 2007 collaborators, along with their anticancer applications, are shown below.	
NCL COLLABORATOR	ANTICANCER APPLICATION IN PRECLINICAL OR CLINICAL DEVELOPMENT
Alnis BioSciences	Iron oxide magnetic resonance imaging (MRI) agents
Avidimer Therapeutics	Folate-targeted, methotrexate-conjugated dendrimers
CytImmune Sciences	Gold nanoparticles with tumor necrosis factor-alpha (TNF- α)
Nanospectra Biosciences	Gold-coated silica nanoparticles for tumor thermal ablation
Carigent Therapeutics	Polymeric particles for controlled release of chemotherapeutics
Cedars-Sinai Medical Center	Polymeric particles for delivery of oligonucleotides
Imperial College London	Nanoliposomes for MRI
Lombardi Comprehensive Cancer Center at Georgetown University	Nanoliposomes for MRI
Northeastern University	Nanoemulsions, nanogels, and polymeric particles for chemotherapeutic delivery
University of Missouri-Columbia	Gum arabic-coated gold nanoparticles
Tego BioSciences	Fullerenes for chemoprotection
Pennsylvania State University	Nanoliposomes for chemotherapeutic delivery



 <p>Liposomes</p> <ul style="list-style-type: none"> • M. Kester (Pennsylvania State University) • E. Chang (Lombardi Comprehensive Cancer Center at Georgetown University) • R. Blumenthal (NCI) • NanoValent Pharmaceuticals • J. Connor (Pennsylvania State University) • W. Zamboni (University of Pittsburgh) • A. Miller (Imperial College London) 	 <p>Dendrimers</p> <ul style="list-style-type: none"> • Dendritic Nanotechnologies, Inc. • Avidimer Therapeutics, Inc. • M. Brechbiel (NCI) • E. Simanek (Texas A&M University)
 <p>Gold Nanoshells</p> <ul style="list-style-type: none"> • Nanospectra Biosciences, Inc. (Rice University) 	 <p>Quantum Dots</p> <ul style="list-style-type: none"> • S. Weiss (University of California, Los Angeles) • Evident Technologies, Inc. • J. Barchi (NCI)
 <p>Colloidal Gold</p> <ul style="list-style-type: none"> • CytImmune Sciences, Inc. • A. Wei (Purdue University) • K. Katti (University of Missouri-Columbia) 	 <p>Nanoemulsions</p> <ul style="list-style-type: none"> • M. Amiji (Northeastern University) • NanoScan Imaging
 <p>Fullerenes</p> <ul style="list-style-type: none"> • Tego BioSciences 	 <p>TiO₂</p> <ul style="list-style-type: none"> • FDA
 <p>Iron Oxide</p> <ul style="list-style-type: none"> • Alnis BioSciences, Inc. 	 <p>Polymers</p> <ul style="list-style-type: none"> • J. Ljubimova (Cedars-Sinai Medical Center) • M. Amiji (Northeastern University) • N. Tarasova (NCI) • D. Ferguson (University of Wisconsin) • V. Torchilin (Northeastern University) • Carigent Therapeutics, Inc.

Portfolio of NCL Nanoparticles. NCL has characterized many different types of nanomaterials, including liposomes, dendrimers, gold nanoshells, quantum dots, colloidal gold, nanoemulsions, fullerenes, TiO₂ nanocrystals, iron oxides, and polymers. The majority of the nanoparticles submitted to NCL are functionalized with drugs and targeting agents. At the end of 2007, there were a total of 108 unique nanoparticles undergoing NCL characterization.

with NCI-Frederick principal investigators Dr. Martin Brechbiel on dendrimer imaging agents and with Dr. Joseph Barchi on gold nanoparticles. In 2007 NCL initiated a collaboration with NCI-Frederick investigator Dr. Nadya Tarasova to perform preclinical characterization of polymer-based therapeutics developed in her laboratory. NCL is also working closely with NCI investigator Dr. Larry Keefer to help in the translational aspects of the promising therapeutic JS-K.

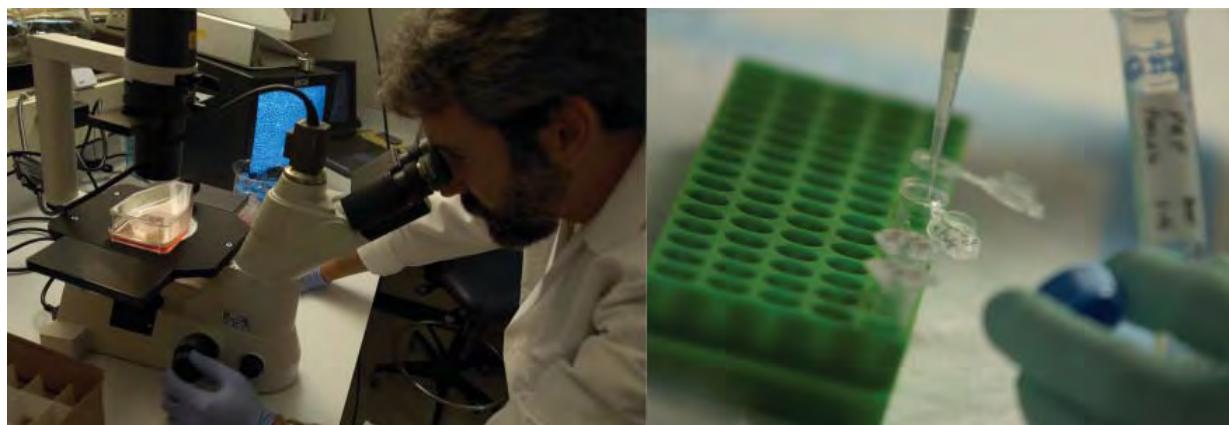
NCL also has ongoing collaborations with the National Toxicology Program, the National Institute of Environmental Health Sciences, and other centers within NIH for long-term toxicity studies on nanomaterials. NCL has initiated collaborative efforts with academic and commercial entities to automate the analysis of nanoparticle transmission electron microscopy (TEM)/atomic force microscopy (AFM) imaging for size and shape characterization. As mentioned previously, NCL also collaborates with formal standards-developing organizations, such as ASTM International, ANSI, and ISO, to develop standards for nanomaterials in medicine. NCL scientists and staff members have leadership roles on committees within these organizations that are tasked with overseeing the development of standards for nanomaterials.

Major Translation Projects in 2007

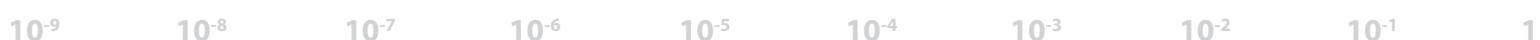
In 2007 NCL began fulfilling its mission by advancing nanostrategies into clinics. One NCL submission, CytImmune Sciences' polyethylene glycol (PEG) PEGylated colloidal gold conjugated with TNF- α has completed Phase I clinical trials. NCL is supporting its progression to Phase II as well as characterizing CytImmune Sciences' next-generation therapeutics. Another NCL submission, Avidimer Therapeutics' folate-targeted, methotrexate-conjugated dendrimer, is scheduled for IND submission to FDA in 2008. The highlights from three major NCL translation projects in 2007 are detailed below.

Avidimer Therapeutics: Folate-Methotrexate Dendrimers

Avidimer Therapeutics, Inc., is a spinoff company based on NCI's UIP-funded work of Dr. James Baker at the University of Michigan. In May 2007 NCL began assisting Avidimer with preclinical characterization of its folate-targeted, methotrexate-conjugated dendrimer for targeted drug delivery. NCL characterized several batches of functionalized dendrimers with spectroscopic and chromatographic methods to determine the number of targeting and drug molecules conjugated to the dendrimer. NCL then compared the targeting efficiency and toxicity of these dendrimers to *in vitro* cell lines. In addition, NCL is helping Avidimer qualify multiple lots of dendrimers by conducting



Characterizing Nanospectra Biosciences' PEGylated AuroShells® in the NCL In Vitro Cascade. The AuroShells® were tested to determine the nature of their interaction with blood components and immune cells. These samples also were examined for various types of potential cytotoxicity.

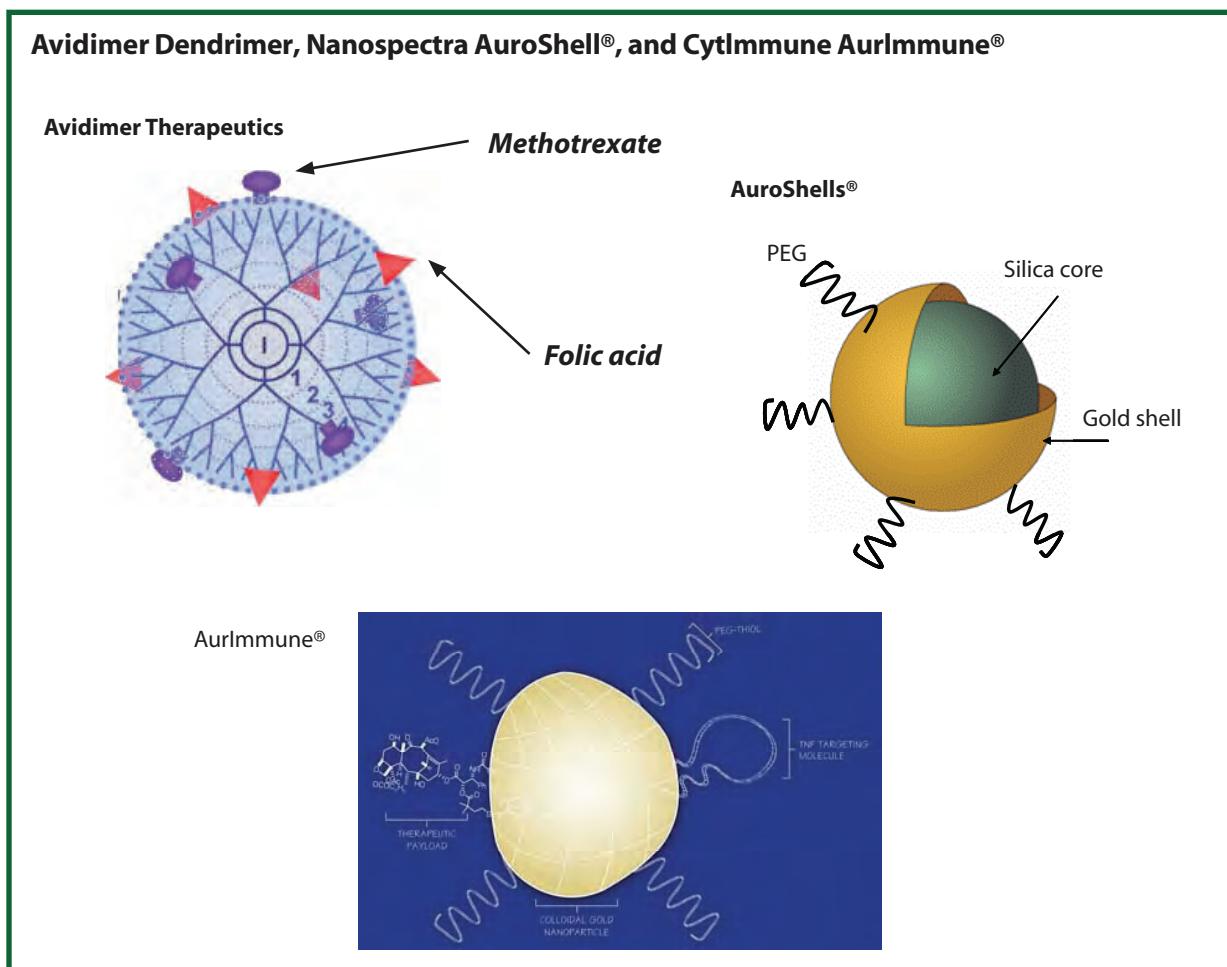


thorough analyses to elicit molecular weight, polydispersity, terminal group functionality, and purity by several orthogonal analytic methods (including nuclear MRI, ultraviolet visible spectroscopy, high-pressure liquid chromatography, size exclusion chromatography coupled with multiangle laser light scattering, mass spectrometry, and titrations).

NCL also examined Avidimer's functionalized dendrimers for hemolysis, platelet aggregation, complement activation, leukocyte proliferation, nitric oxide secretion by macrophages, chemotaxis, effects on bone marrow cells, and phagocytosis. Additional analytical methods are in development, and in vivo studies are planned to further assist Avidimer with its upcoming IND submission to FDA.

Nanospectra Biosciences: PEGylated AuroShells®

Nanospectra Biosciences, Inc., is a Houston, Texas-based company that is commercializing a therapy based on PEG- and gold-coated silica particles initially developed at Rice University. These AuroShell® particles emit heat upon absorption of near-infrared wavelengths of light and can be delivered intravenously to tumors. The particles are designed to selectively absorb tissue-



NCL Value-Add. NCL adds value to promising nanotechnology anticancer concepts. For example, NCL developed an assay to monitor the stability of PEG coatings of Nanospectra Biosciences' AuroShells®, which may be important to their biocompatibility and may affect their shelf life. NCL characterized several batches of Avidimer Therapeutics' functionalized dendrimers and determined the number of targeting and drug molecules conjugated to their surfaces. NCL also compared the targeting efficiency and toxicity of these functionalized dendrimers in *in vitro* cell lines. Finally, NCL helped CytImmune Sciences with optimization of AurlImmune®'s scale-up and employed state-of-the-art methods to identify AurlImmune® in tissue samples to aid CytImmune Sciences in interpretation of the results of its Phase I clinical trial.

penetrating, near-infrared energy at tumor sites, converting the light into heat to thermally destroy tumors without significant damage to healthy tissue.

During 2006 and 2007 NCL assisted Nanospectra Biosciences with extensive preclinical characterization of the AuroShell® particles, including measurement of hydrodynamic size by several methods and as a function of solvent, temperature, freeze-thaw cycle, storage, and pH. Compositional analysis was conducted using an energy-dispersive x-ray analysis (EDX) detector coupled to a scanning electron microscope. Advanced electron microscopic measurements with energy-filtered TEM at NIST laboratories also were conducted to determine the degree to which the AuroShell® gold coatings covered their silica cores.

NCL also examined the biological properties of the AuroShells®. The particles were tested for hemolysis, platelet aggregation, interaction with plasma proteins, complement activation, coagulation, effects on bone marrow cells, leukocyte proliferation, oxidative burst, chemotaxis, phagocytosis, and cytokine secretion. These samples also were evaluated for cytotoxicity to liver and kidney cell lines and in filtrate-retentate comparison studies to determine whether there was a difference in toxicity between the AuroShell® fractions and suspending solutions. NCL also conducted two absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) nonhuman animal studies.

Finally, NCL developed an assay to monitor the stability of the AuroShells® PEG coatings, which may be important for biocompatibility and may affect their shelf life. Beginning in 2008 NCL will conduct a thorough examination of the amount of PEG on the surfaces of several lots of Nanospectra Biosciences AuroShells®.

CytImmune Sciences: Colloidal Gold + TNF- α

CytImmune Sciences, Inc., is based in Rockville, Maryland, and is developing AurlImmune®, a PEGylated colloidal gold nanoparticle with attached TNF- α . The objective of the CytImmune Sciences-NCL collaboration is to generate data that facilitate the entry of CytImmune Sciences' lead candidate into Phase II clinical trials and to lay a framework for characterizing its next-generation

NCL has interacted with several groups within NCI's Alliance for Nanotechnology in Cancer and those from UIP.

Jim Baker	University of Michigan, Avidimer Therapeutics, Inc.
Mansoor Amiji	Northeastern University
Kattesh Katti	University of Missouri-Columbia, Nanoparticle Biochem, Inc.
Robert Langer and Omid Farokhzad	Harvard University, Massachusetts Institute of Technology, BIND Biosciences, Inc.
Joseph DeSimone	The University of North Carolina, Liquidia Technologies, Inc.
Gregory Lanza	Washington University in St. Louis, Kereos, Inc.
Shuming Nie	Emory University, Georgia Institute of Technology
Paras Prasad	State University of New York, Buffalo
Steve Barry	Alnis BioSciences, Inc. (UIP)
John Park	University of California, Los Angeles, Hermes Biosciences, Inc. (UIP)

therapeutics. CytImmune Sciences requested support from NCL in the form of size characterization to assist with process optimization of its scaled-up production and identification of its compound in human and rodent tissue samples by nonradioactive methods.

NCL examined the size and shape of CytImmune Sciences' particles using dynamic light scattering, TEM, and AFM. NCL also compared these physicochemical parameters among several batches of CytImmune Sciences-produced colloidal gold to identify batch-to-batch variability. NCL's analysis allowed the sponsor to proceed with process design to scale up its manufacture.

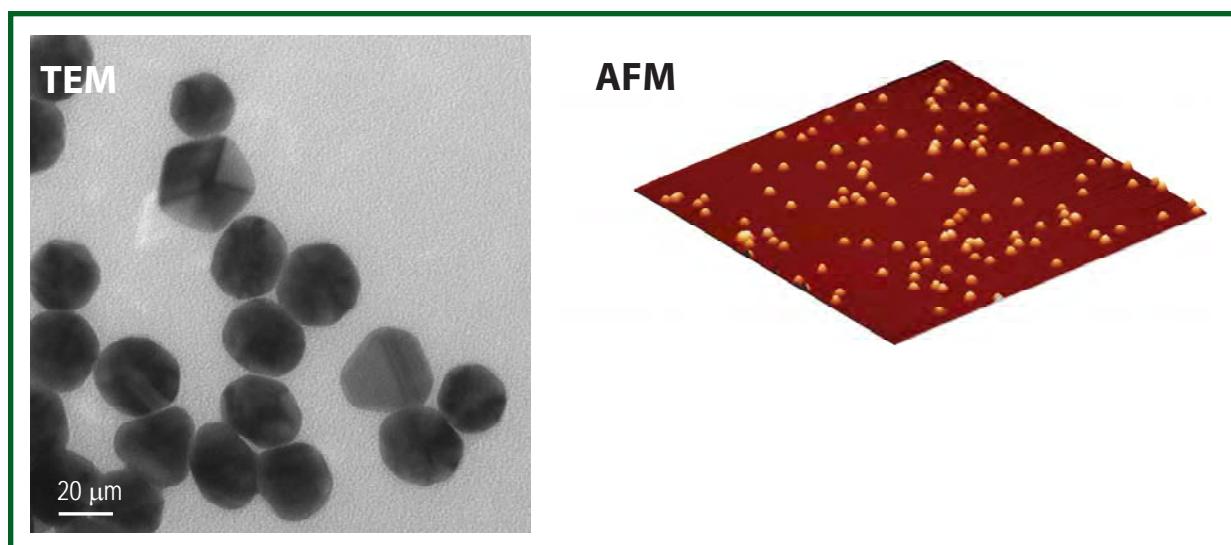
CytImmune Sciences submitted several human and other animal tissue samples for combined TEM/EDX evaluation of gold nanoparticle distribution. NCL's EDX analysis of several tissue samples is helping CytImmune Sciences interpret the results of its Phase I clinical trial.

In addition to these three priority projects, NCL also conducted extensive characterization for Evident Technologies, Inc.; Alnis BioSciences, Inc.; Tego BioSciences, Inc.; Dr. Mansoor Amiji of Northeastern University; Dr. Julia Ljubimova of Cedars-Sinai Medical Center; Dr. Esther Chang of the Lombardi Comprehensive Cancer Center at Georgetown University; Dr. Darin Furgeson of the University of Wisconsin; Dr. Shimon Weiss of the University of California, Los Angeles; Dr. Kattesh Katti of the University of Missouri-Columbia; Dr. William Zamboni of the University of Pittsburgh; and Drs. Mark Kester and James Conner of Pennsylvania State University.

CONDUCT STRUCTURE-ACTIVITY RELATIONSHIP STUDIES

Evolution of the NCL Assay Cascade

The year 2007 saw continuous evolution of the NCL assay cascade to meet the needs of NCL collaborators. NCL moved away from a simple linear progression, from physicochemical to in vitro to in vivo characterization, toward an algorithmic model with individual pathways for each project. This is both more realistic and more efficient, allowing reassessment of a particular drug or diagnostic at several preidentified decision points throughout the assay cascade and tailoring NCL experiments to each project.



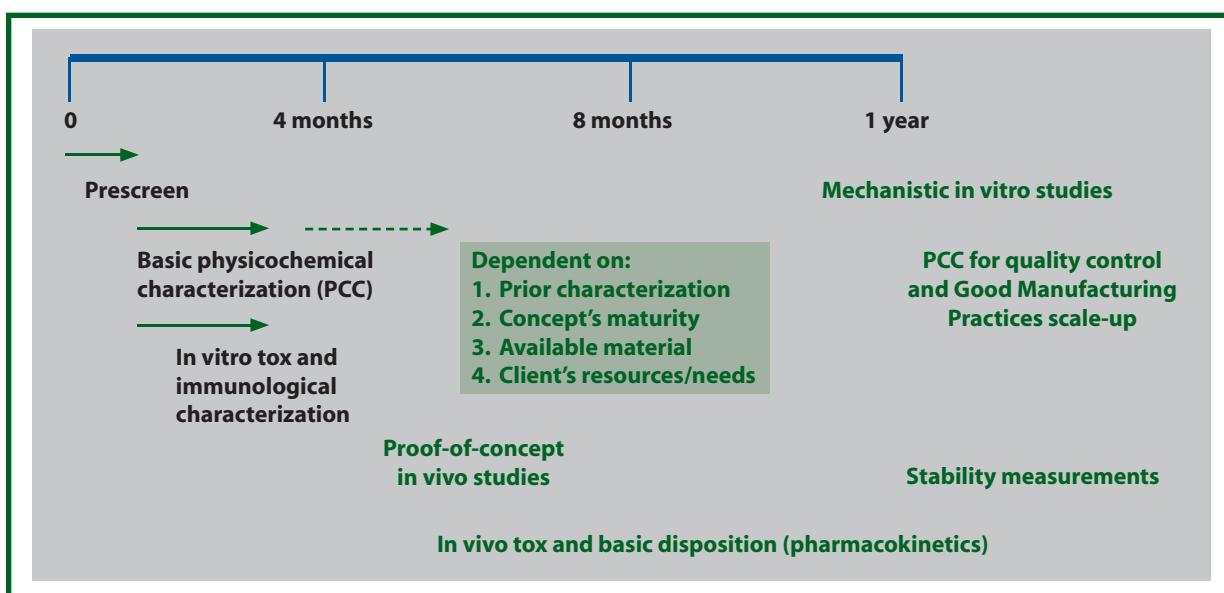
NCL Size Characterization. NCL examined the size and shape of CytImmune Sciences' colloidal gold particles using TEM and AFM and compared the sizes of several lots to assist with scale-up of their synthesis. This graphic shows TEM and AFM images of commercial colloidal gold particles (not CytImmune Sciences' colloidal gold, as those data are confidential).

NCL characterization begins with the NCL prescreen. This consists of sterility testing (for endotoxin, bacterial, yeast, mold, and mycoplasma contamination) and a simple dynamic light scattering measurement of the hydrodynamic size and size-polydispersity in solution. The NCL prescreen is initiated as soon as NCL receives samples from its clients and takes less than 6 weeks to complete.

Samples that are free of contamination and that are sufficiently monodisperse in size pass the NCL prescreen. The next tier of the NCL assay cascade consists of two parts: (1) basic physicochemical characterization to ensure that the samples meet the specifications supplied by the client and (2) characterization of the in vitro toxicity and immunological properties (e.g., hemolysis, platelet aggregation, complement activation, and immune cell function).

The final phase of NCL characterization is highly individual to each concept and is based on several factors, including NCL's prior results, FDA requirements, available material, and input from the client. This phase includes additional purity, compositional analysis, and stability assessments, as well as acute in vivo toxicity and basic biodistribution (pharmacokinetics) nonhuman animal studies and may also include mechanistic in vitro toxicology, in vivo proof-of-concept studies, and/or followup in vivo immunotoxicity studies. For those concepts that have an imaging component, in vivo imaging is conducted in comparison with FDA-approved imaging agents.

Occasionally, NCL characterization efforts identify particular aspects of a formulation that need improvement before the candidate drug can move forward. In these instances, NCL works closely with the collaborator to address the issue as part of NCL efforts to bring the best possible formulations to clinics. New nanoparticles, with potentially new properties, require that NCL start over at square one (the NCL prescreen) and often require the sponsor to revisit its initial proof-of-concept studies to demonstrate that the improved particles are still efficacious. Although this effort can be resource intensive and may require multiple iterations, it is important for the eventual IND submission and will ultimately accelerate the regulatory process. The knowledge gained from these studies also improves NCL by helping NCL decide which assays should be conducted early in the assay cascade.



Timeline of NCL Characterization. The NCL prescreen is the initial step in NCL characterization and takes up to 6 weeks. Subsequently, nanoparticles are subjected to PCC to ensure they meet NCL's collaborator specifications and basic in vitro toxicity and immunological characterization. The final phase of NCL characterization proceeds according to an algorithmic model as NCL works closely with its collaborators. The selection of assays for this phase depends on several factors, including NCL prior results, FDA requirements, available material, and input from the client.

Evolution of the NCL In Vivo Program

In 2007 NCL's in vivo program matured significantly; NCL conducted 18 in vivo studies in 2007 compared with fewer than 10 such studies in 2005 and 2006. Four of the 2007 studies involved imaging modalities. NCL immunological characterization evolved from purely in vitro experiments—aimed at determining mechanisms and identifying areas requiring increased scrutiny during nonhuman animal studies—to in vivo and ex vivo characterization.

NCL's xenograft program is an example of this evolution. In this program, NCL is meeting its collaborators' expressed needs for in vivo proof-of-concept studies. These studies validate the technology while providing NCL clients with externally vetted data that they can use to further secure venture capital funding for the expensive regulatory phases of the development process. The protocol uses tumor size as the therapeutic endpoint, as measured by MRI and caliper measurements. The protocol is very flexible and allows for the use of any tumor line, so that NCL can tailor models to "fit" a given application, such as receptor targeting or drug resistance. The NCL xenograft program, together with the new NCI transgenic cancer model program through the Center for Advanced Preclinical Research, offers NCL clients a wide range of applicable models in which to evaluate their concepts.

Standards Development Activities

Standard Protocols

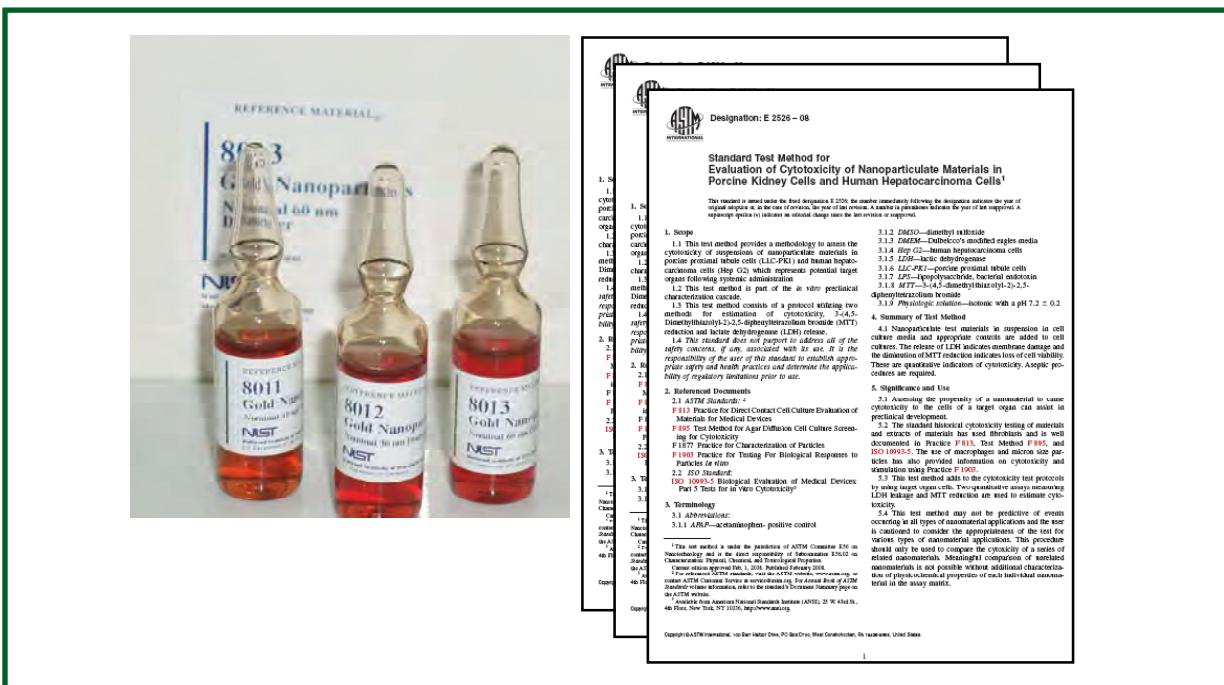
One of NCL's objectives is the development of standard methods to assess safety, toxicity, and quality control. Without such standards, nanotechnology drug developers have to design and validate their own methods, and regulatory agencies must evaluate data generated from techniques without

caNanoLab. NCL continues to support the development of caNanoLab, a data sharing portal designed for laboratories performing assays on nanoparticles. caNanoLab allows users to annotate nanoparticles with characterizations resulting from physical and in vitro nanoparticle assays and the sharing of these characterizations in a secure fashion.

a substantial history of supporting literature. From the beginning, NCL has been involved with standards organizations, such as ASTM International, ANSI, and ISO, in working toward this goal. NCL actively involved itself with ASTM's E56 Nanotechnology Committee to develop voluntary consensus standards in collaboration with other stakeholders. In 2007 three NCL methods for biocompatibility testing of nanomaterials (E2524, E2525, and E2526) went through the final ballot as ASTM International standards. These are the very first formal standards for biocompatibility testing of nanomaterials intended for medical applications:

- E2524 is an NCL protocol for examining the destruction of red blood cells (hemolysis). Hemolysis can lead to anemia, jaundice, and other problems, so all intravenously administered pharmaceuticals must be examined with regard to their hemolytic potential.
- E2525 is an NCL method for evaluating nanoparticle stimulation or inhibition of the maturation of certain bone marrow cells (macrophages). Inhibition of this process is a common side effect of anticancer drugs, and these cells may be particularly sensitive to nanoscale materials.
- E2526 is an NCL method for evaluating nanomaterial toxicity by examining effects on kidney cells and liver carcinomas. Several studies indicate that many nanoparticles are cleared from the body through the kidney or liver, making these organs good choices for evaluating toxicity in target organs. In this standard, two separate assays provide complementary data, so that cross-validation can be used to identify interference.

All three of the new ASTM standards evaluate aspects of nanomaterial toxicity. Whether nanomaterials are more toxic than their macroscale counterparts has been a matter of extensive debate. The scientific literature contains a wide range of findings due to the variety of assays used.



Reference Materials and Protocol Standards. Voluntary consensus standards and standardized RMs contribute to making the development and supply of new technologies safer and more efficient. NCL is involved with standards organizations such as ASTM International, ANSI, and ISO. In 2007 NCL collaborated with NIST to produce a colloidal gold RM for interlaboratory testing and comparison, and three NCL methods passed the final ballot to become ASTM standards.

Arriving at a definitive answer to this question will depend on the use of standardized methods such as E2524, E2525, and E2526.

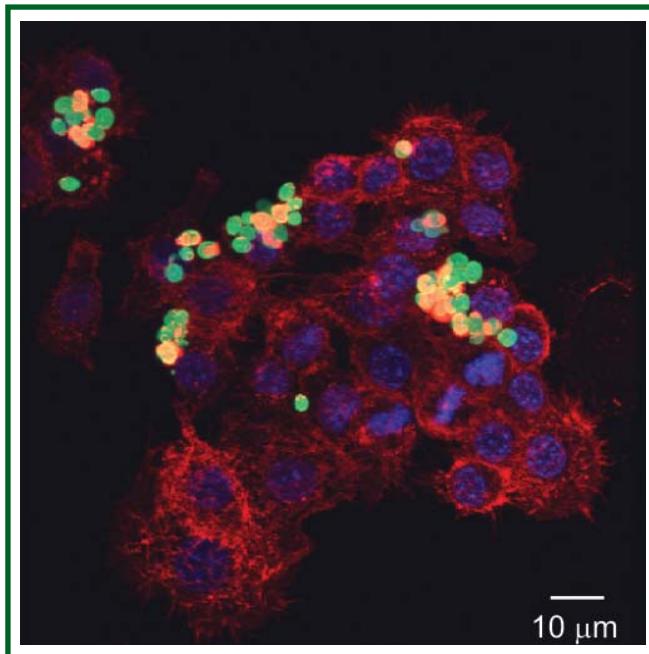
Reference Materials and Protocol Standards

In late December 2007 NIST, in partnership with NCL, released its first set of reference standards for nanoscale particles aimed at the biomedical research community. The new nanoparticulate RMs consist of colloidal gold nanoparticles with nominal diameters of 10, 30, and 60 nm in suspension.

The new NIST RMs are intended for instrument calibration, method qualification, and in vitro experiments used to characterize nanomaterials. These RMs have been characterized extensively by NIST scientists. Each RM aliquot comes with reference and informational values for a number of properties, including particle size determined by multiple methods, pH, conductivity, gold and citrate concentrations, particle surface charge (zeta potential), optical absorption spectra, and verification of sterility.

Both the NIST RMs and these ASTM standards are being used in an ASTM-sponsored interlaboratory study involving more than 100 participating laboratories beginning in spring 2008. This study, coordinated by NCL and NIST scientists, will help isolate sources of data variability from laboratories following identical protocols and using the same standard material.

The RMs (numbered RM8011, RM8012, and RM8013 for 10-, 30-, and 60-nm diameter particles, respectively) are available for purchase (to recover production and distribution costs) on the NIST Web site. The ASTM standards are available for purchase from ASTM International.



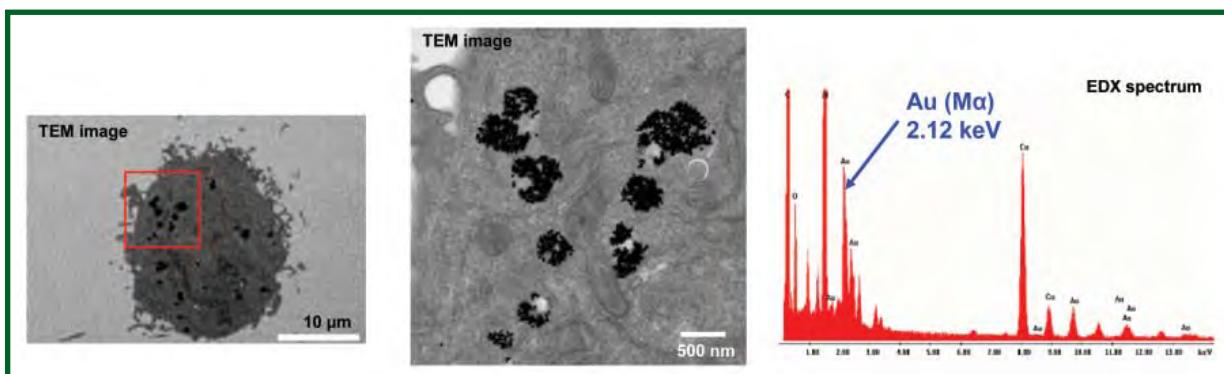
Uptake by the Immune System. It is well known that uptake by macrophages can reduce the efficacy of a targeted drug. A less well understood effect is inhibition of uptake, which is indicative of immune suppression. NCL has developed an assay to evaluate nanoparticle effects on the uptake of zymosan (a micron-size glucan derived from yeast cell membranes). This picture is a confocal micrograph of NCL's evaluation of effects on the uptake of zymosan (green) by macrophages (the nuclei of the macrophages are dyed blue). Extensions of the periphery of the macrophage cells are dyed red.

Assay Development

Over the past year, NCL scientists also have continued to actively develop and validate protocols that rigorously characterize nanoparticle physicochemical properties (e.g., size, aggregation, and surface chemistry), as well as in vitro immunological and cytotoxic characteristics and ADME/Tox profiles in nonhuman animal models. NCL now has more than 30 protocols in its assay cascade,²⁰ of which are publicly available to researchers in the nanotechnology and cancer communities. These assays have undergone extensive in-house validation and are subjected to regular revision to ensure applicability to a variety of nanomaterials. NCL in vitro protocols have been vetted by scientists at FDA, and NCL physicochemical characterization protocols are developed in collaboration with NIST investigators and evaluated for thoroughness and robustness with regard to instrumentation and materials. In 2007 the NCL staff developed nine new characterization protocols for the NCL assay cascade: (1) dynamic light scattering measurement of nanoparticle size, (2) a colorimetric assay for gadolinium quantitation based on Arsenazo III, (3) a lysosomal dysfunction assay, (4) a second lysosomal assay, (5) a reverse transcriptase polymerase chain reaction-based assay for stressor gene (HSP-70 and metallothionein) responses in LLC-PK1 cells, (6) a mycoplasma sterility assay, (7) an assay to monitor nanoparticle uptake into cells via light microscopy, (8) an assay to quantitate gold nanoparticles in biological matrix, and (9) a thin-layer chromatography assay for quantifying ceramide in lipid-based systems.

FACILITATE REGULATORY REVIEW OF NANOTECHNOLOGY CONSTRUCTS

The ultimate goal of NCL's efforts is the generation of data in support of regulatory review of nanotechnology constructs. Particles submitted to NCL are subjected to a series of characterization tests that are based on FDA requirements, the maturity of the project, and input from the developer. The data generated from NCL characterization are intended for use in support of submission of IND or investigational device exemption applications with FDA. NCL studies are not Good Laboratory Practices (GLP) certified but can facilitate and greatly reduce the costs of later GLP studies. In the case of therapeutics, NCL physicochemical data are applied to the chemistry, manufacturing, and controls section of the IND. NCL's charter is to identify properties of nanomaterials that are different from those of traditional small-molecule drugs and then to perform preclinical characterization of the nanoparticles while monitoring those properties. NCL provides FDA with collaborative research resources. NCL's role in these preclinical studies expands and adapts to the continually changing configurations of submitted nanoparticles as NCL develops new preclinical assays.



EDX Spectroscopy To Confirm In Vitro Particle Uptake. The left and center panels show two sequentially (from left to right) higher magnification TEM images of macrophages exposed in vitro to gold nanoparticles. The right panel shows an EDX spectrum of a scan of the black spots inside the vacuoles of the cell. The signature gold peak at 2.12 keV identifies the dark regions in the TEM micrograph as gold nanoparticles.

NCL interfaces with FDA on a number of levels. Senior FDA personnel participate on NCL's Scientific Oversight Committee to review NCL-generated data and to ensure that NCL's assays are capturing important aspects of characterization that are relevant for an IND submission. The NCL director interfaces with FDA policymakers through the NCI-FDA Interagency Task Force and on national-level committees such as those sponsored by the National Nanotechnology Initiative. Finally, the NCL staff actively collaborates and communicates with FDA scientists and reviewers to address specific challenges in nanomedicine, such as characterization of nanomaterials in *in vivo* biological matrix studies. FDA and NCL also cosponsor workshops, seminars, and meetings for standards development and characterization of nanomaterials. In July 2007 NCL hosted FDA for the NCL-FDA Data Review on Nanotechnology-Based Therapeutics on the NCI-Frederick campus.

IDENTIFY AND CHARACTERIZE CRITICAL PARAMETERS RELATED TO NANOMATERIAL ADME/TOX

In 2007 NCL continued its independent and collaborative research programs directed at understanding the relationships between nanoparticle structure and biological activity. One such study analyzed how particle size and surface charge influence the biocompatibility of polyamidoamine dendrimers at the level of interaction with red blood cells and platelets. Polyamidoamine dendrimers were chosen because they are commercially available and are considered to be a promising drug delivery platform. Four dendrimer generations (G3, G4, G5, and G6) and three surface functionalizations (carboxy, hydroxy, and amine) corresponding to different surface charges (anionic, neutral, and cationic) were tested at various doses.

NCL also conducted a collaborative project with FDA to detect, characterize, and quantify localization of TiO_2 nanoparticles in tissue samples of interest after intravenous administration, subcutaneous injection, or topical administration. NCL has presented two reports to FDA detailing NCL's initial findings in this study. NCL also has conducted a study with Evident Technologies, Inc., aimed at identifying the relationships among size, core composition, and the biological activity of quantum dots and a study of potential autophagic activation by quantum dots and fullerenes.



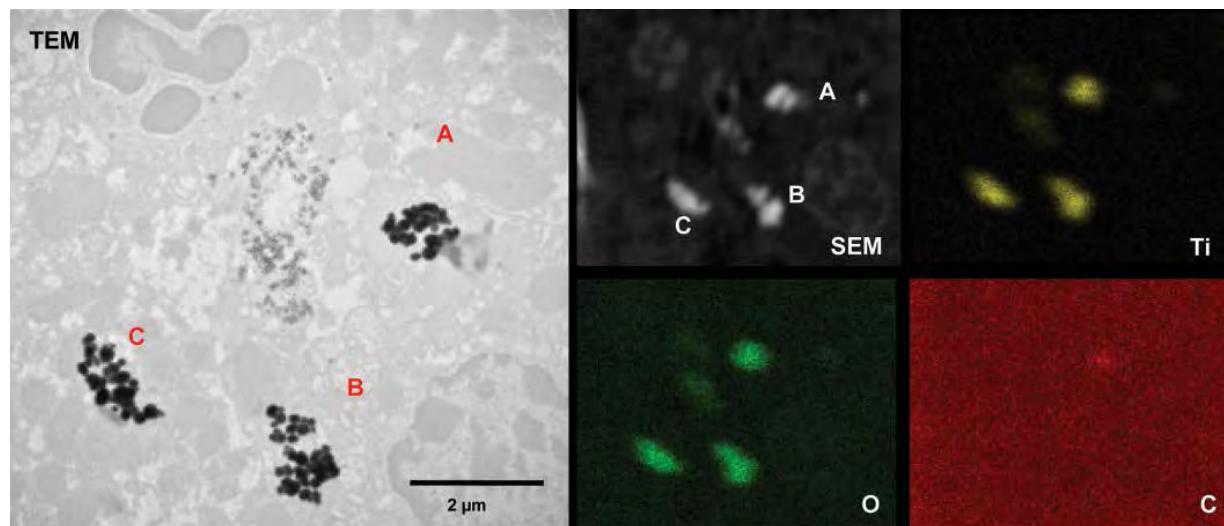
Assay Development. In 2007 the NCL staff developed nine new characterization protocols for the NCL assay cascade. NCL now has more than 30 protocols, 20 of which are publicly available to researchers in the nanotechnology and cancer communities. These assays undergo in-house validation and have been vetted by scientists at FDA and/or NIST. NCL (ncl.cancer.gov) assays are now being promoted as "best practices" by standards development organizations such as ASTM International, ANSI, and ISO.

ENGAGE IN EDUCATIONAL AND KNOWLEDGE SHARING EFFORTS

In 2007 NCL published several reviews in major journals and made presentations at many premier conferences in the fields of pharmaceutical development, materials science, and bionanotechnology. A complete list of journal articles appears in the Appendix on page 27. Of particular note, the NCL staff organized the NCL-NCI-NIST-FDA cosponsored symposium "Engineered Nanoscale Materials for the Diagnosis and Treatment of Disease" at the Materials Research Society spring meeting in San Francisco, California, on April 9-13, 2007, and hosted meetings on the NCI-Frederick campus: "Scientific Needs in Characterization and Modeling of Nanomaterial: Biomaterial"; the "EHS Applications Workshop" in collaboration with Oak Ridge National Laboratory on June 11, 2007; and "NCL-FDA Data Review on Nanotechnology-Based Therapeutics" on July 2, 2007.

Over the course of the past year, NCL has presented its clients with four technical reports detailing characterization results for their strategies. These reports included a study of functionalized fullerenes for C-Sixty, Inc.; characterization of ceramide-containing liposomes for Pennsylvania State University; characterization of folate-targeted, methotrexate-conjugated dendrimers for Avidimer Therapeutics; and a report to FDA on a study of the organ deposition of TiO_2 nanoparticles injected into mice. NCL provided the results of these characterization projects to the clients, and a few of these are available to the cancer and nanotechnology research communities via the NCL Web site (<http://ncl.cancer.gov>).

Finally, in 2007 NCL continued its support of the development of the caNanoLab, a database for sharing scientific information inside NCI's Alliance for Nanotechnology in Cancer and with the greater nanotechnology and cancer research communities.



EDX Mapping To Identify and Locate Nanoparticles in Tissue. The left panel shows a TEM image of tissue from nonhuman animals injected with nanosize TiO_2 particles. The panel labeled "SEM" shows a scanning electron microscope (SEM) image of the same area of tissue. Notice that the SEM image is of lower resolution and reverse contrast. (In TEM, the beam passes through the sample so that electron-dense regions appear dark, whereas in SEM the beam scans the top of the sample so that electron-dense regions appear light.) The other panels are EDX mappings of the same tissue region showing the location of titanium (Ti), oxygen (O), and carbon (C). These maps confirm that the black spots in the TEM image (left panel) contain titanium and oxygen, identifying them as TiO_2 nanoparticles.

OVERSIGHT

NCL conducted two formal technical reviews during 2007. The technical review consists of an onsite review by NCL's Scientific Oversight Committee, which comprises representatives from NCI, FDA, NIST, and industry. NCL scientists present and defend data that have been generated by NCL since the previous committee meeting. The most recent NCL technical reviews were held in February and November 2007. NCL's operations and progress were also reviewed during 2007 by Dr. John E. Niederhuber, Director of NCI, and Dr. Anna Barker, Deputy Director of NCI. Regular meetings of NCL's Scientific Oversight Committee and visits from the leadership of NCI ensure that NCL stays on mission. This oversight continues into 2008.

APPENDIX

2007 NCL Journal Articles

Chan KC, Patri AK, Veenstra TD, McNeil SE, Issaq HJ. Analysis of fullerene-based nanomaterial in serum matrix by CE. *Electrophoresis* 2007;28:1518-24.

Dobrovolskaia MA, McNeil SE. Immunological properties of engineered nanoparticles. *Nature Nanotechnol* 2007;23(8):469-78.

Hall JB, Dobrovolskaia MA, Patri AK, McNeil SE. Characterization of nanoparticles for therapeutics. *Nanomedicine* 2007;2(6):789-803.

McNeil SE. Medical opportunities of nanotechnology. *Iso Focus* 2007; Nanotechnologies issue:16-8.

Stern ST, McNeil SE. Nanotechnology safety concerns revisited. *Toxicol Sci* 2008;101(1):4-21.

Yim P, Dobrovolskaia AM, Kang HG, Clarke M, Patri AK, Hwang J. Nanocrystal-based biomimetic system for quantitative flow cytometry. *Proceedings of SPIE* 2007;6430:64301T.

2007 NCL Client Reports

NCL200701A Functionalized Fullerenes for C-Sixty, Inc.

NCL200702A Ceramide Liposomes for Mark Kester, Pennsylvania State University

NCL200702B Detection of TiO_2 Particles in Rodent Tissue for FDA

NCL200712A Folate-Targeted Methotrexate-Conjugated Dendrimers for Avidimer Therapeutics, Inc.

CONTACT INFORMATION

Nanotechnology Characterization Laboratory

National Cancer Institute at Frederick
Attn: Nanotechnology Characterization Laboratory
P.O. Box B
Building 469
1050 Boyles Street
Frederick, MD 21702-1201

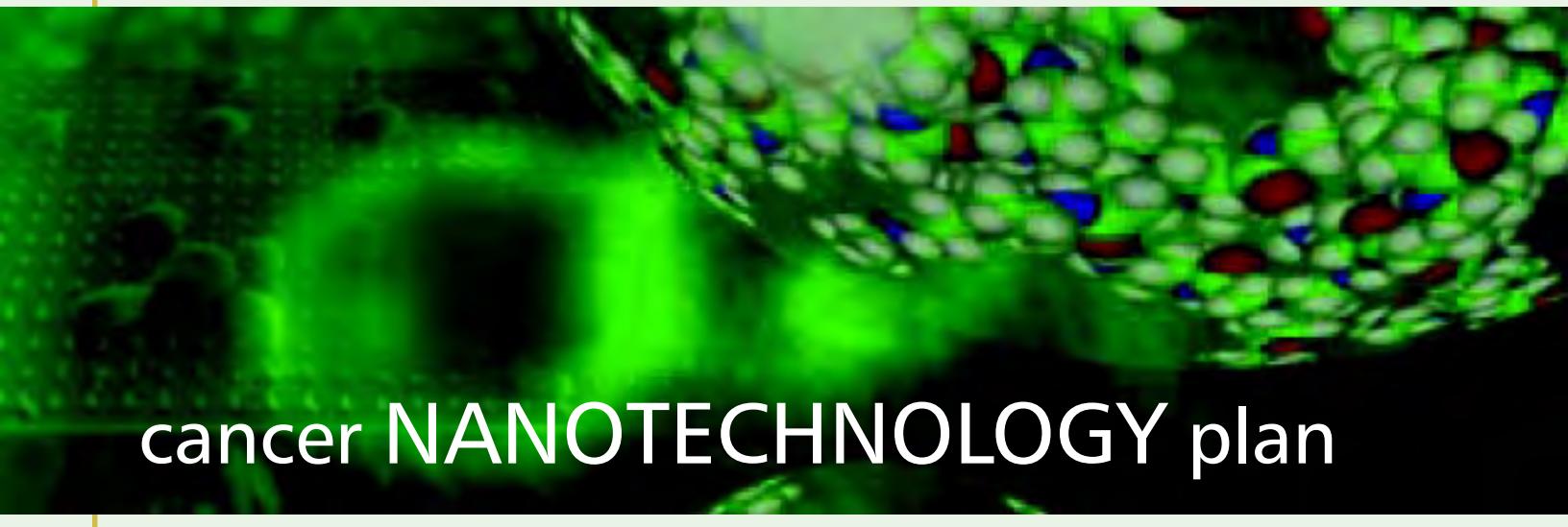
Phone Number: 301-846-6939

Fax: 301-846-6399

E-mail: ncl@ncifcrf.gov

Web Address: <http://ncl.cancer.gov>

The Nanotechnology Characterization Laboratory is a collaborating partnership of the National Cancer Institute and the U.S. Food and Drug Administration of the U.S. Department of Health and Human Services, and the National Institute of Standards and Technology, U.S. Department of Commerce.

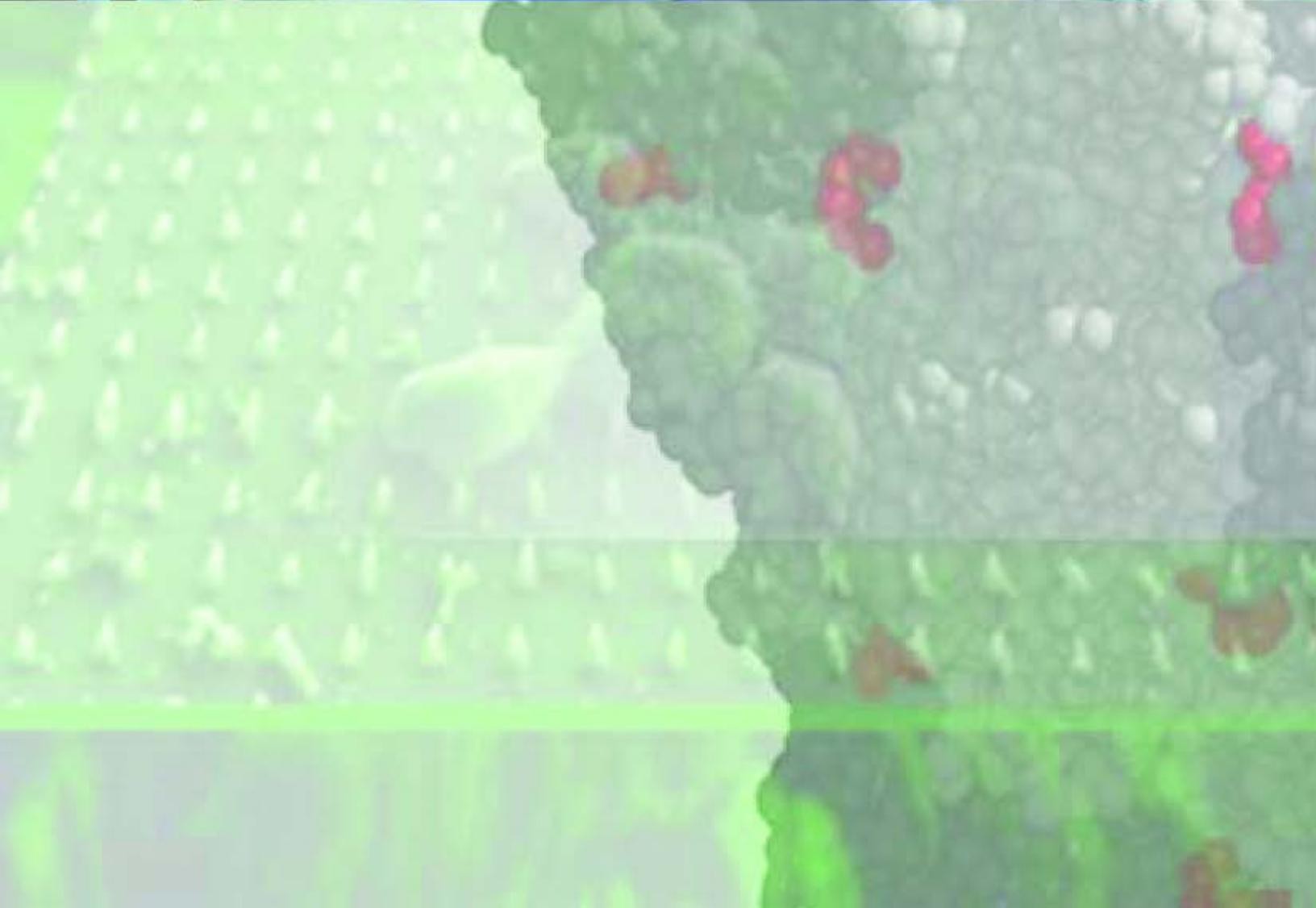


cancer NANOTECHNOLOGY plan

A Strategic Initiative To Transform Clinical Oncology
and Basic Research Through the Directed
Application of Nanotechnology

July 2004

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute



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Message From the Director

To help meet the Challenge Goal of eliminating suffering and death from cancer by 2015, the National Cancer Institute (NCI) is engaged in a concerted effort to harness the power of nanotechnology¹ to radically change the way we diagnose, treat, and prevent cancer. Over the past 5 years, the NCI has taken the lead in *integrating nanotechnology* into biomedical research through a variety of programs. The results of these initial funding efforts have demonstrated clearly that melding nanotechnology and cancer research and development efforts will have a profound, disruptive effect on how we diagnose, treat, and prevent cancer.

The application of nanotechnology to cancer research could not come at a more opportune time given the recent exponential increase in our understanding of the *process of how cancer develops*. It is my belief that nanomaterials and nanodevices will play a critical and unique role in turning that knowledge into clinically useful advances that detect and interact with the cancer cell and its surroundings early in this process. By doing so, we will change for the better the way we diagnose, treat, and ultimately prevent cancer.

Thanks to the scientific expertise and translational development capacity concentrated in our Comprehensive Cancer Centers, SPOREs (Specialized Programs of Research Excellence), research networks, and intramural program, the NCI is well positioned to seize this important opportunity. In particular, I believe it is possible that a concerted, *multidisciplinary* research effort will quickly yield new technologies that will detect and pinpoint the molecular signatures of cancer at its earliest stages and enable physicians to determine early whether an anticancer therapeutic is working. These advances will change the way we care for cancer patients. Such technological advances will have an even greater impact because of their ability to change the way new cancer therapies will be tested and approved, increasing the speed with which new science is turned into new therapies.

Future developments from nanotechnology also include multifunctional nanoscale devices capable of simultaneously detecting and treating cancer. Also in the offing are novel methods for preventing cancer and ameliorating the symptoms that negatively impact a patient's quality of life. Nanotechnology will also create a host of powerful tools that cancer researchers will use to make the next generation of discoveries that will ultimately lead to clinical advances.

To ensure that we capitalize on this opportunity to make dramatic progress today, the NCI has developed this Cancer Nanotechnology Plan (CNPlan). Over the past year, the NCI has held numerous symposia exploring the intersections of nanotechnology and cancer research, and the NCI staff has solicited input from a broad cross-section of the cancer research and clinical oncology communities. Intramural and extramural research working groups have discussed how best to apply the lessons of the NCI's initial explorations into nanotechnology to a focused and coordinated translational research effort that will have near-term benefits for patients.

Created with input from these experts, the CNPlan lays out a pathway and a set of directed mechanisms through which nanotechnology will be the fundamental driver of advances in oncology and cancer research conducted by multidisciplinary teams. The CNPlan will rely heavily on our substantial investments in our Comprehensive Cancer Centers and SPOREs, but it also calls for the development of as many as five Centers of Cancer Nanotechnology Excellence (CCNEs) that will contribute their expertise in nanotechnology to milestone-driven projects. To avoid duplicating efforts conducted through other Federal programs, including the National Nanotechnology Initiative and the NIH Roadmap for Medical Research, the projects initiated

¹Nanotechnology refers to the interactions of cellular and molecular components and engineered materials—typically clusters of atoms, molecules, and molecular fragments—at the most elemental level of biology. Such nanoscale objects—typically, though not exclusively, with dimensions smaller than 100 nanometers—can be useful by themselves or as part of larger devices containing multiple nanoscale objects.

under the CNPlan will be integrated, milestone driven, and product oriented, with *targeted objectives and goals*, and will use a project-management approach to capitalize in relatively short order on today's opportunities to create the tools that both clinicians and cancer researchers need now to eliminate suffering and death from cancer by 2015. Recognizing the importance of bringing expertise from many areas, *partnership* opportunities with other Federal agencies and the private sector will be critical, particularly in terms of clinical development activities and in our efforts to ensure that nanoscale devices will not themselves be harmful to cancer patients or the environment.

Ultimately, this is not just a plan for the NCI, but a call to action for the cancer research community. It emphasizes the process of building partnerships between the private and public sectors with the goal of creating teams best equipped to translate today's knowledge about cancer biology and nanotechnology into clinically useful products. By joining together, I am confident that we will continue to make substantial scientific and medical progress to achieve the one goal that matters most: the reduction and elimination of the burden of cancer for all who are in need.

Andrew C. von Eschenbach, M.D.

Director

National Cancer Institute

Vision Statement

Nanotechnology offers the unprecedented and paradigm-changing opportunity to study and interact with normal and cancer cells in real time, at the molecular and cellular scales, and during the earliest stages of the cancer process. Through the concerted development of nanoscale devices or devices with nanoscale components spearheaded by the NCI, the Comprehensive Cancer Centers, and the SPOREs, and in collaboration with other Federal agencies, nanotechnology will be the enabling technology for:

- Early imaging agents and diagnostics that will allow clinicians to detect cancer in its earliest, most easily treatable, presymptomatic stage
- Systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents at high local concentrations, with physiologically appropriate timing, directly to cancer cells and those tissues in the microenvironment that play a critical role in the growth and metastasis of cancer
- Agents capable of monitoring predictive molecular changes and preventing precancerous cells from becoming malignant
- Surveillance systems that will detect mutations that may trigger the cancer process and genetic markers that indicate a predisposition for cancer
- Novel methods for managing the symptoms of cancer that adversely impact quality of life
- Research tools that will enable investigators to quickly identify new targets for clinical development and predict drug resistance

In taking a leadership role, the NCI recognizes that these translational initiatives would benefit greatly from a concerted and coordinated effort to characterize and standardize the wide range of nanoscale devices that are now available for use by the research community and that will undoubtedly be developed in the near future. This role will be filled by the Nanotechnology Characterization Laboratory (NCL), which the NCI will establish at its NCI-Frederick facility. A primary objective of the NCL is to develop data on how nanomaterials and nanodevices interact with biological systems. These research endeavors will chart the common baseline and scientific data that would inform research and development (R&D) as well as future regulatory actions involving nanoscale diagnostics, imaging agents, and therapeutics. Moreover, this information will be linked to the Comprehensive Cancer Centers and related programs through public databases available through the Cancer Biomedical Informatics Grid (CaBIG).

Achieving this vision will also require training a cadre of researchers who are skilled in applying the tools of nanotechnology to critical problems in cancer research and clinical oncology. And given the complex nature of this endeavor, building multidisciplinary teams will be essential to realizing this vision.² Thus, the NCI must take a leadership role by providing the necessary funds and opportunities for the cross-disciplinary training and collaboration that will be needed to maximize the impact that nanotechnology can have on meeting the Challenge Goal of eliminating the suffering and death from cancer by 2015.

The CNPlan lays out the pathway and directed programmatic mechanisms through which nanotechnology will become a fundamental driver of advances in oncology and cancer research. The CNPlan reflects a consensus among the entire cancer community that four significant obstacles impede the revolutionary changes that must occur to meet the 2015 Challenge Goal³:

²National Institutes of Health. *Catalyzing Team Science: Report from the 2003 BECON Symposium*. http://www.becon2.nih.gov/symposia_2003/becon2003_symposium_final.pdf.

³National Cancer Institute. *Leveraging Multi-Sector Technology Development Resources and Capabilities to Accelerate Progress Against Cancer: A National Cancer Institute Roundtable*. 2004.

- The need for cross-disciplinary collaborations
- The widening “gap” between late discovery and early development of diagnostics and therapeutics
- The critical lack of available standards
- The requirement for cross-cutting technology platforms

By taking the pathway and utilizing the mechanisms detailed in the CNPlan, which rely heavily on capacity already developed by the NCI through its national infrastructure, the CNPlan will lower the barriers for developing technology that will become integrated in clinical, basic, and applied research. Nanotechnology will thereby become a core component in the training and translational programs at all leading cancer research institutions and a significant part of comprehensive cancer care. Thus, the focus will be achieving product-driven goals with demanding timelines, realizing that such an approach is necessary to meet the 2015 Challenge Goal.

Key Opportunities for Cancer Nanotechnology

On the basis of discussions with a wide range of clinicians, cancer researchers, and technologists, it is clear that nanotechnology is ready today to solve mission-critical problems in cancer research. Indeed, one of the goals of the CNPlan is to increase the visibility and availability of nanomaterials and nanoscale devices technology within the cancer research and development community to allow investigators the opportunity to do what they do best—discover and invent using new tools, just as they are doing with other disruptive technologies such as DNA microarrays and proteomic analysis.

But the NCI's major goal for the CNPlan is to catalyze targeted discovery and development efforts that offer the greatest opportunity for advances in the near and medium terms and to lower the barriers for those advances to be handed off to the private sector for commercial development. The CNPlan focuses on translational research and development work in the following six major challenge areas, where nanotechnology can have the biggest and fastest impact.

Molecular Imaging and Early Detection

Nanotechnology can have an early, paradigm-changing impact on how clinicians will detect cancer in its earliest stages. Exquisitely sensitive devices constructed of nanoscale components—such as nanocantilevers, nanowires, and nanochannels—offer the potential for detecting even the rarest molecular signals associated with malignancy. Collecting those signals for analysis could fall to nanoscale harvesters, already under development, that selectively isolate cancer-related molecules such as proteins and peptides present in minute amounts from the bloodstream or lymphatic system. Investigators have already demonstrated the feasibility of this approach using the serum protein albumin (a naturally existing nanoparticle), which happens to collect proteins that can signal the presence of malignant ovarian tissue.

Another area with near-term potential is detecting mutations and genome instability *in situ*. Already, investigators have developed novel nanoscale *in vitro* techniques that can analyze genomic variations across different tumor types and distinguish normal from malignant cells. Nanopores are finding use as real-time DNA sequencers, and nanotubes are showing promise in detecting mutations using a scanning electron microscope. Further work could result in a nanoscale system capable of differentiating among different types of tumors accurately and quickly, information that would be invaluable to clinicians and researchers alike. Along similar lines, other investigators have developed nanoscale technologies capable of determining protein expression patterns directly from tissue using mass spectroscopy. This technique has already shown that it can identify different types of cancer and provide data that correlate with clinical prognosis.

In addition, nanoscale devices can enable new approaches for real-time monitoring of exposures to environmental and lifestyle cancer risk factors. Such information would be important not only for identifying individuals who may be at risk for developing cancer, but also for opening the door to complex studies of gene-environment interactions as they relate to the development of or resistance to cancer.

In Vivo Imaging

One of the most pressing needs in clinical oncology is for imaging agents that can identify tumors that are far smaller than those detectable with today's technology, at a scale of 100,000 cells rather than 1,000,000,000 cells. Achieving this level of sensitivity requires better targeting of imaging agents and generation of a bigger imaging signal, both of which nanoscale devices are capable of accomplishing. When attached to a dendrimer, for example, the magnetic resonance imaging (MRI) contrast agent gadolinium generates a 50-fold stronger signal than in its usual form, and given that nanoscale particles can host multiple gadolinium ions, affords an opportunity to create a powerful contrast agent. When linked to one of the increasing number of targeting agents, such a construct would have the potential of meeting the 100,000 cell detection level.

First-generation nanoscale imaging contrast agents are already pointing the way to new methods for spotting tumors and metastatic lesions much earlier in their development, before they are even visible to the eye. In the future, implantable nanoscale biomolecular sensors may enable clinicians to more carefully monitor the disease-free status of patients who have undergone treatment or individuals susceptible to cancer because of various risk factors.

Imaging agents should also be targeted to changes that occur in the environment surrounding a tumor, such as angiogenesis, that are now beyond our capability to detect in the human body. Already, various nanoparticles are being targeted to integrins expressed by growing capillaries. Given that angiogenesis occurs in distinct stages and that antiangiogenic therapies will need to be specific for a given angiogenic state, angiogenesis imaging agents that can distinguish among these stages will be invaluable for obtaining optimal benefit from therapeutics that target angiogenesis.

Reporters of Efficacy

Today, clinicians and patients must often wait months for signs that a given therapy is working. In many instances, this delay means that should the initial therapy fail, subsequent treatments may have a reduced chance of success. This lag also adversely impacts how new therapies undergo clinical testing, since it leaves regulatory agencies reluctant to allow new cancer therapies to be tested on anyone but those patients who have exhausted all other therapeutic possibilities. Unfortunately, this set of patients is far less likely to respond to any therapy, particularly to those molecularly targeted therapies that aim to stop cancer early in its progression, an approach that virtually all of our knowledge says is the best approach for treating cancer.

Nanotechnology offers the potential for developing highly sensitive imaging agents and *ex vivo* diagnostics that can determine whether a therapeutic agent is reaching its intended target and whether that agent is killing malignant or support cells, such as growing blood vessels. Targeted nanoscale devices may also enable surgeons to more readily detect the margins of a tumor before resection or to detect micrometastases in lymph nodes or tissues distant from the primary tumor, information that would inform therapeutic decisions and have a positive impact on patient quality-of-life issues.

The greatest potential for immediate results in this area would focus on detecting apoptosis following cancer therapy. Such systems could be constructed using nanoparticles containing an imaging contrast agent and a targeting molecule that recognizes a biochemical signal seen only when cells undergo apoptosis. Using the molecule annexin V as the targeting ligand attached to nanoscale iron oxide particles, which act as a powerful MRI contrast agent, investigators have shown that they can detect apoptosis in isolated cells and in tumor-bearing mice undergoing successful chemotherapy. Further development of this type of system could provide clinicians with a way of determining therapeutic efficacy in a matter of days after treatment. Other systems could be designed to detect when the p53 system is reactivated or when a therapeutic agent turns on or off the biochemical system that it targets in a cancer cell, such as angiogenesis.

Another approach may be to use targeted nanoparticles that would bind avidly, or perhaps even irreversibly, to a tumor and then be released back into the bloodstream as cells in the tumor under apoptosis following therapy. If labeled with a fluorescent probe, these particles could be easily detected in a patient's urine. If also labeled with an imaging contrast agent, such a construct could double as a diagnostic imaging probe.

Multifunctional Therapeutics

Because of their multifunctional capabilities, nanoscale devices can contain both targeting agents and therapeutic payloads at levels that can produce high local levels of a given anticancer drug, particularly in areas of the body that are difficult to access because of a variety of biological barriers, including those developed by tumors. Multifunctional nanoscale devices also offer the opportunity to utilize new approaches to therapy, such as localized heating or reactive oxygen generation, and to combine a diagnostic or imaging agent with a therapeutic and even a reporter of therapeutic efficacy in the same package. "Smart"

nanotherapeutics may provide clinicians with the ability to time the release of an anticancer drug or deliver multiple drugs sequentially in a timed manner or at several locations in the body. Smart nanotherapeutics may also usher in an era of sustained therapy for those cancers that must be treated chronically or to control the quality-of-life symptoms resulting from cancers that cannot be treated successfully. Smart nanotherapeutics could also be used to house engineered cellular “factories” that would make and secrete multiple proteins and other antigrowth factors that would impact both a tumor and its immediate environment.

The list of potential multifunctional nanoscale therapeutics grows with each new targeting ligand discovered through the use of tools such as proteomics. Nanoscale devices containing a given therapeutic agent would be “decorated” with a targeting agent, be it a monoclonal antibody or F_v fragment to a tumor surface molecule, a ligand for a tumor-associated receptor, or other tumor-specific marker. In most cases, such nanotheapeutics could double as imaging agents.

Many nanoparticles will respond to an externally applied field, be it magnetic, focused heat, or light, in ways that might make them ideal therapeutics or therapeutic delivery vehicles. For example, nanoparticulate hydrogels can be targeted to sites of angiogenesis, and, once they have bound to vessels undergoing angiogenesis, it should be possible to apply localized heat to “melt” the hydrogel and release an antiangiogenic drug. Similarly, iron oxide nanoparticles, which can serve as the foundation for targeted MRI contrast agents, can be heated to temperatures lethal to a cancer cell merely by increasing the magnetic field at the very location where these nanoparticles are bound to tumor cells.

In some instances, nanoscale particles will target certain tissue strictly because of their size. Nanoscale dendrimers and iron oxide particles of a specific size will target lymph nodes without any molecular targeting. Nanoscale particles can also be designed to be taken up by cells of the reticuloendothelial system, which raises the possibility of delivering potent chemotherapeutics to the liver, for example.

Nanoscale devices should also find use in creating immunoprotected cellular factories capable of synthesizing and secreting multiple therapeutic compounds. Early-stage research has already demonstrated the value of such cellular factories, and a concerted effort could turn this research into a powerful multivalent therapeutic capable of responding to local conditions in a physiologically relevant manner.

Prevention and Control

Many of the advances that nanotechnology will enable in each of the four preceding challenge areas will also find widespread applicability in efforts to prevent and control cancer. Advances driven by the NCI’s initiatives in proteomics and bioinformatics will enable researchers to identify markers of cancer susceptibility and precancerous lesions, and nanotechnology will then be used to develop devices capable of signaling when those markers appear in the body and deliver agents that would reverse premalignant changes or kill those cells that have the potential for becoming malignant. Nanoscale devices may also prove valuable for delivering polyepitope cancer vaccines that would engage the body’s immune system or for delivering cancer-preventing nutraceuticals or other chemopreventive agents in a sustained, time-release and targeted manner.

One intriguing idea for preventing breast cancer comes from work suggesting that breast malignancies may derive from a limited population of pluripotent stem cells in breast tissue. Should this prove true, it may be possible to develop a nanoscale device that could be injected into the ductal system of the breast, bind only to those stem cells, and deliver an agent capable of killing those cells. Such an agent could then be administered to women who are at an increased risk of breast cancer as a preventive therapy.

Research Enablers

Nanotechnology offers a wide range of tools, from chip-based nanolabs capable of monitoring and manipulating individual cells to nanoscale probes that can track the movements of cells, and even individual

molecules, as they move about in their environment. Using such tools will enable cancer biologists to study, monitor, and alter the multiple systems that go awry in the cancer process and identify key biochemical and genetic “choke points” at which the coming wave of molecular therapies might best be directed. As such, nanotechnology can serve as the perfect complement to other technology platforms, such as proteomics and bioinformatics, that the NCI is emphasizing in its research initiatives as critical components of the discovery and development engine that will power both near-term and long-term advances in cancer diagnosis, treatment, and prevention.

The discussion above has already highlighted the potential for nanoscale devices to act as molecular harvesting agents. Such a tool would be invaluable to proteomics efforts aimed at identifying tumor-specific indicators. Similarly, nanoscale devices that can detect the biological changes associated with therapeutic efficacy should also find widespread use as a tool for understanding how cells respond to a variety of perturbations. One of the most powerful near-term uses of nanotechnology to accelerate basic research will come from using molecular-size nanoparticles with a wide range of optical properties, such as quantum dots, to track individual molecules as they move through a cell or individual cells as they move through the body. In combination with the new generation of mouse models that more accurately reproduce the genetic, biochemical, and physiological properties of human cancers, these nanolabels will prove invaluable for systems-scale research. Increased focus on the development of nanoscale devices for making simultaneous biochemical measurements on multiple cells, particularly those grown in such a way as to mimic tissue development *in vivo*, will also have a significant impact on basic cancer research.

Nanoscale devices should also enable direct analysis of single nucleotide polymorphisms (SNPs) and large-scale mutational screening for cancer susceptibility genes. Real-time methylation analysis should also benefit from various nanoscale tools and devices. Indeed, nanotechnology should prove to be a valuable technology platform for the burgeoning field of cancer molecular epidemiology.

New Strategies for Cancer Nanotechnology

Funding activities conducted within the framework of the CNPlan will occur in four areas as detailed below. The first will be to develop three to five CCNEs that will provide engineering and physical science expertise to leverage the cancer biology expertise and access to cancer patients at the Nation's Comprehensive Cancer Centers, SPOREs, and large population infrastructures, such as the Breast and Colon Cancer Family Registries. Second, the CNPlan will fund cross-disciplinary training programs as a means of fostering the creation of the multidisciplinary teams needed to integrate nanotechnology and cancer biology. Third, the CNPlan will fund focused nanotechnology development initiatives that will be milestone driven and product oriented, with an emphasis on commercialization through small-business and larger private-sector project team members. Fourth, the CNPlan will fund projects that apply nanotechnology in cancer biology and translational research, through basic research project grants and other mechanisms. Since the R01 mechanism has historically not been the best mechanism to fund individual investigator-initiated technology development and application projects, the NCI will also make use of program announcements, requests for applications, and request for proposals, as well as a variety of program management and funding mechanisms that have been shown to be successful in prior technology development programs. The NCI will also examine opportunities through the Small Business Innovation Research/Small Business Technology Transfer Research (SBIR/STTR) programs as well as administrative supplements to existing awards to accelerate the integration of nanotechnology into the NCI research program.

In addition to the largely extramural focus of the CNPlan, a variety of demonstration projects in the NCI intramural program will add to this overall effort by acting as developmental catalysts. For example, the NCI has contracted with a nanotechnology foundry to fabricate materials and provide engineering expertise to aid *in vivo* projects using nanoscale devices. The NCI's intramural expertise, when used in this type of synergistic manner, will accelerate the development of new nanotechnology-driven advances in oncology.

Helping guide these programmatic activities will be the Cancer Nanotechnology Working Group (CNWG), which was recently formed from the Cancer Nanotechnology Intramural Working Group and the Cancer Nanotechnology Extramural Intramural Working Group. The CNWG will have a tracking function and will continue (as the two subgroups have for the past year) to act in an advisory capacity as the CNPlan moves forward. The CNWG is playing a key role in planning an NCI-sponsored intramural nanotechnology seminar series scheduled for fall 2004 and coordinating symposia held at regional cancer and advanced technology centers.

The CNPlan will also include development of program evaluation tools related to the programmatic milestones proposed in this plan as well as mechanisms for conducting annual evaluations. The evaluation processes will involve independent, outside review teams and will assess how program activities conducted as part of the CNPlan meet the goals and milestones set forth in this plan. Feedback from these evaluations will facilitate appropriate milestone adjustment course corrections in the implementation of the plan.

Centers of Cancer Nanotechnology Excellence (CCNEs)

The primary goal of the CCNEs is to integrate nanotechnology development into basic and applied cancer research that is necessary to rapidly facilitate the application of this science to clinical research. The critical requirements for each CCNE will be:

- Integration with a Comprehensive Cancer Center/SPORE program
- Affiliation with university or research centers of engineering and physical sciences (e.g., mathematics, chemistry, physics, and material sciences)
- Advanced biocomputing capabilities
- Required existing not-for-profit/private technology development partnerships

Outcomes objectives (performance measures) represent technologies that are developed and effectively utilized to overcome cancer processes. A steering committee will coordinate efforts across all the CCNEs, to facilitate data and technology transfer across centers, interconnecting and leveraging the strengths and advances of each.

Nanotechnology Characterization Laboratory (NCL)

Nanoscale particles and devices are similar in size to biomolecules and can easily enter most cells. Our ability to manipulate the physical, chemical, and biological properties of these particles affords researchers the ability to engineer and use nanoparticles for drug delivery, as image contrast agents, and for diagnostic purposes. NCI is establishing the Nanotechnology Characterization Laboratory (NCL) at its NCI-Frederick facility to provide critical infrastructure support to this rapidly developing field. The intent of the NCL is to accelerate the transition of basic nano-biotech research into clinical applications. (See page 23 for more information on the NCL.)

Building Research Teams

The NCI will create the incentives necessary to integrate nanotechnology into the mainstream of basic and applied cancer research. The CNPlan's approach is centered on supporting training and career development initiatives to establish integrated teams of cancer researchers, including epidemiologists, and engineers with the cancer biology and physical science skills and knowledge base of nanotechnology to approach the fundamental challenges of cancer. One policy consideration is to investigate opportunities for naming multiple principal investigators per project as an incentive for conducting team science.

Under the CNPlan, the NCI will initially use existing training and career development mechanisms to direct talent to this area as quickly as possible. The NCI recognizes, however, that new mechanisms for developing multidisciplinary teams may be needed. The NCI will also encourage programs to be developed with interfaces to the training programs of other Federal agencies as components of the National Nanotechnology Initiative (NNI). The advantages are to rapidly translate knowledge from fundamental nanotechnology sciences to directed application in cancer biology.

Other possible mechanisms for fostering team-building include the Bioengineering Research Partnerships (BRPs) and Bioengineering Research Grants (BRGs). The BRPs are designed to fund basic, applied, and translational multidisciplinary research that addresses important biological or medical research problems. In the context of this program, a partnership is a multidisciplinary research team that applies an integrative, systems approach to developing knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior. The partnership must include appropriate bioengineering or allied quantitative sciences in combination with biomedical and/or clinical components. The smaller BRG awards support multidisciplinary research performed in a single laboratory or by a small number of investigators that applies an integrative, systems approach to developing knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior. A BRG application may propose hypothesis-driven, discovery-driven, developmental, or design-directed research at universities, national laboratories, medical schools, large or small businesses, or other public and private entities.

Outcome objectives (performance measures) represent institutions with training programs and scientists and engineers who are trained in cancer nanotechnology. A 3- to 5-year benchmark is to support the entry of 30 scientists with formal training experiences in nanotechnology applied to cancer biology. Recommended mechanisms include the following:

- **F33 NIH National Research Service Awards for Senior Fellows.** This approach would enable experienced cancer researchers and engineers/physical scientists with directed programs of training to be independent researchers and to provide the future building of training programs.

- **F32 NIH National Research Service Awards for Individual Postdoctoral Fellows.** This approach would provide cross-disciplinary research training opportunities for postdoctoral fellows with training in either cancer or technology to gain experience in the other discipline.
- **K08 and K25 Mentored Clinical Scientist Development Awards.** This approach begins to develop research teams with clinical applications of nanotechnology to allow integration of nanotechnology into the clinical assessment phase. At present, there are no programs that support technology development and applications training for clinical researchers. This gap will be an important one to facilitate the clinical testing of nanotechnologies. In these programs, clinical researchers will be offered opportunities in developing clinical assessment paradigms for diagnosis, treatment, and prevention using nanotechnologies.
- **T32 Institutional Training Grant Program.** This approach enables eligible institutions to develop or enhance research training opportunities for predoctoral or postdoctoral trainees, who are training for careers in specified areas of biomedical and clinical research.
- **R25 Cancer Education Grant Program.** This mechanism will be used to develop critical educational programs for cancer biologists, engineers/physical scientists, and trainees. The focus will be on developing programmatic activities at CCNEs to develop curricula, educational programs/seminars, and national forums focused on cancer nanotechnology.

Planning for future training and career development needs will be developed on the basis of the initial success of the above strategies and the assessment of program needs. The NCI recognizes, for example, that there will likely be a need to foster curriculum development for undergraduate and graduate programs that would cross-fertilize training in the biological sciences with engineering, chemistry, and other physical sciences and vice versa.

Creating Cancer Nanotechnology Platforms Through Directed Research Programs

Using Broad Agency Announcements (BAAs), NCI will identify to the R&D community three to five critical technology platform needs for cancer, such as *in vivo* nanotechnology imaging systems and nanotechnology-enabled systems for rapidly assessing therapeutic efficacy and addressing cancer biology processes. The program will fund 3-year technology projects through a contract mechanism that is overseen by project specialists. The project will target cancer centers, small businesses, and Federal laboratories that prepare and submit concepts and project objectives. Upon review of initial submissions, full solicitations will be sought from those of highest value. Technology programs will create platforms that are aimed at deployment for clinical application in cancer research. Applicants will be required to team with the Comprehensive Cancer Centers or SPOREs with a plan for dissemination of the technology.

Basic and Applied Initiatives for Nanotechnology in Cancer

Requests for Application (RFAs) and Program Announcements (PAs) will be issued to solicit applications for projects that apply nanotechnology for specific opportunities in cancer biology and translational research. These may focus on investigator-initiated proposals that address specific biology processes, diagnostic technologies, or drug development methods. Research projects that address the fundamental biology questions identified in the CNPlan will be considered.

Mechanisms for funding would consider R21/R33 approaches for phased innovation with programmatic review of attainment of project milestones. The small-business community would be targeted for use of R41 and R43 mechanisms in this area.

Timeline and Programmatic Milestones

A defining element of the CNPlan is that it calls for the NCI to mark progress in six key areas (see Key Opportunities for Cancer Nanotechnology) over two time periods. During the initial 1 to 3 years, the CNPlan will accelerate selected projects that are already under way and catalyze the development of products that are primed for near-term clinical application. The second period, 3 to 5 years, will see projects come to fruition that reflect solving more difficult technological and biological problems or that require the integration of multiple technological components but have the potential for making paradigm-changing impacts on the detection, treatment, and prevention of cancer. Milestones reached during this latter period will also reflect the growth of the investigator pool that will be catalyzed by the CNPlan. By the end of 5 years, we expect that most of these efforts will generate products in clinical trials or even in clinical use.

The CNPlan represents an integrated program of activities to use a disruptive technology—nanotechnology—as an enabler of rapid clinical and research advances and as a means of lowering the barriers to technology development and commercialization by the private sector, particularly among small businesses. Over the next 5 years, a timeframe merited by the urgency of meeting the NCI's 2015 Challenge Goal and supported by the solid foundation of promising advances from the NCI's basic research portfolio, the CNPlan calls for the use of targeted contract funding with project management oversight to meet the following milestones:

Key Opportunity	1-3 Years	3-5 Years
Molecular Imaging and Early Detection	<ul style="list-style-type: none">• Begin clinical trials of nanotechnology-assisted automated assay for rapid detection of genetic abnormalities.• Refine <i>in vitro</i> nanotechnology systems (cantilevers, nanowires, nanochannels) for rapid, sensitive analysis of cancer biomarkers. Such systems will be easily expanded as new markers are identified.	<ul style="list-style-type: none">• Disseminate nanoscale devices for routine validation of cancer biomarkers.• Develop rapid multifactorial genomic and proteomic diagnostic system for tumor identification and staging.• Begin clinical trials with multicomponent nanotechnology platform early diagnosis and therapeutic monitoring.
<i>In Vivo</i> Imaging	<ul style="list-style-type: none">• File Investigational New Drug (IND) application to begin clinical trials of nanoscale MRI contrast agents capable of identifying fewer than 100,000 actively aggressive cancer cells.• Conduct clinical trials for three targeted nanoscale imaging agents using a variety of imaging modalities, including MRI, ultrasound, and near-infrared optical imaging.	<ul style="list-style-type: none">• Complete clinical trials and file New Drug Application (NDA) for first nanoscale imaging agent capable of detecting <100,000 actively aggressive tumor cells.• Begin clinical trials with multiple nanoscale imaging agents.• Develop capabilities for monitoring active cellular processes as they change over time.

Key Opportunity	1-3 Years	3-5 Years
Reporters of Efficacy	<ul style="list-style-type: none"> Begin clinical trials for nanoscale device (imaging-based or <i>ex vivo</i>) that can rapidly assess apoptosis in clinical trials. Develop capabilities for monitoring disruption of vascular networks associated with primary solid tumors and metastatic lesions. Develop nanoscale devices to identify and quantify biological and chemical changes (other than apoptosis) resulting from therapeutic treatment. Demonstrate proof of concept for nanoscale devices (imaging-based or <i>ex vivo</i>) that can be used with a variety of therapeutics to determine biodistribution <i>in vivo</i>. Begin clinical trials with one optical imaging device capable of showing surgical margins using nanoscale agents. 	<ul style="list-style-type: none"> Demonstrate multiple systems (imaging-based or <i>ex vivo</i>) that can rapidly assess therapeutic efficacy in terms of apoptosis, angiogenesis regression, and other markers. Demonstrate multiple systems for monitoring real-time drug distribution. Promote routine use of nanoscale efficacy reporters for surrogate end point measurements in clinical trials.
Multifunctional Therapeutics	<ul style="list-style-type: none"> File IND to begin clinical trials of one targeted sensitizer (radiation, light, magnetic field). File IND to begin clinical trials of one multifunctional therapeutic complete with accompanying therapeutic assessment tool. Develop nanoscale devices capable of multivariate targeting and intervention. File IND application to begin clinical trials of one nanoscale therapeutic targeting reticuloendothelial system. 	<ul style="list-style-type: none"> Conduct multiple clinical trials with targeted sensitizers (radiation, light, magnetic field). File INDs to begin clinical trials of multiple targeted therapeutics, complete with accompanying therapeutic assessment tool. File IND to begin clinical trials of one multifactorial targeted therapeutic agent at IND stage. Demonstrate five "failed" drugs reconstituted in targeted, "smart" nanoscale devices for retesting in new generation of preclinical models.
Prevention and Control	<ul style="list-style-type: none"> Demonstrate proof of concept for nanoscale device capable of monitoring genetic changes associated with early cancer processes and hyperplasia with the aim of preventing subsequent development of cancer. 	<ul style="list-style-type: none"> File IND to begin clinical trials of a nanoscale device capable of identifying markers of early cancer processes. Demonstrate proof of concept for nanoscale device capable of metastasis detection.

Key Opportunity	1-3 Years	3-5 Years
Research Enablers	<ul style="list-style-type: none"> • Develop nanoscale harvesting devices for proteomics analysis and biomarker identification. • Create prototype for real-time, <i>in situ</i> genome sequencing of malignant and pre-malignant cells. • Develop instrumented cell coculture systems biology research. • Refine cell and cell-component labeling with nanoparticulates such as quantum dots for application to studies of integrated pathways and processes in cancer. • Develop toxicology database for nanoscale devices and nanoparticulates. • Create a scientific framework for regulatory approval of nanoscale diagnostics, therapies, and preventive agents. 	<ul style="list-style-type: none"> • Develop nanoscale analytical devices to study DNA methylation and protein phosphorylation. • Promote routine use of nanoscale technology to characterize tumor heterogeneity. • Demonstrate nanoscale technology for detecting multiple mutations <i>in vivo</i>. • Promote routine use of nanoscale analytical tools for studying cellular signaling pathways.

Overcoming Barriers

To rapidly harness the potential of nanotechnology to meet our 2015 Challenge Goal of eliminating suffering and death from cancer, the NCI has crafted the CNPlan. Over the past year, the NCI has held several workshops and symposia exploring the intersections of nanotechnology and various areas of cancer research, and the NCI staff has solicited input from a broad cross-section of the cancer research and clinical oncology communities. Intramural and extramural research working groups have discussed how best to apply the lessons of the NCI's initial forays into nanotechnology to a concerted translational research effort that will have near-term benefits for patients. During this time, the NCI also convened a roundtable of leaders from the private sector, foundations, patient advocacy groups, the Comprehensive Cancer Centers, academia, and other government agencies to identify new ways of leveraging technology to aid in our battle against cancer.³

During the course of these fact-finding discussions, it became clear that nanotechnology offers tremendous opportunities, the most promising of which are presented in this report and represent the major focus of the CNPlan. However, these discussions also increased the NCI's awareness that there are a number of nonscientific barriers that could impede the rapid translation of cancer nanotechnology research into clinically useful, paradigm-changing advances in diagnosing, treating, and preventing cancer. Though numerous in detail, these potential barriers followed several themes:

- **Cross-Disciplinary Collaborations.** For cancer nanotechnology to have its biggest impact, barriers to multidisciplinary and multiple partner collaborations must fall. Though there are many institutional barriers to such research collaborations over which the NCI has no direct control, the NCI can use alternative funding mechanisms to encourage and facilitate such collaborations. In particular, the NCI can use these funding mechanisms to promote increased collaborations among the public, private, and nonprofit sectors that reduce overall development risk.
- **“Gap” Between Late Discovery and Early Development of Diagnostics and Therapeutics.** Too many potential products that reach clinical development fail as they move forward because of a lack of solid science to back up regulatory filings. Moreover, to conduct clinical trials, there is insufficient financial and intellectual support for smaller companies to move novel products through the testing and regulatory approval process and, ultimately, failure to match development goals with clinical and patient needs.
- **Regulatory Uncertainty.** There is no clear regulatory pathway for approval of nanoscale devices, increasing the risk for private-sector development of promising new diagnostics, therapies, and preventive agents. In particular, there is a concern that each new use of a given nanoscale device, such as a particular type of particle, will require full-scale preclinical and clinical testing, a requirement that would dramatically drive up development costs. There is also concern about the difficulty of gaining regulatory approval for nanoscale devices that combine diagnostic and therapeutic modalities or multiple therapeutic agents in the same construct.
- **Standardization and Characterization.** Because nanotechnology is such a new field, there are few standards and little reference physical and biological characterization data that researchers can use to choose which nanodevices might be most suitable for a given clinical or research application. A lack of standard assay and characterization methods also makes it difficult to compare results from different laboratories.
- ***In Vivo* Behavior.** There is good reason to expect that critical *in vivo* properties of nanoscale devices, such as pharmacokinetics, pharmacodynamics, and biodistribution, will differ markedly from that of current imaging and therapeutic agents; yet there is a marked lack of data on these base characteristics. There is also, however, little ongoing research that will generate these essential data.
- **Technology Transfer and Knowledge Exchange.** Cancer nanotechnology is inherently a discipline that will succeed because of its combinatorial nature—Any given nanoscale technology or device may be combined with any number of diagnostic, imaging, therapeutic, or preventive agents. As a result, there is a need for new mechanisms for sharing and cross-licensing intellectual property to facilitate technology

transfer and knowledge exchange. Though the NCI cannot by itself create such a system, it can work with other Federal agencies to act as a facilitator among the multiple interest groups by convening roundtable events for discussion and problem-solving.

Awareness of these overarching concerns had a great impact on the development of the CNPlan. A major role of the NCL, for example, will be to eliminate barriers resulting from the current lack of standards and characterization data. The CNPlan addresses potential barriers by making the U.S. Food and Drug Administration (FDA) an important partner in this endeavor. The CNPlan's emphasis on contract-based funding will place a premium on collaborations, particularly between the public and private sectors.

NCI Program Development in Nanotechnology

Although the NCI is a strong supporter of investigator-initiated, R01-supported research, the Institute also recognizes that this funding mechanism is not universally applicable to all its research initiatives. In particular, the NCI believes that to be effective, the CNPlan must utilize funding mechanisms that place a premium on meeting project goals on a timely basis, produce a desired deliverable at the end of the project's lifetime, and integrate with other planning initiatives within the NCI. Through its experience with existing technology development programs and with input from the research community and from other government agencies—specifically the Defense Advanced Research Projects Agency (DARPA) and the Homeland Security Advanced Research Projects Agency (HSARPA)—the NCI recognizes that project-management style contracts with specified goals, timelines, and deliverables must be the central funding mechanism used in conjunction with the CNPlan if this initiative is to achieve its admittedly aggressive vision and associated goals and milestones.

Utilizing contract-based, project-management style funding will require that NCI program officers work closely with potential contracting groups, with an emphasis on helping prospective participants put together the multidisciplinary teams that the NCI envisions will be needed to accomplish the aggressive goals of the CNPlan. Such teams, which will preferentially include private-sector partners and small-business participation, will form the core element of CNPlan-related contracts.

Coordination with other NCI initiatives will be monitored by both the program officers and the planning coordinator in the Office of the NCI Director. Though the NCI has been funding nanotechnology research for a number of years now, nanotechnology, as part of the new NIH Roadmap initiative, has emerged as an area of interest across the entire NIH. The current goals of the NIH nanomedicine initiative are much more basic and obviously less focused than those laid out in the CNPlan. The nanomedicine roadmap group has just released a solicitation that will lead by the end of 2005 to the funding of planning awards for nanomedicine center development. The goal of this initiative is to fund centers using and developing nanotechnology to examine biological processes compatible with the missions of the various NIH institutes. This supports a long-term goal of the NIH to support infrastructure development in nanomedicine. In contrast, the CNPlan is a focused plan to capitalize on past NCI investment in nanotechnology and focus those and new efforts on the immediate mission of the NCI. The plan carries a shorter timeline and specific milestones to achieve the NCI goals. The NCI plans on continued support and participation with the NIH nanomedicine as well as all of the roadmap working groups where appropriate.

Discussions with leaders in academia, at the NCI Comprehensive Cancer Centers and SPOREs, and in the private sector indicate that this type of managed, targeted, milestone-driven, team-based funding mechanism, though admittedly novel for most researchers in the public sector, will be embraced by those members of the cancer research community who want to see their work turned rapidly into advances that help cancer patients. Furthermore, the consensus among the entire cancer community is that this type of project-management structure is critically needed at this very moment in order to most efficiently and rapidly translate 21st century science and technology into the tools and products that will revolutionize the detection, treatment, and prevention of cancer.

Reflecting the recommendations of the NIH Bioengineering Consortium report on promoting team science, the CNPlan places a premium on supporting cross-disciplinary teams that partner with the Comprehensive Cancer Centers, SPOREs, CCNEs, large existing population infrastructures such as the Breast and Colon Cancer Family Registries, and the private sector. Such partnerships, operating in a project-management environment, present an opportunity to leverage existing skills in a way that enables such teams to meet the milestones and deliverables that will be called for under CNPlan contracts and grants. By placing a premium on building cross-disciplinary teams, the CNPlan will also bring in expertise, such as in population genetics and epidemiology, that is often overlooked in terms of potential contributions to research and development efforts.

In addition, the CNPlan will initially utilize existing F33, K08, and K25 training grant programs to incentivize cross-disciplinary research through training. F33 awards go to experienced scientists who wish to make major changes in the direction of their research careers or wish to broaden their scientific background by acquiring new research capabilities. These awards will enable current established cancer investigators to train in the labs of leading nanotechnologists to facilitate bringing the technology back to their own labs to be applied toward future research activities. Alternatively, nanotechnologists could be funded to spend a year gaining insight into cancer research so that these problems could be addressed when returning to the nanotechnologist's lab. In both cases, the spillover of ideas from the trainee to the mentor's lab will continue to cross-pollinate the cancer and nanotechnology fields. The K08 and K25 mechanisms provide for specialized postdoctoral study for individuals with a health professional doctoral degree committed to a career in laboratory or field-based research. These awards will bring clinicians into nanotechnology-focused laboratories as a means of providing clinical expertise to nanotechnology-driven development programs. After 3 years, the NCI will evaluate the success of these programs to increase cross-disciplinary activities and determine whether new programs are necessary. For now, however, these existing mechanisms will provide a needed boost to such efforts. (For additional recommendations on how training can be used to incentivize cross-disciplinary activities, see Appendix A.)

Today, thanks in part to the growing acceptance of the 2015 Challenge Goal by the cancer community, the NCI believes that the majority of cancer researchers now appreciate the need to pick the most promising areas of research and focus on conducting the translational work needed to turn promise into clinical benefit. Indeed, there is a realization within the broad cancer community that while R01-style research efforts are key to generating the stream of discoveries upon which the CNPlan will capitalize, the time is ripe to select the most promising projects for focused development. The CNPlan represents the NCI's effort to capitalize on the gathering momentum within the field to do something different.

Interagency collaborations will also play a critical role in realizing the CNPlan's vision, achieving its goals, and meeting its milestones, and the NCI is already in discussions with multiple Federal agencies and other NIH Institutes to develop such cooperative efforts. In particular, a potential joint collaboration with the National Institute of Standards and Technology (NIST) and the FDA is a high priority. This collaboration will focus on developing standards for nanoscale devices and both *in vitro* and *in vivo* characterization assays that could serve as a starting point for regulatory filings. The NCI-FDA Interagency Oncology Task Force, which facilitates dialogue between the two agencies on research and policy issues, will also be addressing nanotechnology programs. The U.S. Department of Defense, which has its own cancer research programs and appreciates the growing burden that cancer represents for current and former members of the Armed Forces, is also a potential collaborator. Both the DARPA and the HSARPA, which have extensive, successful experience using project-management, product-focused research contracts, are providing guidance to the NCI as it develops new funding mechanisms. The NCI and the U.S. Department of Energy, which has a significant biomedical research initiative, are also discussing areas of joint interest in the nanotechnology field. The NCI recognizes the importance of science that supports safe use of nanomaterials in humans and will work with other institutes and centers as well as other programs, such as the National Institute of Environmental Health Sciences and the National Toxicology Program, to characterize any potential health and environmental issues with biomedical nanoscale devices.

Nanotechnology Characterization Laboratory for Cancer Research

During the course of the NCI's activities to develop the CNPlan, it became clear that the lack of standards and characterization data for the many nanoscale devices being developed could become a significant obstacle on the development and regulatory approval pathways. On the basis of input from the academic and private sectors, the NCI believes that the most effective manner for removing this potential obstacle is to establish and fund a national Nanotechnology Characterization Laboratory (NCL), which would work in concert with the NIST and the FDA to perform and standardize the preclinical characterization of nanoscale devices in a way that will facilitate the accelerated regulatory review and translation of these devices into the clinical realm.

The NCL, which will be operated under a contract with SAIC-Frederick, will have the following goals:

- Standardize the preclinical testing and characterization of nanoscale devices to speed the regulatory review of novel diagnostics, therapeutics, and prevention strategies that use nanoscale devices.
- Perform preclinical toxicology, pharmacology, and efficacy testing of nanoscale devices created by both NCI intramural and extramural efforts as well as the private sector.
- Facilitate collaborations between the NCI, academia, and the private sector to accelerate the translation of basic nanotechnology research into clinical advances.
- Serve as a nexus for multidisciplinary research, development, and clinical applications of nanotechnology; provide resources, knowledge, tools, and methods for intramural and extramural cancer researchers.
- Collaborate with other government agencies to leverage resources and expertise in pursuit of common goals in the acceleration of the use of nanotechnology for critical national applications, and team with industry to bring those applications to market.

A key activity of the NCL will be to work together with FDA scientists to develop an assay cascade that can serve as the standard protocol for preclinical toxicology, pharmacology, and efficacy testing of nanoscale devices. This assay cascade will characterize a nanoscale device's physical attributes, its *in vitro* biological properties, and its *in vivo* compatibility.

In carrying out these functions, the NCL will provide a comprehensive set of baseline characterization parameters that will enable cancer biologists, drug and diagnostic developers, and clinical oncologists to concentrate on what they do best—applying these tools to solving problems that most affect cancer patients. This work will also lay a scientific foundation that will enable the FDA to make sound decisions concerning testing and approval of nanoscale cancer diagnostics, imaging agents, and therapeutics.

From its discussions with experts in academia and the private sector, the NCI believes that the NCL's activities will markedly speed the development of nanotechnology-based products for cancer patients, reduce the risk of doing so, and encourage private-sector investment in this promising area of technology development. By taking on this role, the NCL will greatly accelerate the development of the paradigm-changing advances needed to meet the goal of eliminating suffering and death from cancer by 2015.

Interfacing With the Cancer Research Community

A central goal of the NCL is to leverage the existing resources in science and technology which are needed to accelerate the translation of basic research into clinical advances, whether in the public or the private sector. Substantial investments have been made and continue to be made in nanoscience and nanotechnology:

- Through funding from the National Nanotechnology Initiative to support fundamental and applied research, the establishment of multidisciplinary centers of excellence, and the development of infrastructure,
- Through NCI-funded intramural and extramural projects, such as those funded by the Unconventional Innovations Programs (UIP), to support development of novel technologies for noninvasive detection, diagnosis, and treatment of cancer,

- Through other government agency investment, such as the Nanomedicine Roadmap Initiative at NIH to understand molecular pathways and networks and to use that knowledge to design and develop new technologies and devices to improve human health, and
- Through private investment across industry, but primarily through the increasing investment in small businesses to bring new nanomaterials and nanotechnology products to market.

There has also been large investment in technology areas that are critical to the rapid development and application of nanotechnology, such as:

- Investments in microfluidics, MEMS, biotechnology, and bioinformatics, and
- Development of new and advanced measurement technologies and devices, such as the atomic force microscope and MALDI-TOF spectroscopy, which are capable of providing measurements with unprecedented detail and precision.

The new Advanced Measurement Laboratory at NIST, created to respond to the need for advanced measurement methods and standardization in research and development, is another example of the type of facilities that can be leveraged to achieve the NCI's 2015 Challenge Goal.

In order to accelerate the transition of nanotechnology to clinical applications, the NCL must also work closely with regulatory bodies, primarily the FDA, in providing a much closer relationship with industry throughout the pre-clinical tests and clinical trials. The mechanism for this enhanced relationship is already in place in the NCI/FDA Oncology Task Force, an interagency agreement between NCI and FDA to share knowledge and resources to facilitate the development of new cancer drugs and speed their delivery to patients. The NCL can play a significant role in accelerating the transition of nanomaterials and nanodevices to aid in delivering and targeting new cancer drugs as well as contrast agents and reporters to aid in cancer detection and diagnosis.

This relationship with the FDA is crucial in the NCL's interaction with industry. Industry presently assumes significant risk in nanoparticles R&D for clinical applications; the regulatory guidelines are presently undefined. A standardized assay cascade, developed in collaboration with the FDA, will "incentivize" industry to submit nanomaterials to the NCL for characterization, thereby reducing the high risks associated with regulatory approval.

The lack of knowledge concerning the health and safety of nanomaterials may also become an obstacle to the rapid implementation of nanotechnology. Although industry has long manufactured fine and ultra-fine particles for use in a variety of applications, the effects of those particles on human health has been studied only for a small number of materials and applications. In addition, the waste streams generated by the manufacturing and assembly processes for nanomaterials and by their disposal have generally not been subjected to detailed examination and analysis. The assay cascades developed by the NCL to characterize the effect of nanomaterials and platforms in *in vitro* and *in vivo* tests can also provide standardized measures of the effect of these materials, devices, and waste products on human safety—especially the carcinogenic properties of nanomaterials. This additional NCL service will require close collaboration with nanotechnology research institutions and product developers and manufacturers to develop the appropriate standard assays and protocols in response to this public need.

It is precisely this sharp focus on the many facets of cancer research that enables the NCL to serve as a nexus for trans-disciplinary research, development, and clinical applications of nanotechnology. The NCL seeks to provide resources, knowledge, tools, and methods for cancer researchers. It does not seek to duplicate the efforts of established and emerging programs by academia, industry, or government in nanotechnology or to intrude on the domain of other programs. Rather it seeks to partner with these programs. To this end the NCL will collaborate wherever possible with other government agencies, academia, and industry to leverage their resources and expertise in pursuit of common goals and to accelerate the use of nanotechnology in critical national applications to cancer.

Scientific Foundations for the Cancer Nanotechnology Plan

What Is Nanotechnology?

Nanotechnology refers to the interactions of cellular and molecular components and engineered materials—typically clusters of atoms, molecules, and molecular fragments—at the most elemental level of biology. Such nanoscale objects—typically, though not exclusively, with dimensions smaller than 100 nanometers—can be useful by themselves or as part of larger devices containing multiple nanoscale objects. At the nanoscale, the physical, chemical, and biological properties of materials differ fundamentally and often unexpectedly from those of the corresponding bulk material because the quantum mechanical properties of atomic interactions are influenced by material variations on the nanometer scale.

Nanoscale devices and nanoscale components of larger devices are of the same size as biological entities. They are smaller than human cells (10,000 to 20,000 nanometers in diameter) and organelles and similar in size to large biological macromolecules such as enzymes and receptors—hemoglobin, for example, is approximately 5 nanometers in diameter, while the lipid bilayer surrounding cells is on the order of 6 nanometers thick. Nanoscale devices smaller than 50 nanometers can easily enter most cells, while those smaller than 20 nanometers can transit out of blood vessels, offering the possibility that nanoscale devices will be able to penetrate biological barriers such as the blood-brain barrier or the stomach epithelium that can make it difficult for therapeutic and imaging agents to reach certain tumors. And because of their size, nanoscale devices can readily interact with biomolecules on both the cell surface and within the cell, often in ways that do not alter the behavior and biochemical properties of those molecules.

Such ready, noninvasive access to the interior of a living cell affords the opportunity for unprecedented gains on both the clinical and basic research frontiers. The ability to simultaneously interact with multiple critical proteins and nucleic acids at their own molecular scales should provide the data needed to better understand the complex regulatory and signaling networks that govern the behavior of cells in their normal state and as they undergo the changes that transform them into malignant cells. In particular, nanotechnology will provide an important platform for integrating efforts in proteomics with other scientific investigations into the molecular nature of cancer. Similarly, nanoscale devices are already proving that they can deliver therapeutic agents that can act where they are likely to be most effective, that is, within the cell or even within specific organelles. Yet despite their small size, nanoscale devices can also hold tens of thousands of small molecules, such as an MRI contrast agent or a multicomponent diagnostic system capable of assaying a cell's metabolic state, creating the opportunity for unmatched detection sensitivity of cancer in its earliest stages.

In some instances, nanotechnology will take advantage of years of clinically relevant technological developments at larger scales. A good example of this approach will capitalize on existing “lab-on-a-chip” and microarray technologies developed at the micron scale. Widely used in biomedical research and clinical diagnostic applications today, these technologies will find new uses when shrunk to the nanoscale. There, they will be able to interact with an individual cell in real time and in that cell's native environment. The CNPlan, with its targeted approach to development, will take advantage of such synergies through several projects directed toward developing real-time diagnostics, reporter systems, and new tools for studying cancer cell and molecular biology.

Current Progress in Cancer Nanotechnology

Today, clinical, cancer-related nanotechnology research is proceeding on two main fronts: laboratory-based diagnostics and *in vivo* diagnostics imaging and therapeutics. Here are just a few of the illustrative highlights of progress in these areas, as well as with the use of nanotechnology to extend our understanding of cancer cellular and molecular biology.

Nanotechnology and Molecular Imaging

- 1-2 nanometer-wide wires built on a micron-scale silicon grid can be coated with monoclonal antibodies directed against various tumor markers, leading to a hundredfold increase in sensitivity over current diagnostic techniques with minimal sample preparation.
- Nanoscale “lab-on-a-chip” applications are now capable of conducting real-time analysis of single biochemical markers.
- Quantum dots have been used to tag and follow multiple individual molecules within cells, providing an opportunity to study the biochemical and genetic systems that go awry in cancer.
- Nanoscale “harvesting” devices have collected proteins capable of distinguishing cancerous tissue from normal tissue.

Nanotechnology and *In Vivo* Imaging

- Nanoscale MRI contrast agents, containing paramagnetic iron nanoparticles, dramatically improve the ability to detect metastatic lesions in lymph nodes associated with breast and prostate cancer.
- Gold nanoparticles demonstrate usefulness contrast agents for *in vivo* endoscopic optical imaging of specific molecular cancer markers.
- Gas-filled lipid nanoparticles have shown promise for use as acoustically activated imaging agents, and perhaps targeted drug delivery systems, for tumors with a spatial resolution of 0.5 to 1.0 millimeters and a temporal timeframe of several images per second.
- Her-2 conjugated, gold-coated nanoparticles with a dielectric silicon core can identify breast carcinoma cells *in vivo*. Once bound to their target cells, these nanoparticles were subjected to increased optical power, turning them into nanoscale thermal scalpels that attain cell-killing temperatures.

Nanotechnology and Cancer Therapy

- A wide variety of synthetic nanoscale particles are shown to target tumor cells, enter cancer cells, and release therapeutic agents.
- Engineered virus particles can serve as multifunctional, targeted non-immunogenic nanoscale devices with potential for a broad range of *in vivo* uses.
- Photosensitizers used in photodynamic therapy, in which light is used to generate reactive oxygen locally within tumors, have also been entrapped in targeted nanoscale devices. The next step in this work is to also entrap a light-generating system, such as the luciferin-luciferase pair, in such a way as to trigger light production only after the nanoparticles have been taken up by a targeted cell. If successful, such an approach would greatly extend the usefulness of photodynamic therapy to include treatment of tumors deep within the body.

Nanotechnology as a Research Enabler

- Construction and testing of nanoplatforms can consolidate cell biology lab tests on a chip. These nanoplatforms can be constructed to accurately mimic the microenvironment in which a particular cell normally grows, producing a system capable of both perturbing cells and recording their responses in a manner more representative of how those cells would behave in the body than is observed in cells grown in standard tissue culture systems.
- A nanoscale device analyzes genome complexity and shows that early-stage tumors expressing similar phenotypes can be distinguished on the basis of how each tumor selects a slightly different approach to derange its genome.

Opportunities From the Fundamental Understanding of Cancer Processes

Nanotechnology offers a wide range of tools, from chip-based nanolabs capable of monitoring and manipulating individual cells to nanoscale probes that can track the movements of cells, and even individual molecules, as they move about in their environment. Using such tools will enable cancer biologists to study, monitor, and alter the multiple systems that go awry in the cancer process and identify key biochemical and genetic “choke points” at which the coming wave of molecular therapies might best be directed. As such,

nanotechnology can serve as the perfect complement to other technology platforms, such as proteomics and bioinformatics, that the NCI is emphasizing in its research initiatives as critical components of the discovery and development engine that will power both near-term and long-term advances in cancer diagnosis, treatment, and prevention. More importantly, however, nanotechnology will serve as a versatile development platform that will be able to quickly turn biological insights into clinically useful products.

Thirty years ago, cancer was a poorly understood and usually deadly disease. This is no longer the case. Today, we know that a cell becomes malignant as a result of changes to its genetic material and that accompanying biological characteristics of the cell also change over a progression of steps that can take years to reach the stage at which a cell becomes malignant and develops into a tumor. These changes are unique molecular “signatures” and serve as signals of the presence of cancer and of the cellular states that precede cancer. This more robust understanding of the genetic alterations that occur within a cancer cell has changed the course of cancer research and has fueled new approaches to prevention, detection, diagnosis, and treatment. One goal of the CNPlan is to foster the development of nanoscale devices that can identify the early molecular signatures of cancer and deliver therapeutic or preventive agents that can intervene in the cancer process at this early stage.

However, the cancer cell is only part of the story in cancer development. As a cancer cell grows within the elaborate architecture of the body’s tissues and organs, it interacts with its surrounding environment. Mounting evidence now suggests that a dynamic interaction occurs between the cancer cell and its local and systemic microenvironment, with each profoundly influencing the behavior of the other. This “tumor microenvironment” is populated with a variety of different cell types, is rich in growth factors and enzymes, and includes parts of the blood and lymphatic systems. It promotes some of the most destructive characteristics of cancer cells and permits the tumor to grow and spread. Nanoscale devices, because of their designed multifunctionality, offer the opportunity to manage this complex interaction in ways that could stop the growth and spread of cancer.

The microenvironment can also influence the access of therapeutic agents to tumor cells, the body’s processing of treatment agents, and the development of resistance to cancer treatments. Again, these are problems that nanoscale devices should be able to address. Although the cells in the microenvironment may not be genetically altered, their behavior can be changed through interactions with tumor cells. Physicians now realize that they confront a tumor entity that consists of malignant cells combined with their host tumor environment when treating a cancer patient. The tumor cells and their surrounding environment both need to be fully characterized to understand how cancer grows in the body, and both need to be considered when developing new interventions to fight it.

We now understand that cancer is the culmination of many biochemical and genetic processes going awry in the malignant cell and its microenvironment and that no one change will cause a cell to become cancerous. Thus, we now view cancer as a “systems” disease, one that involves the interactions of many cellular processes. The changes that affect these processes fall into seven broad categories, which can be characterized as follows:

Cancer Cells Attain Self-Sufficiency in Growth Signals

Cells grow and multiply in response to a wide variety of growth signals that trigger a series of orchestrated biochemical and genetic events. The production of these growth signals is tightly controlled in a normal cellular environment, but malignant cells have developed numerous ways of either producing their own growth signals or short-circuiting the control mechanisms associated with these growth signals. Many of the oncogenes discovered to date give cancer cells the ability to mimic normal growth signaling processes. Because of the multifactor nature of growth factor activity, it may be necessary to deliver several molecularly targeted agents to a tumor to control its growth, a task for which multifunctional nanoscale devices are ideally suited.

Cancer Cells Become Insensitive to Antigrowth Signals

The normal cellular environment also provides multiple antigrowth signals that act as a check to unregulated cellular reproduction. These growth-controlling signals come mainly from neighboring cells and the extracellular matrix, and they too trigger a series of orchestrated biochemical and genetic events that regulate the cell cycle. Our current understanding of these systems suggests that these signals come through three closely related receptors on the cell surface and that cancer cells are able to disrupt these receptors or the systems that these receptors control. Again, the multifunctional nature of nanoscale devices offers the potential for interacting with more than one of these receptors simultaneously.

Cancer Cells Escape Apoptosis

A third mechanism for regulating improper cell growth involves apoptosis, a set of programmed cellular processes that result in cell death. It is clear from a variety of studies that cancer cells acquire the ability to avoid apoptosis and that effective cancer therapies are able to trigger reactive apoptosis in malignant cells. A cell's apoptotic machinery consists of sensors that monitor the internal and external state of a cell and its environment and effectors that trigger apoptosis when the sensors detect abnormal conditions. The loss of the p53 protein, characteristic of over half of all cancers, allows cells to avoid apoptosis. It appears, however, that cancer cells with damaged apoptotic systems may possess redundant, though inactive, mechanisms for triggering apoptosis. Nanoscale devices will be critical to detecting the reappearance of apoptosis as a sign that cancer therapy is working.

Cancer Cells Gain Limitless Potential for Replication

Telomeres, a stretch of repeat sequences located at the ends of chromosomes, represent a fourth mechanism for controlling the unlimited cellular growth that characterizes cancer. Each time a cell reproduces normally, its chromosomes fail to fully replicate the telomeres, and when the telomeres reach a defined, shortened length, the chromosomes begin to fuse, triggering apoptosis. Thus, telomeres act as a "reproduction counter" that limits a cell's potential for immortality. Some 85 to 90 percent of all cancer cells develop the ability to turn on expression of telomerase, an enzyme that can maintain normal telomere length and that is strongly suppressed in almost all normal cells. The remaining 10 to 15 percent develop a mechanism that maintains telomere length through chromosome-to-chromosome sequence exchange. Nanoparticles, because of their ability to deliver substances to specific cells, and perhaps compartments within a cell, may be the technological platform needed for therapeutic and preventive agents that would intervene in this process.

Cancer Cells Trigger Sustained Angiogenesis

All solid tumors develop the ability to trigger angiogenesis in order to provide oxygen and nutrients. Incipient tumors do not immediately trigger angiogenesis, but at some point tumors are able to alter the balance between angiogenic and antiangiogenic factors in favor of capillary growth in a multi-step process that can be reversed. Recent work with mouse models has shown that different antiangiogenic factors are effective at turning off angiogenesis and starving tumors at specific stages of the angiogenesis and tumor growth. It is also clear that different types of tumor cells use distinct molecular strategies to trigger angiogenesis. Nanoscale devices capable of imaging angiogenesis could provide a new early detection technology; multifunctional nanoscale devices will be able to deliver multiple angiogenesis inhibitors simultaneously.

Cancer Cells Metastasize and Invade Other Tissues

Approximately 90 percent of all cancer deaths result from metastatic spread of the primary tumor. At some point in their development, some number of malignant cells develop an ability to dissociate themselves from the primary tumor mass, invade adjacent tissues, and spread to sites throughout the body. It is clear that invasion and metastatic spread result from a complex series of biochemical and genetic events that affect numerous systems, both in the metastatic cell and in the tissues that it invades. Though most of these events are still poorly characterized, recent work has established that the molecular systems involved in maintaining the normal contact between neighboring cells become altered prior to metastasis. In addition, metastatic cells turn on the expression of proteases capable of degrading the extracellular matrix. Nanoscale analytical devices may be able to detect the early molecular signatures of metastasis before secondary tumors are detectable by other means.

Cancer Cell Genomes Become Unstable

There is little doubt that most of the six molecular characteristics of cancer cells listed above result from genetic changes in a cancer cell, but acquiring multiple mutations through random processes is unlikely given the enormous effort that cells put into maintaining the integrity of their genomes. Yet, cancer cells do accumulate the necessary mutations needed to change from normal to pre-malignant to malignant, suggesting that cancer cells must also have genomes that are unnaturally unstable; indeed, recent research has shown that malignant cells do have grossly rearranged genomes, including multiple copies of specific chromosomes. Furthermore, this research has shown that cells can acquire one or more of the above traits, but they will not become cancerous until their genomes exhibit such instability. Already, nanoscale devices are being developed that can detect genetic mutation and genome instability.

Toxicology and Environmental Issues

Some of the unanswered questions concerning nanoscale devices relate to their potential toxicity or their fate in the environment, neither of which has yet to be studied in any concerted manner. To date, the few published studies in these areas have concentrated on the potential toxicity of inhaled nanoscale particles, specifically various forms of C60, including “buckyballs” and single-walled carbon nanotubes. That such nanoparticles, when inhaled, might have the potential to damage lung tissue is no surprise given the well-documented hazardous nature of nanoscale diesel exhaust particles. However, such particles are not currently envisioned as having use in the clinical setting. Nevertheless, these studies reinforce the recognized need to conduct thorough toxicology studies on nanoscale devices. Of course, given that any material envisioned for use in humans must undergo rigorous toxicology studies as part of the regulatory approval process, this requirement is neither unexpected nor onerous.

To help address such safety issues, the NCI plans several approaches to supplement the standard complement of toxicology studies that the private sector or any public-private partnerships will conduct as part of the preclinical development process. Under the aegis of the CNPlan, the NCL, in close collaboration with the FDA, will develop a battery of toxicology and safety tests as part of its assay cascade. The NCL will then make these assays available to the field at large as well as use them to develop baseline toxicology data for a wide range of nanoscale particles and devices. The NCI will be evaluating future collaborations and partnerships with the National Toxicology Program and the National Institute of Environmental Health Sciences for these important areas of science.

The CNPlan and 2015

The NCI's CNPlan dovetails perfectly with the Institute's Action Plan for 2005 and various initiatives aimed at meeting the Challenge Goal of eliminating suffering and death due to cancer by 2015. In particular, the CNPlan stresses work that strengthens the Institute's core multidisciplinary scientific areas of emphasis, including:

- Elucidating the *Signatures of the Cancer Cell and Its Microenvironment*
- Validating and developing effective agents aimed at *Molecular Targets of Prevention, Diagnosis, and Treatment*
- Optimizing *Cancer Imaging and Molecular Sensing* technologies

The CNPlan's heavy emphasis on development and delivery are consistent with goals that the NCI has laid out in its Plan and Budget Proposal for FY 2005. In addition, the CNPlan's activities fit with the Institute's high-profile initiatives in developing new platforms for and enablers of discovery, development, and delivery.

The CNPlan's use of novel, team-oriented funding mechanisms will continue the NCI's work on building capacity through large-scale collaborations. These funding mechanisms also build on efforts to increase translational research involving public-private partnerships.

Appendix A: Training and Cross-Disciplinary Collaboration

One important challenge to reaching the goals of the CNPlan involves bridging the gulf between those who are experts in nanotechnology and those who possess the vision and knowledge to apply this technology to the task of eliminating suffering and death due to cancer. To develop a well-trained cadre of cancer researchers who can bring nanotechnology to the fight against cancer, the NCI anticipates taking a multi-pronged approach. Current, technologically nonspecific funding mechanisms exist that would facilitate building a cancer nanotechnology research program. These can be viewed in terms of immediate impact and future impact. The mechanisms are broken down into categories based on their anticipated effect on the field of cancer nanotechnology.

Immediate Impact Mechanisms

In the short term, the NCI must bring together nanotechnology specialists and cancer specialists for the exchange of ideas, focused educational opportunities, and short-term training and mentoring. Possible mechanisms for accomplishing this goal include:

F33 Awards

- *F33 NIH National Research Service Awards for Senior Fellows.* “(T)he National Institutes of Health (NIH) awards NRSA senior fellowships (F33) to experienced scientists who wish to make major changes in the direction of their research careers or who wish to broaden their scientific background by acquiring new research capabilities. These awards will enable individuals with at least seven years of research experience beyond the doctorate, and who have progressed to the stage of independent investigator, to take time from regular professional responsibilities for the purpose of receiving training to increase their scientific capabilities. In most cases, this award is used to support sabbatical experiences for established independent scientists.”

This mechanism would allow current established cancer investigators to train in the labs of leading nanotechnologists to facilitate bringing the technology back to their own labs to be applied toward future research activities. Alternatively, nanotechnologists could be funded to spend a year gaining insight into cancer research so that these problems could be addressed when returning to the nanotechnologist's lab. In both cases, the spillover of ideas from the trainee to the mentor's lab will continue to cross-pollinate the cancer and nanotechnology fields.

K05 Awards

- *K05 Established Investigator Award in Cancer Prevention, Control, Behavioral, and Population Sciences.* “The purpose of the NCI Established Investigator Award in Cancer Prevention, Control, Behavioral and Population Research (K05) is to provide established investigators protected time to devote to research and to act as mentors for new investigators and junior faculty members. The target candidates are outstanding established scientists who have demonstrated a sustained, high level of research productivity and significant contributions to cancer prevention, control, behavioral and/or population cancer research. They must demonstrate the need to develop and enhance their own research and a commitment to serve as mentors to new scientists.”

This mechanism can be used by established scientists to free themselves of some administrative responsibilities so that they may mentor recipients of training and career awards in cancer nanotechnology.

R25 Awards

- *R25E Cancer Education Grant Program.* “The Cancer Education Grant Program (CEGP) of the National Cancer Institute is a flexible, curriculum-driven program aimed at developing and sustaining innovative educational approaches that ultimately will have an impact on reducing cancer incidence,

mortality and morbidity, as well as on improving the quality of life of cancer patients. The CEGP invites investigator-initiated R25 Grant applications that pursue a wide range of objectives from short courses, national forums, seminars, and/or hands-on workshops designed to educate scientists, health care professionals and the lay community; to the design, development and evaluation of new curricula of special significance to cancer in educational institutions; to structured short-term didactic and research experiences designed to motivate high school; college; and medical, dental and other health professional students to pursue careers in cancer research; to the development and evaluation of new educational methods and tools directed at different audiences with the intent of having an impact on reducing cancer incidence and mortality. The R25 can also be used to fund symposia and support rapidly evolving areas (e.g., courses in innovative screening).

Education Grants such as the R25 can focus on education activities before, during and after the completion of a doctoral level degree (e.g., Ph.D., M.D., D.P.H., D.D.S., and D.N.S.) as long as they address a need that is not fulfilled adequately by any other grant mechanism available at the National Institutes of Health and are dedicated to areas of particular concern to the National Cancer Institute. The CEGP encourages innovative uses of the R25 grant to explore educational approaches that will help promote progress in preventing and curing cancer.”

This mechanism can be an integral part of the ability to rapidly adjust to changes in science technology. Nanotechnology workshops, short-term courses, training seminars, and so forth can be developed and funded through this mechanism to quickly bridge the gap and bring nanotechnology to cancer research.

Future Impact Mechanisms

The core of the future cancer nanotechnology cadre will be based not on current established investigators who have adopted a new technology or a new application for their technology but on those who have extensive training in both nanotechnology and cancer research. This core will come from those postdoctoral fellows and junior investigators who, over a 3- to 5-year period, train extensively outside their discipline. Ultimately, the field of cancer nanotechnology will be populated by scientists who have received training that has integrated nanotechnology into the research curriculum. The development of these curricula and the implementation and evaluation of these programs will take time but result in cancer researchers who are as versant in nanotechnology as they are in molecular biology, imaging, or any other technology.

K25 Awards

- *K25 Mentored Quantitative Research Career Development Award.* “The K25 mechanism is meant to attract to NIH-relevant research those investigators whose quantitative science and engineering research has thus far not been focused primarily on questions of health and disease. Examples of quantitative scientific and technical backgrounds considered appropriate for this award include, but are not limited to: mathematics, statistics, economics, computer science, imaging science, informatics, physics, chemistry, and engineering. This award provides support for a period of supervised study and research for productive professionals with quantitative backgrounds who have the potential to integrate their expertise with NIH-relevant research and develop into productive investigators. It is intended for research-oriented investigators from the postdoctoral level to the level of senior faculty.”

This mechanism is already bringing in scientists with quantitative and engineering backgrounds to apply different technologies and backgrounds to cancer research. Although certain areas were specifically mentioned, nanotechnology was not. We have begun to specifically mention nanotechnology in these announcements to attract this group to cancer research. This mechanism, in conjunction with mechanisms facilitating mentoring opportunities can, within 5 years, bring about a small cadre of nanotechnology-based, independent cancer researchers.

K01 Awards

- ***K01 Howard Temin Award.*** “The goal of the National Cancer Institute’s (NCI) Howard Temin Award is to bridge the transition from a mentored research environment to an independent basic cancer research career for scientists who have demonstrated unusually high potential during their initial stages of training and development. This special award is aimed at fostering the research careers of outstanding junior scientists in basic research who are committed to developing research programs directly relevant to the understanding of human biology and human disease as it relates to the etiology, pathogenesis, prevention, diagnosis, and treatment of human cancer. The major objective of the award is to sustain and advance the early research careers of the most promising M.D.s and Ph.D.s while they consolidate and focus their independent research programs and obtain their own research grant support. To achieve this objective, the Howard Temin Award offers candidates up to five years to gain additional skills and knowledge in human cancer research during a period of one to three years in a mentored environment, followed by transition to the equivalent of a junior faculty position to develop an independent research program.”

The Temin Award offers the opportunity for junior scientists, on the cusp of independence, to receive 1 to 3 years of mentoring before setting out as independent investigators. The 1- to 3-year mentoring period is well suited to applying a new technology to a cancer project. These grants, along with the K25, have the ability to build a cadre of young cancer nanotechnologists who can become the nuclei of cancer nanotechnology programs.

K07 Awards

- ***K07 Cancer Prevention, Control, Behavioral and Population Sciences Career Development Award.*** “The purpose of the Cancer Prevention, Control, Behavioral and Population Sciences Career Development Award (K07) is to support the career development of investigators who have made a commitment to focus their research endeavors on cancer prevention, control, behavioral and the population sciences. This is achieved by providing protected time through salary and research support for up to 5 years to individuals with a health professional or science doctoral degree who are 1) already proficient in general epidemiology, behavioral sciences, or other relevant disciplines, and now want to make use of these proficiencies in cancer-focused research careers in prevention, control, population and/or the behavioral sciences, or 2) already trained in cancer epidemiology, etiology, prevention, control and the behavioral and population sciences but are not yet fully independent investigators. Examples of relevant disciplines for this Program Announcement (PA) include any aspect of human cancer prevention (modifiable risk factors, new animal models and extrapolation of these models to human cancer, genetic predisposition to cancer and detection of precursor lesions, patient-oriented research focused on cancer prevention, and behavioral research and behavioral intervention trials in cancer prevention), epidemiology (biochemical, genetic, molecular), biostatistics, human cancer genetics, clinical oncology, human nutrition, behavioral and social sciences, health promotion, health services and health policy research; and medical decision analysis, survivorship and quality of life as they relate to cancer.”

The K07 is a mentored award designed for researchers in the area of prevention, control, behavioral, and population sciences. K07 recipients often progress to the K22 Transition Career Development Award as they begin their independent research career.

K08 Awards

- ***K08 Mentored Clinical Scientist Development Award.*** “The purpose of the Mentored Clinical Scientist Development Award (K08) is to support the development of outstanding clinician research scientists. This mechanism provides specialized study for individuals with a health professional doctoral degree committed to a career in laboratory or field-based research. Candidates must have the potential to develop into independent investigators. The K08 supports a three, four, or five year period of supervised research experience that may integrate didactic studies with laboratory or clinically based research. The proposed research must have intrinsic research importance as well as serving as a suitable vehicle for learning the methodology, theories, and conceptualizations necessary for a well trained independent researcher.”

The K08 mechanism provides a postdoctoral experience for clinically degreed individuals. It is anticipated that this mechanism will be used in a similar manner as the F32 with the added possibility that research produced under the K08 mechanism may have an increased capacity to be translated into the clinic due to the clinical degrees of the applicants. Many K08 recipients progress to the K22 mechanism as they transition to independence.

K22 Awards

- ***K22 NCI Transition Career Development Award.*** “This K22 award is intended to facilitate the transition of investigators from the mentored to the independent stage of their careers in cancer research, by providing ‘protected time’ for newly independent investigators to develop and receive support for their initial cancer research programs. The award applies to clinicians who are pursuing basic science careers; clinicians who are pursuing careers in patient-oriented research; and to individuals pursuing careers in the prevention, control and population sciences. To apply, a candidate must have completed two years of postdoctoral, mentored research or have been in an independent position for less than two years at the time the application is submitted. The unique feature of this award is that individuals may apply without a sponsoring institution while they are still in a ‘mentored’ position. Successful postdoctoral applicants will be given up to 12 months to identify an independent, preferably tenure-track, position at a sponsoring institution before an award can be activated. For postdoctoral applicants, the sponsoring institution for a K22 award can be their current institution or a new institution.”

As our career awardees develop and are ready to achieve independence, it will be critical to provide them with the protected time to establish their own labs and with the preliminary data required to successfully compete for research grants. The K22 award is designed to bridge the time between mentored status and independently funded investigator.

R25T, K12, and T32 Awards

- ***R25T Cancer Education and Career Development Program.*** “The purpose of NCI Cancer Education and Career Development Program (R25) is to train predoctoral and postdoctoral candidates in cancer research settings that are highly interdisciplinary and collaborative. This Program requires sustained leadership, dedicated faculty time, specialized curriculum development and implementation, interdisciplinary research environments, and more than one mentor per trainee to achieve career development research and education objectives. Areas of research particularly applicable but not all inclusive to interdisciplinary training are cancer prevention and control, nutrition, population sciences, behavioral sciences, imaging and molecular diagnostics.”
- ***K12 Institutional Clinical Oncology Research Career Development Program.*** “The purpose of the National Cancer Institute (NCI) Institutional Clinical Oncology Career Development Program is to increase the number of medical doctors and doctorally degreed Oncology Registered Nurses who are motivated and properly trained to: (1) communicate and collaborate with basic/behavioral research scientists in order to expedite the translation of basic/behavioral research information into patient-oriented cancer research; (2) perform independent clinical oncology research that develops and tests rational scientific hypotheses based on fundamental and clinical research findings with the potential for improving the medical care of cancer patients; and (3) design and test innovative clinical protocols and manage all phases (i.e., pilot/Phase I, Phase II, and Phase III) of clinical trials research. To achieve this purpose, awards are made to institutions for up to five years for the development and implementation of training programs providing clinicians with all of the necessary information and training that will enable them to design, implement and manage all phases of cancer clinical trials research. The distinguishing features of this career development Program are that a Program Leader in the institution together with an Advisory Committee selects the candidates and oversees the course of their training, and that candidates are likely to have more than one mentor as they are exposed to the basic sciences and to the many disciplines critical to the clinical sciences.”

- **T32 NIH National Research Service Award Institutional Research Training Grants.** “The National Institutes of Health (NIH) will award National Research Service Award (NRSA) Institutional Training Grants (T32) to eligible institutions to develop or enhance research training opportunities for individuals, selected by the institution, who are training for careers in specified areas of biomedical, behavioral, and clinical research. The purpose of the NRSA program is to help ensure that a diverse and highly trained workforce is available to assume leadership roles related to the Nation’s biomedical and behavioral research agenda. Accordingly, the NRSA program supports predoctoral, postdoctoral, and short-term research training experiences.”

All three mechanisms are designed to create a training environment within the institutions. Through these mechanisms, cancer nanotechnology training programs can be created in basic research (T32), prevention, control, behavioral, and population sciences (including screening, diagnostic, and imaging) (R25T) and, as the field matures and products are ready to enter the clinic, clinical oncology (K12).

F32 Awards

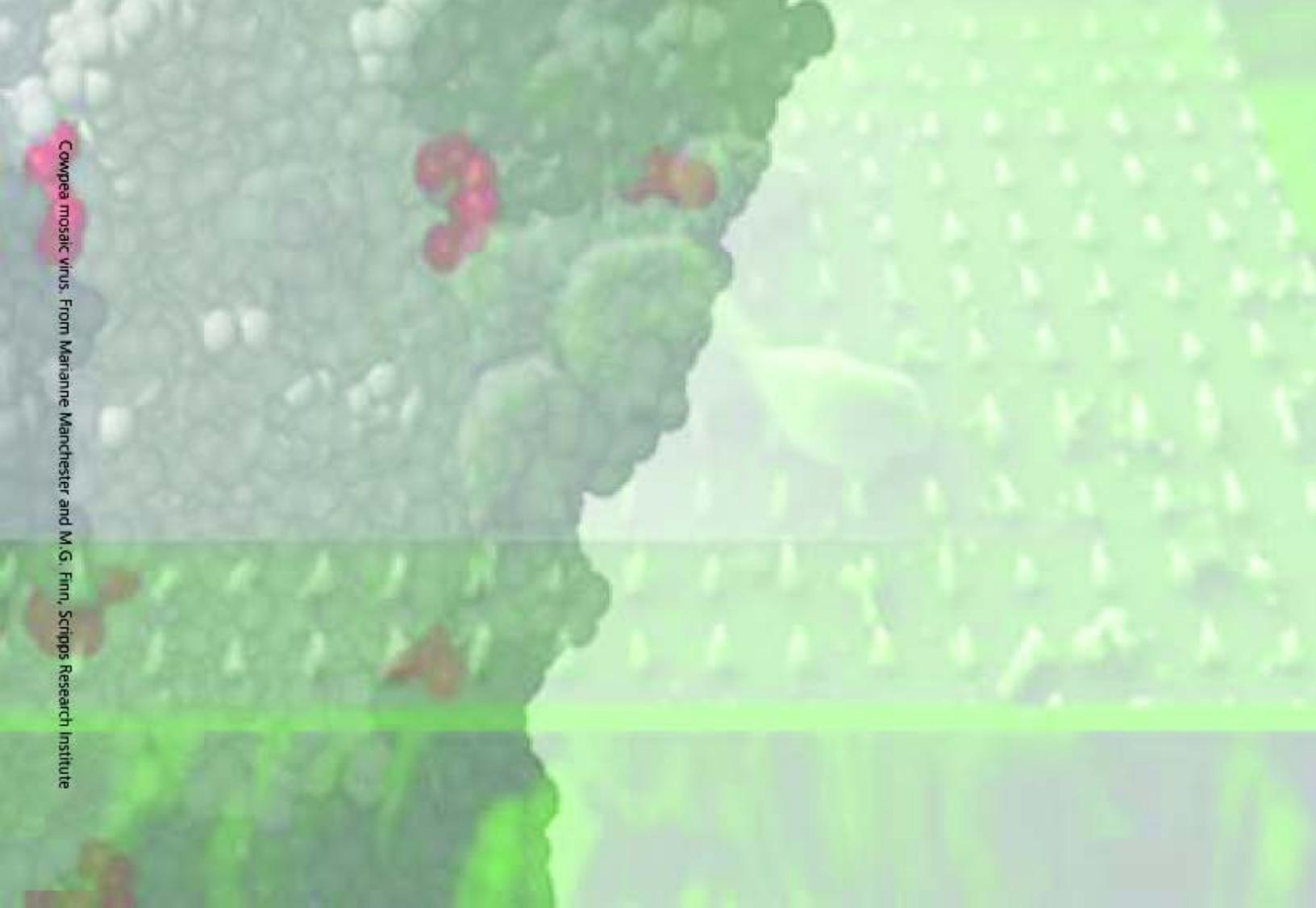
- **F32 Ruth L. Kirschstein National Research Service Awards for Individual Postdoctoral Fellows.** “The Congress of the United States enacted the National Research Service Award (NRSA) Program in 1974 to help ensure that highly trained scientists will be available in adequate numbers and in appropriate research areas to carry out the Nation’s biomedical and behavioral research agenda. Under this congressional authority, the National Institutes of Health (NIH) awards NRSA individual postdoctoral fellowships (F32) to promising applicants with the potential to become productive, independent investigators in fields related to the mission of the NIH constituent institutes and centers.”

This is the basic postdoctoral funding mechanism and will undoubtedly provide the bulk of the future nanotechnology-focused cancer researchers. In the short term, it is anticipated that Ph.D.s with training in either cancer or technology will use the F32 to gain postdoctoral experience in the other discipline. Eventually, once a cadre of cancer nanotechnology researchers has been established, graduates will be able to obtain research experience specifically in cancer nanotechnology.

K23 and K24 Awards

- **K23 Mentored Patient-Oriented Research Career Development Award.** “The purpose of the Mentored Patient-oriented Research Career Development Award (K23) is to support the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research. This mechanism provides support for three to five years of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research.”
- **K24 Midcareer Investigator Award in Patient-Oriented Research.** “The purpose of the Midcareer Investigator Award in Patient-Oriented Research (K24) is to provide support for clinicians to allow them protected time to devote to patient-oriented research and to act as mentors for beginning clinical investigators. The target candidates are outstanding clinical scientists who are actively engaged in patient-oriented research. Candidates are generally within 15 years of their specialty training. Candidates must be able to demonstrate the need for a period of intensive research focus as a means of enhancing their clinical research careers and must be committed to mentoring the next generation of patient-oriented researchers. The award is intended to further both the research and mentoring endeavors of outstanding patient-oriented investigators, to enable them to expand their potential for significant contributions to their field, and to act as mentors for beginning clinician researchers.”

As the cancer nanotechnology field matures and products begin to make their way to the clinics, it will be important to develop cancer nanotechnology researchers who are involved in patient-oriented research. The K23 mechanism provides a mentored experience for patient-oriented researchers and the K24 provides the mentors with the protected time to do patient-oriented research and act as mentors for K23 fellows.



Cowpea mosaic virus. From Marianne Manchester and M.G. Finn, Scripps Research Institute



Printed July 2004

REQUEST FOR EC/BSA CONCEPT APPROVAL
REQUESTS FOR APPLICATIONS (RFAs)/CONTRACTS (RFPs)

Title: **The NCI Alliance for Nanotechnology in Cancer**

PA ___ RFA X⁽³⁾ Coop. Ag. X Activity Codes (e.g. R01) ___ RFP ___
F32, F33, R01, U54
New X Reissue___

Division: Division of Cancer Biology; Division of Cancer Prevention; Division of Cancer Treatment and Diagnosis; Division of Cancer Control and Population Sciences; Office of the Director

Program Coordinator: Greg Downing

Division Director: Anna Barker

Length of Award (Yrs.): 5 Source of Funds: RPG X Control ___ Centers X

Anticipated Award Date: **FY 2005** Other Res. ___ Construct. ___ NRSA

RFAs (Set Aside):

Amount of Set Aside 01 Year: \$16.2 million

Est. Number of Awards: F32: 15 F33: 15 R01: 12 U54: 3-5 (over five-year program period)

Est. Cost for Project Period: \$109.5 – 144.3 million

Justification for Use of RFA/RFP Mechanism:

Attached: X

Congressional Mandate:

Other:

I. Background

Nanotechnology and Cancer. Nanotechnology offers the unprecedented and paradigm-changing opportunity to study and interact with normal and cancer cells in real time, at the molecular and cellular scales, and during the earliest stages of the cancer process. Through the concerted development of nanoscale devices or devices with nanoscale materials and components, this initiative will facilitate their integration within the existing cancer research infrastructure. This initiative will bring enabling technologies for:

- Imaging agents and diagnostics that will allow clinicians to detect cancer in its earliest stages
- Systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents directly to cancer cells and those tissues in the microenvironment that play a critical role in the growth and metastasis of cancer
- Agents that can monitor predictive molecular changes and prevent precancerous cells from becoming malignant
- Novel methods to manage the symptoms of cancer that adversely impact quality of life
- Research tools that will enable rapid identification of new targets for clinical development and predict drug resistance

Conceptual Framework for the NCI Alliance for Nanotechnology in Cancer. Based on the strategies outlined in the NCI Cancer Nanotechnology Plan, the Alliance for Nanotechnology in Cancer (the Alliance) builds on the Institute's successes in building nanotechnologies and facilitates their integration into translational research. The Alliance supports the development of consortia of laboratories collectively identified as a "center" that consists of multidisciplinary teams of biological and physical scientists working together on specific projects that meet one of the 6 programmatic areas of emphasis. The centers will provide a nexus of interactions aimed at the assembly of components from materials sciences that with interface with biological systems that provide unique capabilities for conducting scientific explorations of the cancer cell at atomic level. Other components of the Alliance include individual investigator initiated projects and career development initiatives to accelerate the translation of nanotechnology platforms in clinical research. Collectively, these programs will facilitate the detailed examination and rigorous validation necessary to prepare promising agents and diagnostics for clinical trials. The ultimate goal of the Alliance is to benefit the cancer patient through the delivery of novel therapeutics and enhanced diagnostic tools.

The core elements of the Alliance for Nanotechnology in Cancer include:

- The establishment of **Centers for Cancer Nanotechnology Excellence** (CCNEs), which will serve as hubs to develop and apply nanotechnology solutions to the diagnosis, prevention, and treatment of cancer.
- Support the **career development** of investigators for multi-disciplinary nano-oncology research and,
- Individual **investigator-initiated projects** in nanotechnology development and applications.

An overview of the components, mechanisms, and budgets is shown below.

Proposed Mechanisms for NCI Alliance for Nanotechnology in Cancer		
<u>Individual Investigator Research Projects</u>	<u>Centers of Cancer Nanotechnology Excellence</u>	<u>Multidisciplinary Career Development</u>
<ul style="list-style-type: none"> Bioengineering Research Grants and Partnerships (BRGs and BRPs) (R01) 	<ul style="list-style-type: none"> Cooperative Agreement (U54) Each CCNE is a consortium of ~ 4 institutions/programs 3 – 5 CCNEs \$5 million/CCNE/year 	<ul style="list-style-type: none"> Postdoctoral Fellows (F32) – 15 fellows Senior Fellows (F33) – 15 fellows
Total: up to \$38M/5 years	Total: \$56–90.8M/5 years	Total: up to \$15.5M/3 years

II. RFAs for Components of the NCI Alliance for Nanotechnology in Cancer

As a collective, these RFAs will catalyze a research environment where a variety of trained researchers can use nanotechnology to solve mission-critical problems in cancer research. It is expected that these RFAs will spur and support the translational research and development that will provide advances in cancer diagnostics and therapy, in both the long and short terms.

The specific purpose of each of three RFAs is highlighted separately below.

A. *Centers for Cancer Nanotechnology Excellence (CCNEs)*

Purpose. The CCNEs are the core units of the science and technology programs supported by the Alliance. Each CCNE will function as a consortia or network of laboratories and research facilities organized to address one or more specific cancer nanotechnology platform needs. Each CCNE will be required to identify at least one of the following 6 programmatic areas of emphasis as its focus for technology platform development: molecular imaging/early detection, *in vivo* imaging, reporters of efficacy, multifunctional therapeutics, prevention and control, and research enablers. Within the context of the specific areas of emphasis identified, the CCNEs will offer the full range of support necessary to develop products suitable for clinical trial assessment, from fabrication and synthesis of nanomaterials, to combinatorial assembly of components (vectors, targeting agents, and biosensors) to pre-clinical testing with animal models. It is expected that each CCNE will undertake develop and prototype nanotechnology platforms, each with discrete milestones and a dedicated research team. Outcomes objectives (performance measures) for the CCNEs represent technologies that are developed and effectively utilized to overcome cancer processes.

Critical requirements for each CCNE include:

- Integration with a Comprehensive Cancer Center, SPORE program, or related NCI core programs
- Affiliation with university or research centers of engineering and physical sciences (e.g., mathematics, chemistry, physics, and material sciences)
- Nanomaterials fabrication and synthesis capabilities
- Facilities and expertise to support animal models and small animal imaging
- Advanced biocomputing capabilities
- Required existing not-for-profit/private technology development partnerships
- Well-developed modules for integrative training in key areas relevant to the enterprise (e.g., biomaterials, clinical applications of nanotechnology)
- Education programs to disseminate information to the clinical oncology community

- Technology assessment capabilities to identify and bring in new nanomaterials and nanotechnologies for cancer research

Program management will be conducted through a steering committee with representation from each CCNE representative and NCI program managers. The functions of the steering committee include:

- Prioritize projects (external to the CCNEs) for integration into the Alliance
- Promote access to and collaborations with fabrication/biosynthesis facilities
- Match appropriate technologies to individual Centers
- Assess the appropriate destinations/areas for export of technologies developed at the CCNEs
- Encourage input into development of common clinical trials protocols (i.e., endpoints, safety assessment, measurements of clinically relevant activity)
- Coordinate with the nanotechnology characterization laboratory for characterization of nanodevices and nanomaterials
- Establish interfaces with the clinical trials programs
- Establish informatics capabilities (i.e., common data elements and data architecture) that coordinate with caBIG to allow pooling and/or comparisons across and among the CCNEs
- Creation of an interactive web site partitioned for public access and password-protected study access to foster public-private partnerships in technology development
- Development of policies and procedures for the CCNEs to encourage sharing of knowledge and materials
- Organize conference calls and investigator meetings
- Provide senior biostatistical and bioinformatics expertise

Integration with Existing Resources. By balancing structured directives with investigator-initiated research, these Centers will bring together the interdisciplinary teams and provide the infrastructure necessary to develop and translate nanotechnology advances to the clinic. Nanotechnology interfaces basic sciences, biomedical and clinical disciplines, engineering, and computer science, making coordinated program integration an essential component for the translation of discoveries into clinical application. CCNEs will therefore be required to provide training modules in relevant areas, such as biomaterials fabrication or clinical application of nanotechnology.

The CCNEs will be further integrated into a network of extant NCI resources that will assist to increase the visibility and availability of nanomaterials and nanoscale device technology within the cancer research and development communities. Examples of these resources and their specific areas of relevance include:

1. The Developmental Therapeutics Program (DTP) – As the drug discovery and development arm of the NCI, the DTP plans, conducts, and facilitates development of therapeutic agents for cancer. A resource for research materials, including Web-accessible data and tools, vialled and plated compounds, tumor cells, animals, and Investigational New Drug (IND)-directed studies, the DTP will facilitate toxicology testing of materials developed under the Alliance.
2. The Academic Public Private Partnership Program (AP4) – The purpose of the Academic Public Private Partnership Program (AP4) is to create partnerships between academia, industry, non-profit institutions, and government to stimulate novel cancer therapeutic, prevention, diagnostic, and imaging intervention-directed research which takes advantage of the latest discovery and development technologies with a focus on orphan diseases, using a multidisciplinary approach. By bringing together the necessary expertise to discover and develop novel cancer interventions, the AP4 initiative will shorten the time required to bring these critical new therapeutic agents, preventive, diagnostic and imaging agents to clinical

- trials. The AP4 initiative will facilitate nanotechnology-related drug development within the Cancer Centers.
3. The Early Detection Research Network (EDRN) – The EDRN develops and tests promising cancer biomarkers, evaluates promising biomarkers and technologies, and operates a network of collaborations focused on all aspects of early cancer detection. The EDRN's expertise in the tools and technologies for biomarker discovery and evaluation will support relevant Alliance objectives.
 4. Development of Clinical Imaging Drug Enhancers (DCIDE) – DCIDE expedites and facilitates the development of promising imaging enhancers (contrast agents) or molecular probes and their translation from laboratory synthesis to IND application. DCIDE's expertise in molecular and cellular imaging will be a resource for assistance with steps in pre-clinical development (e.g., pharmacokinetics, dosimetry, imaging feasibility, toxicology), regulatory affairs, and access to probes for pre-clinical protocols.
 5. Mouse Models of Human Cancers Consortium (MMHCC) – The MMHCC is a collaborative program designed to derive and characterize mouse models and to generate resources, information, and innovative approaches to the application of mouse models in cancer research. In addition to providing a repository of mouse cancer models, the MMHCC offers resources and expertise in small animal imaging and *in vivo* imaging.

Through interactions with these NCI resources, as well as other Federal and private sector groups, it is expected that this initiative will catalyze targeted discovery and development efforts and spawn new partnerships with the private sector. The NCI will also implement established small business funding mechanisms, such as the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, to interface with appropriate small business and R&D programs. As a result of this multi-faceted effort, new business development opportunities will be created and new frontiers of investigator-initiated research in the diagnosis and treatment of cancer will be launched.

Mechanism of Support. The CCNE program will use the U54 Cooperative Agreement mechanism for funding. For this program, it is anticipated that 3 to 5 CCNEs will be needed and established to reach the programmatic goals as defined in the cancer nanotechnology plan.

B. Development of Multidisciplinary Research Teams through Career Development

Purpose. Given the multidisciplinary nature of nanotechnology research, investigators with basic science and clinical backgrounds will require training to optimize the capabilities of the Alliance, particularly regarding the translation of nanotechnologies toward clinical oncology applications.

The NCI will initially use existing training and career development mechanisms to direct talent to this area as quickly as possible and to incentivize cross-disciplinary research through training. When necessary, the NCI will investigate innovative policy considerations, such as naming multiple principal investigators per project, as incentives for conducting team science. The NCI will also encourage programs to be developed with interfaces to the training programs of other Federal agencies as components of the National Nanotechnology Initiative (NNI). The advantages are to translate knowledge rapidly from fundamental nanotechnology sciences to directed application in cancer biology.

Outcome objectives (performance measures) are represented by institutions with training programs and scientists and engineers who are trained in cancer nanotechnology. A 3- to 5-year benchmark is to support the entry of 20–30 scientists with formal training experiences in nanotechnology applied to cancer biology who can lead new programs in technology development through the cancer research enterprise in the next five years and beyond.

Mechanisms of Support. Career development will use the following mechanisms for the training of individual researchers: the F33 National Research Service Awards for Senior Fellows and the F32 Ruth L. Kirschstein National Research Service Awards (for postdoctoral training in biomedical, behavioral, or clinical research that serves health-related sciences).

C. *Investigator-Initiated Research Projects*

Purpose. Of key importance in the implementation of the Alliance for Nanotechnology in Cancer is the interaction of individual investigator-based projects with the Centers. The NCI has issued a Request for Information (RFI) to identify opportunities, programs, and contracts for specified nanotechnology platforms in cancer research. From the input gained from the RFI process, NCI will develop concepts for individual Requests for Applications (RFAs) and Requests for Proposals (RFPs) that focus on technology development for specific nanotechnologies. It is anticipated that these research initiatives for developing and assessing nanotechnology platforms will be integrated with the Alliance initiatives presented here.

Mechanism of Support. NCI anticipates using the R01 mechanism via Bioengineering Research Partnerships (BRPs) and Bioengineering Research Grants (BRGs). The BRPs are designed to fund basic, applied, and translational multidisciplinary research that addresses important biological or medical research problems. In the context of this program, a partnership is a multidisciplinary research team that applies an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior. The partnership must include appropriate bioengineering or allied quantitative sciences in combination with biomedical and/or clinical components. The smaller BRG awards support multidisciplinary research performed in a single laboratory or by a small number of investigators that applies an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior. A BRG application may propose hypothesis-driven, discovery-driven, developmental, or design-directed research at universities, national laboratories, medical schools, large or small businesses, or other public and private entities.

III. Program Assessment and Evaluation

The NCI will track progress in six key areas: molecular imaging and early detection, *in vivo* imaging, reporters of efficacy, multifunctional therapeutics, prevention and control, and research enablers. During the first three years, the NCI will accelerate selected projects that are already under way and catalyze the development of products that are primed for near-term clinical application. The following years will see projects come to fruition that reflect solving more difficult technological and biological problems or that require the integration of multiple technological components but that have the potential to make paradigm-changing impacts on the detection, treatment, and prevention of cancer. Milestones reached during this latter period will also reflect the growth of the investigator pool that will be catalyzed by the NCI Alliance for Nanotechnology in Cancer.

Each RFA will include provisions for programmatic assessment that includes specific program milestones and outcomes objectives, as detailed in the Cancer Nanotechnology Plan. The NCI will use its considerable expertise in program operations to inform and develop specific assessment criteria. For example, the NCI has recognized expertise in evaluating extramural and intramural nanotechnology activities in response to the Government Performance and Results Act (GPRA) reporting on the scientific research outcome goal related to nanotechnology (for which NCI is the lead Institute).

Each RFA will also incorporate a technical review process. A committee will be appointed to evaluate progress in the context of stated objectives and milestones and suggest program changes as necessary. Given the groundbreaking nature of the Alliance objectives, it is expected that these initiatives will require reevaluation in context of breakthroughs and developments.

The Alliance for Nanotechnology in Cancer represents an integrated program of activities to use a disruptive technology—nanotechnology—as an enabler of rapid clinical and research advances and as a means of lowering the barriers to technology development and commercialization by the private sector, particularly among small businesses, for clinical application.

Centers of Cancer Nanotechnology Excellence

RFA Number: RFA-CA-05-024

Part I Overview Information

Department of Health and Human Services

Participating Organizations

National Institutes of Health (NIH), (<http://www.nih.gov/>)

Components of Participating Organizations

National Cancer Institute (NCI), (<http://www.nci.nih.gov/>)

Announcement Type

New

Update: The following update relating to this announcement has been issued:

- [December 2, 2004](#) (NOT-CA-05-006) - NCI will hold a pre-application meeting for investigators planning to submit applications in response to RFA-CA-05-024.

Catalog of Federal Domestic Assistance Numbers

93.393, 93.399

Key Dates

Release Date: December 2, 2004

Pre-application Meeting Date: December 14, 2004

Letters-Of-Intent Receipt Date: February 25, 2005

Application Receipt Date: March 25, 2005

Peer Review Date: June/July 2005

Council Review Date: September 2005

Earliest Anticipated Start Date: September 2005

Additional Information To Be Available Date (URL Activation Date): Not Applicable

Expiration Date: March 26, 2005

Due Dates for E.O. 12372

Not Applicable

Executive Summary

The NCI invites applications from investigators interested in participating in an initiative to establish up to five Centers for Cancer Nanotechnology Excellence (CCNEs). The CCNEs will be a national resource that will integrate the basic and clinical sciences with engineering to develop and apply nanotechnology to cancer research to accelerate the application of this science to the clinic. Using the NIH U54 cooperative agreement mechanism, the NCI intends to commit approximately \$90.8 M in FY 2005-2009 (approximately \$20 M in FY 2005) to fund up to five CCNEs. Eligible organizations include for-profit or non-profit organizations; public or private institutions, such as universities, colleges, hospitals, and laboratories; units of State and local governments; eligible agencies of the Federal government; and domestic institutions and organizations. Foreign institutions may participate as subcontractors within a Center. Any individual with the skills, knowledge, and resources necessary to

carry out the proposed research is invited to work with his or her institution to develop an application for support. An individual can be the PI on only one application submitted under this announcement. However, an individual may be listed as a participant in multiple CCNE applications provided that his/her research proposals are discrete. Application materials are available from the NIH Office of Extramural Research (OER); <http://grants.nih.gov/grants/oer.htm>. Telecommunications for the hearing impaired is available at: TTY 301-451-0088.

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

Purpose

The NCI invites applications from investigators interested in participating in an initiative to establish up to five Centers for Cancer Nanotechnology Excellence (CCNEs). The CCNEs will be a national resource that will integrate nanotechnology development into basic and applied cancer research to facilitate the rapid application of this science in the clinic. Nanotechnology has potentially widespread application in cancer research and treatment, and this initiative will support the development of nanomaterials and nanoscale devices for molecular imaging and early detection, *in vivo* imaging, reporters of efficacy, multifunctional therapeutics, prevention and control, and research enablers. The intent of this RFA is to establish interdisciplinary research teams that collectively have the breadth of expertise to not only identify approaches, but to validate and translate nanotechnology for a variety of cancer applications, up to and including pre-clinical testing.

The over-arching goals of the CCNE initiative are to design and test nanomaterials and nanodevices and to translate their use into clinical research, resulting ultimately in the introduction of novel diagnostic tools and techniques to modulate and overcome cancer processes. The NCI's primary objective for this effort is to develop products and devices that constitute a new set of research tools for use by scientists in both the public and private sectors. In addition, it is anticipated that many of these developments will be made available to both public and private sector scientists as new diagnostic and therapeutic platforms. Outcomes objectives (performance measures) represent technologies that are developed and effectively utilized to overcome cancer processes.

On the basis of discussions with a wide range of clinicians, cancer researchers, and technologists, it is clear that virtually unlimited possibilities exist for using nanotechnology to solve mission-critical problems in cancer research. This initiative will increase the visibility and availability of nanomaterials and nanoscale device technology within the cancer research and development communities. This initiative will catalyze targeted discovery and development efforts that offer the greatest opportunity for advances in the near and medium terms and will lower the barriers for those advances to be translated to the private sector for commercial development. The CCNEs will be the hub of a network

of translational research and development, addressing challenges in those areas where nanotechnology can have the biggest and fastest impact.

In this regard, the NCI recognizes that significant issues exist concerning intellectual property rights with respect to patentable inventions developed within the CCNE program. This subject is discussed more fully below. Within this context, however, it is the NCI's intent that inventors will exercise any intellectual property rights retained on inventions developed as part of the CCNE program in a way that will promote wide accessibility to and further development of the resources that are generated.

Background

Nanotechnology offers an unprecedented and paradigm-changing opportunity to study and interact with normal and cancer cells in real time, at the molecular and cellular scales, and during the earliest stages of the cancer process. As a result, nanotechnology will be a mission-critical tool to meet the NCI's Challenge Goal of eliminating death and suffering from cancer. Through the focused development of nanoscale devices or devices with nanoscale components, the following areas of cancer research will be advanced:

- Early imaging agents and diagnostics that will allow clinicians to detect cancer in its earliest, most easily treatable, presymptomatic stage;
- Systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation;
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents at high local concentrations, with physiologically appropriate timing, directly to cancer cells and those tissues in the microenvironment that play a critical role in the growth and metastasis of cancer;
- Agents capable of monitoring predictive molecular changes and preventing precancerous cells from becoming malignant;
- Novel methods for managing the symptoms of cancer that adversely impact quality of life; and
- Research tools that will enable investigators to quickly identify new targets for clinical development and predict drug resistance.

To enable nanotechnology to become a fundamental driver of advances in clinical oncology and cancer research, the NCI has developed a series of directed programmatic mechanisms known collectively as the NCI Alliance for Nanotechnology in Cancer (<http://nano.cancer.gov>). The Alliance is an integrated 5-year initiative to develop and apply nanotechnology to cancer prevention, detection, diagnosis, and treatment. The Alliance will support the creation and maintenance of the CCNEs, provide support necessary to train members of a cross-disciplinary workforce, and support directed research programs that employ nanotechnology for the detection and treatment of cancer. Specifically, the NCI seeks to address the following significant obstacles:

- The need for cross-disciplinary collaborations to enable the integration of the fundamental biological knowledge base with physical sciences and engineering approaches to address cancer processes
- The widening “gap” between discovery and early development of diagnostics and therapeutics;
- The requirement for cross-cutting technology platforms;
- The critical lack of available standards or publicly available datasets of characterized (e.g., physically, chemically, and physiochemically) nanoscale devices and their interactions with living systems; and
- The application and adaptation of extant technology to mission-oriented tasks.

The NCI recognizes that these translational initiatives will benefit greatly from a concerted and coordinated effort to characterize and standardize the wide range of nanoscale devices that are now

available for use by the research community. A primary objective is to develop data on how nanomaterials and nanodevices interact with biological systems. These research endeavors will chart the common baseline and scientific data that would inform research and development (R&D) and define clinical and commercial pathways for integration of nanoscale diagnostics, imaging agents, and therapeutics. Moreover, this information will be linked to the Comprehensive Cancer Centers and related programs through public databases available through the Cancer Biomedical Informatics Grid [caBIG] <http://cabig.nci.nih.gov/>.

Through the creation of the CCNEs, the NCI aims to overcome biological barriers in cancer research by supporting the development and assessment of nanotechnology platforms. In the future, nanotechnology may become a core component in the training and translational programs at all leading cancer research institutions and a significant part of comprehensive cancer care.

Achieving this vision will also require training a cadre of researchers who are skilled in applying the tools of nanotechnology to critical problems in cancer research and clinical oncology. Given the complex nature of this endeavor, multidisciplinary teams will be essential to realize this vision, and the NCI supports the creation and development of multidisciplinary research teams for this initiative. Solicitation for career development of interested applicants who wish to participate in these teams will be provided by the NCI in a separate RFA (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-025.html>).

Organizational Structure of the CCNEs

The CCNEs represent the core units of the NCI Alliance for Nanotechnology in Cancer (<http://nano.cancer.gov>). Each CCNE will be a “virtual” center, headed by a Principal Investigator (PI), and comprised of a network of laboratories and research facilities (academic and/or private sector) that represents various sites throughout the country or the world. The CCNEs will be established as collaborative research networks of investigators with complementary abilities organized to address one or more specific cancer nanotechnology platform needs. Applicants must provide a signed, binding agreement between all institutions comprising the CCNE to share knowledge, research materials, and any other resources necessary and relevant to the Center's particular focus.

Each CCNE must demonstrate the following critical components explicitly (provide examples and plans) and all components must be adequately addressed for an application to be eligible for peer review:

- A focus on cancer applications, as demonstrated through integration with an NCI-designated Cancer Center and/or Specialized Program of Research Excellence (SPORE) which are involved in each Center project, with established, formal arrangements for team interactions;
- Explicit affiliation(s) with academic or research centers of engineering or physical sciences (e.g., mathematics, chemistry, physics, computational and/or materials science) that are directly involved with and actively contribute to the Center projects (such a relationship is required for each proposed project but does not need to be unique for each);
- Nanomaterials fabrication/synthesis facilities and/or collaborative capabilities;
- Facilities and capabilities for animal models/small animal imaging;
- Biocomputing capabilities to support proposed projects and the capacity to link with the NCI's Cancer Biomedical Informatics Grid (caBIG); <http://cabig.nci.nih.gov>;
- Modules for integrative training (i.e., programs that provide and develop a knowledge base relevant to cancer biology that includes biophysics, materials engineering, and physical sciences e.g., graduate programs, courses, seminars, and workshops);
- Education and outreach programs to disseminate information to the clinical oncology community (e.g., CDs, pamphlets, web sites, seminars);
- Technology assessment capabilities to identify new nanomaterials for development;

- Existing private/not-for-profit technology development partnerships that are specific to the technologies proposed;
- Mechanisms to share students and postdoctoral fellows among participating labs; and
- A framework to disseminate the products (e.g., research tools, nanomaterials, or diagnostic devices).

NCI does not specify how these functions are to be organized. The applicant may choose to organize the proposed Centers in terms of separate Cores or in any other manner deemed appropriate for the implementation of an effective pipeline. However, the applicant must clearly address how the proposed organization of the Center will ensure that each of these functions is effectively accommodated. Because of the complexity of each CCNE, NCI program staff expect to visit each CCNE periodically to conduct an administrative site visit. U54 centers must be prepared for annual site visits and must budget appropriately (including travel for collaborators to participate on site and other necessary costs).

One overarching goal of the CCNEs is to provide an environment that will foster integration among the physical, biological, and clinical sciences with respect to nanoscience for cancer. As a whole, the CCNEs will span the range from exploratory research to technology innovation and will involve a broad spectrum of disciplines such as engineering, mathematics, computer science, and the physical, biological, environmental, and materials sciences. Applicants must therefore demonstrate a commitment to, and a strategy for, engaging physical science, materials science, and engineering programs. Centers will bring together researchers with diverse expertise to address complex, interdisciplinary challenges involved with designing and testing nanomaterials and nanodevices in biological systems. CCNEs will integrate research with education both internally and through a variety of partnership activities, and each CCNE must have an overarching research and education theme, well-integrated programs, and a coherent and effective management plan.

CCNE applicants are strongly encouraged to take advantage of the range of existing opportunities in nanotechnology research and development through partnerships with other Federal agencies, such as the National Science Foundation (NSF); <http://www.nsf.gov> and the Department of Energy (DOE); <http://www.energy.gov>. Crosscutting national nanotechnology initiatives such as the NSF Nanoscale Science and Engineering (NSE); <http://www.nsf.gov/home/crssprgm/nano/start.htm>; <http://www.nsf.gov/pubs/2004/nsf04043/nsf04043.htm> and the DOE Nanoscale Science Research Centers (NSRCs); http://foundry.lbl.gov/nsrc/nsrc_prog.html offer opportunities for partnerships commensurate with those expected from the CCNEs. The NSE and DOE programs are components of the National Nanotechnology Initiative (<http://www.nano.gov/>), a multi-agency framework of nanotechnology research that may serve as a resource for applicants to this RFA.

In addition to the functions described above, there are a number of other issues important to the successful operation of the CCNEs that should be addressed separately in the application. Details of the governance structure for the CCNEs, which includes Center-specific Steering Committees and CCNE Coordinating and Governance Committee to oversee all Centers, are provided in [Section VI.2.A.](#), “Cooperative Agreement Terms and Conditions of Award.” To assist with these activities, the NCI will appoint program staff scientists consisting of a Program Director who will have responsibility for normal program oversight and stewardship of the CCNEs and one or more NCI Project Scientists to have substantial scientific involvement during the conduct of this activity above and beyond normal program stewardship for grants.

Applicants will be required to submit an intellectual property management plan and a plan to disseminate research results as a condition of award (just-in-time requirements). Details of these requirements are found in [Section IV.6, “Other Submission Requirements.”](#)

Objectives

The NCI will facilitate the use of nanotechnology to accelerate the discovery and development of research tools, diagnostic tools, and therapeutic agents (e.g., ligands, imaging probes, and nanoscale devices) that will reduce the suffering and death due to cancer. It is anticipated that the CCNEs will catalyze scientific breakthroughs that will contribute to the creation of materials or devices that have potential benefit for the development of therapeutics or diagnostics by the private sector. In accordance with the principles of the Alliance, the NCI has identified six thematic/programmatic areas of focus for directed nanotechnology-based research platforms (detailed below) where nanotechnology can have pronounced short- and long-term impacts.

The examples listed below in each of thematic/programmatic area represent a subset of the potential applications in which NCI's goals could be pursued. The specific cancer nanotechnology applications described under each thematic/programmatic area illustrate the diverse tools and strategies of cancer nanotechnology research supported by this RFA and are not meant to be comprehensive.

Thematic/programmatic areas of focus for nanotechnology in cancer include:

- 1) Molecular imaging and the early detection of cancer - Novel nanotechnologies can complement and augment existing genomic and proteomic techniques to analyze variations across different tumor types, thus offering the potential to distinguish between normal and malignant cells. Sensitive biosensors constructed of nanoscale components (e.g., nanocantilevers, nanowires, and nanochannels) can recognize genetic and molecular events and have reporting capabilities, thereby offering the potential to detect rare molecular signals associated with malignancy. Such signals may then be collected for analysis by nanoscale harvesters that selectively isolate cancer-related molecules from tissues. Another area with near-term potential for early detection is the identification of mutations and genomic instability *in situ*.
- 2) *In vivo* imaging - A pressing need in clinical oncology is for imaging methods (e.g., optical, magnetic resonance-based, ultrasound) that can identify tumors that are orders of magnitude smaller than those detected with current technology. When utilized in conjunction with powerful contrast agents, and coupled with nanoparticles such as dendrimers, these methods can improve targeting capability and increase signal intensity. In the future, implantable nanoscale biomolecular sensors may enable clinicians to more carefully monitor the disease-free status of patients who have undergone treatment or individuals susceptible to cancer because of various risk factors. Furthermore, imaging agents that target changes in the environment surrounding a tumor, such as angiogenesis, will further augment methodologies and will be invaluable to obtain optimal benefit from therapeutics that target such specific cancer-related processes.
- 3) Reporters of therapeutic efficacy - Nanotechnology offers the potential to develop highly sensitive imaging-based devices and *ex vivo* diagnostics that can determine whether a therapeutic agent is reaching its intended target and whether that agent is killing malignant or support cells. Optical imaging devices that use nanoscale agents may also enable surgeons to more readily detect the margins of a tumor prior to resection or to detect micrometastases in lymph nodes or tissues distant from the primary tumor. Nanoparticle-based systems to detect apoptosis or reactivation of the critical tumor suppressor systems and targeted nanoparticles that can bind to a tumor and be re-released into the bloodstream as tumor cells undergo apoptosis following therapy represent another potential application of nanotechnologies as reporters of efficacy.
- 4) Multifunctional therapeutics . Because of their multifunctional capabilities, nanoscale devices can contain both targeting agents and therapeutic payloads, particularly in areas of the body that are difficult to access because of a variety of biological barriers, including those developed by tumors. Multifunctional nanoscale devices also offer the opportunity to utilize new approaches to therapy, such as localized heating or reactive oxygen generation, and to combine a diagnostic or imaging agent with a therapeutic and/or a reporter of therapeutic efficacy. "Smart" nanotherapeutics may

provide clinicians with the ability to time the release of an anticancer drug or deliver multiple drugs sequentially in a timed manner or at several locations in the body, potentially ushering in an era of sustained therapy for cancers that must be treated chronically. Such nanotherapeutics could also house engineered cellular “factories” that make and secrete proteins and other antigrowth factors that impact a tumor and/or its immediate environment. Many nanotherapeutics (e.g., nanoparticulate hydrogels, nanoparticles, and quantum dots) can also double as imaging agents.

5) Prevention and control of cancer - Many of the advances that nanotechnology will enable in each of the four preceding areas will also find widespread applicability in efforts to prevent and control cancer. Once specific biomarkers of cancer susceptibility and precancerous lesions have been identified, nanotechnology can enable devices that signal their presence and deliver targeted therapy. Nanoscale devices may also prove valuable for delivering or mimicking polyepitope cancer vaccines that engage the immune system or cancer-preventing nutraceuticals or other chemopreventive agents in a sustained, timed-release, and targeted manner.

6) Research enablers - Nanotechnology offers a wide range of tools, from chip-based nanolabs capable of monitoring and manipulating individual cells to nanoscale probes that can track the movements of cells, and even individual molecules, as they move about in their environments. Using such tools will enable cancer biologists to study, monitor, and alter the multiple systems that are implicated in cancer processes and to identify key biochemical and genetic targets for future molecular therapies. As such, nanotechnology can complement other technology platforms, such as proteomics and bioinformatics. Another near-term application of nanotechnology to accelerate basic research is to use molecular-size nanoparticles with wide ranges of optical properties (e.g., quantum dots) to track individual molecules or cells as they move through local environments, thereby monitoring multiplexed cellular and molecular events in real time. When combined with mouse models that reproduce the genetic, biochemical, and physiological properties of human cancers, these nanolabels will be useful for integrative, systems biology research. Finally, nanoscale devices that enable simultaneous biochemical measurements (e.g., time, size, dynamic events) on multiple cells, particularly those grown in such a way as to mimic tissue development *in vivo*, will open new dimensions to basic cancer research.

Project Design

Successfully applying nanotechnology to cancer research requires an understanding of how synthetic materials interface with biological systems. Thus, each CCNE will be required to demonstrate expertise with both the biological and non-biological aspects of this work. Applicants must clearly describe how their proposals will address fundamental principles of cancer biology (e.g., protein synthesis and assembly, apoptosis, DNA repair, angiogenesis, cell cycle regulation) at the molecular and sub-cellular levels. Emphasis should be placed on why the approach is revolutionary within the context of related research and how it will overcome biological barriers and interfere with the biological processes involved in carcinogenesis.

In a general sense, applications must include:

- A pre-formed group of named investigators that will interact as a multidisciplinary team;
- A nanotechnology* or nanomaterials synthesis/fabrication component;
- An application to cancer research, with an emphasis on translational research;
- A focus toward ultimate application in clinical care (e.g., preparation of nanomaterials for future use in clinical trials); and
- A framework to disseminate the products developed at the CCNEs (e.g., research tools, nanomaterials, or diagnostic devices), defined explicitly in letters of commitment and/or signed consortia agreement from each participating institution.

* To be characterized as “nanotechnology” under this solicitation, the following criteria must be met: 1) Applicants must propose devices or base materials that are less than 1000 nm in size although the assembly, synthesis, and/or fabrication of components at dimensions less than 300 nm should be demonstrated and 2) Projects must incorporate synthetic materials or biomaterials engineered to provide novel properties or modified functions based on nanoscale size, i.e., nanomaterials. Projects that propose only the use of naturally-occurring materials (e.g., carbohydrates, proteins, viruses) that are not specifically engineered or modified for a biomedical application will not be considered. Furthermore, projects focused primarily on genetic engineering or gene therapy (e.g., DNA sequencing or gene vector methods) are not appropriate for these Centers. For the purposes of this application, applicants are encouraged to use the National Nanotechnology Initiative (NNI); <http://nano.gov/html/facts/whatisNano.html> definition as a guideline.

More specifically, applicants must select one or more of the six thematic/programmatic areas of focus for directed nanotechnology-based research programs as described previously: molecular imaging/early detection, *in vivo* imaging, reporters of efficacy, multifunctional therapeutics, prevention and control, and research enablers. Within the context of the area(s) identified, the homeostatic changes in the cancer cell that Center research will address (e.g., apoptosis, protein folding and assembly, DNA repair, recognition of mutational deletions in lymphocytes, loss of heterozygosity) must be defined clearly. Applicants must describe how the proposed research will modulate or measure these changes at the sub-cellular and molecular levels in terms of the biology and chemistry involved (e.g., energy transfer and cellular thermodynamics, surface properties and phenomena, molecular self-assembly). In addition, applicants must demonstrate how the proposed approach is a revolutionary way to address these issues.

Applicants must then propose a multidisciplinary team of researchers that will comprise a CCNE, with a single PI, that meets the Center critical components listed in the following section, “Organizational Structure of the CCNEs.” This team must include representatives of fields necessary to complete the proposed basic research and translational projects, and it should include expertise from these areas: molecular biology, chemistry, physics, materials science, biomedical engineering, computational science, clinical oncology, and mathematics. Involvement of basic and clinical scientists and engineers who may not have a specific record in cancer research, but who possess the potential to provide experience crucial to the success of the CCNE, is encouraged.

For each CCNE, a minimum of five (and as many as eight) projects focused on multiple nanotechnology platforms should be proposed for the first year, each with discrete, quantitative milestones and a dedicated research team. The individual Center Steering Committee will review and select projects to support on a rolling basis, such that the Center will always maintain five to eight active projects. Applications must include explicit discussions of both the specific aims of the research projects and the applicant's efforts to forge creative new links between disciplines. Applicants must also provide a set of quantitative milestones for the CCNE as a whole and a plan to assess overall Center progress.

Within the context of the specific directed research program(s) identified, each CCNE will offer the full range of support necessary to develop products suitable for clinical trial testing, including:

- Creating or supplying the appropriate “starting materials,” such as relevant nanomaterials (e.g., contrast agents for imaging or nanoshells for targeted delivery) or prototype research tools (e.g., simulated biological systems that can be used to model drug disposition, trafficking, or systems biology);
- Establishing proof-of-concept through *in vitro* studies;
- Conducting *in vivo* studies in animal models, including safety profiles and toxicology studies;
- Conducting pharmacologic studies (e.g., pharmacodynamic and pharmacokinetics) studies necessary for pre-clinical trials;
- Conducting *in situ* studies using animal models; and

- Providing quality assurance and control and proof of reproducibility.

Note: This initiative will not support clinical trials or *in vivo* studies in human subjects. However, *in vitro* investigations that employ clinical biospecimens or the theoretical modeling of human systems are within the scope of activities that will be considered for support by this initiative.

Partnerships

The CCNEs will increase the ability of investigators in the public and private sectors to deploy nanotechnology in basic biological research and to translate the resultant findings into discovery and therapeutics development for cancer. While the CCNEs are expected to provide a comprehensive array of pre-clinical technology evaluation services, the Centers will be integrated with NCI-supported resources that includes Comprehensive Cancer Centers (<http://www3.cancer.gov/cancercenters/>), Specialized Programs of Research Excellence (<http://spores.nci.nih.gov/>), and the Early Detection Research Network (<http://www3.cancer.gov/prevention/cbrg/edrn/>). CCNEs will also engage with relevant NCI initiatives such as the Developmental Therapeutics program (http://dtp.nci.nih.gov/docs/raid/raid_index.html), the Academic Public Private Partnership Program (<http://grants2.nih.gov/grants/guide/rfa-files/RFA-CA-04-005.html>), the Development of Clinical Imaging Drug Enhancers program (<http://www3.cancer.gov/bip/dcide.htm>), the Integrative Cancer Biology Program (<http://dcb.nci.nih.gov/branchdetail.cfm?branch=1>), *In vivo* Cancer Molecular Imaging Centers (<http://imaging.cancer.gov/programsandresources/specializedinitiatives/icmics>), the Innovative Molecular Analysis Technologies program (<http://otir.nci.nih.gov/tech/imat.html>), Unconventional Innovations Program (<http://otir.nci.nih.gov/tech/uip.html>), the Fundamental Technologies for Biomolecular Sensors program (<http://otir.nci.nih.gov/tech/ftbs.html>), and the Mouse Models of Human Cancer Consortium (<http://emice.nci.nih.gov/>), that will increase the visibility of availability of nanomaterials and nanoscale device technology within the cancer research and development communities. The CCNEs will therefore serve as hubs to integrate and assimilate nanotechnologies for cancer application, conducting the testing necessary to support investigational new drug (IND) applications and becoming the pivot points to usher new materials and technologies into clinical development. As such, collaboration with these and other programs is strongly encouraged, and applicants should identify mechanisms and approaches that will be used to promote and enable collaboration.

The CCNEs are also encouraged to interface with the Nanotechnology Characterization Laboratory for Cancer Research (NCL), a resource developed by the NCI in partnership with the National Institute for Standards and Technology (NIST) to perform preclinical characterization of nanoscale devices in a way that will accelerate regulatory review and translation of these devices into the clinical realm. The NCL will develop an assay cascade that can serve as the universal protocol for preclinical toxicology, pharmacology, and efficacy testing of nanoscale devices. This assay cascade will characterize a nanoscale device's physical attributes, *in vitro* biological properties, and *in vivo* compatibility. In carrying out these functions, the NCL will provide a comprehensive set of baseline characterization parameters that will enable researchers to apply these tools to clinical oncology, while establishing a scientific foundation that will help provide a pathway for clinical development and commercialization concerning the testing and approval of nanoscale cancer diagnostics, imaging agents, and therapeutics. When appropriate, CCNEs are encouraged to use the NCL characterization resources for nanoscale technologies developed and tested at the CCNEs.

The CCNEs will describe existing as well as planned partnerships with private/not-for-profit technology development partners that are specific to the technologies proposed. The applicant must describe the role of commercial partners in the development of the proposed technology platforms. Applicants may also consider SBIR program partners as a means of leveraging resources for cancer technology development and commercialization.

Progress Reviews – Milestones and Evaluations

The progress of the CCNEs will be reviewed annually by the NCI Program Director and Project Scientists to assure that satisfactory progress is being made in achieving the project objectives. During the first year of funding, and during subsequent years if deemed necessary by the Program Officer(s) as described above, reviews may be more frequent. The adherence of the CCNEs to the approved data sharing plan and intellectual property plans, which will be part of the Terms and Conditions of award (see [Section VI.3. Award Criteria](#)) , will also be reviewed annually. Should problems arise in the conduct of the study, the NCI Program Director may require that the Center awardee submit quarterly reports on progress and fiscal matters.

Quantitative Milestones. All applications must include a specific section labeled “Milestones” for each proposed project in the Center. Milestones should be annual, well-described, quantitative, and scientifically justified and not simply a restatement of the specific aims. Rather, the milestones should offer a timeline and a “pathway” for the development of the proposed technology. These milestones will be used to judge the success of the proposed research on an individual-project basis and evaluate the criteria for the program. Applications that lack this information as determined by the NCI program staff will be returned to the applicant without review.

As evaluation of progress is an increasing priority for NCI, CCNEs will be required to participate in global Center evaluation activities that will be established and conducted by the CCNE Coordinating and Governance Committee in conjunction with NCI Program Officers and staff. Outcomes include: peer-reviewed publications, applied model development, new intervention formats, new research tools, and opportunities for effective dissemination. The purpose of the evaluation component is to monitor and assess the performance of the CCNEs in achieving the goals of this RFA. This component includes evaluating the quality and innovation of the science conducted at the CCNEs, as well as assessing critical intermediate indicators of success, such as infrastructure development and capacity building, career development, linkages and resource and data sharing arrangements within and among Centers, and the interdisciplinary and multilevel nature of the research. Criteria for the evaluation component will be developed in partnership between the CCNE Coordinating and Governance Committee and NCI program staff.

Objective criteria for the evaluation component will include the extent to which: 1) the overall capacity to employ nanotechnology to understand and intervene in the mechanisms of carcinogenesis in the CCNEs has increased as a result of the new funding; 2) collaborative relationships within and among Centers have been established and institutionalized; 3) training and career development opportunities exist for new and established investigators; 4) a transdisciplinary research culture has been engendered that takes into account multiple levels of analysis; and 5) CCNE investigators' ability to compete for future research project grants and participate in other research mechanisms has been enhanced.

The evaluation will also examine intermediate markers of the importance and potential impact of the science conducted by CCNE investigators in deploying nanotechnologies to prevent, detect, diagnose, and treat cancer. Possible metrics include: 1) the design of new cancer diagnostic tools; 2) the fabrication and testing of novel nanomaterials for cancer research; 3) new treatments or interventions; and 4) novel and/or improved models of human cancers.

The progress report will have two components. The first will be the standard NIH progress report (Form 2590). The second will be a more specialized report that will be developed by the CCNE Coordinating and Governance Committee. This specialized report should be included as an attachment to the standard progress report and will go to the NCI Program Director.

The contents or the report may be changed according to programmatic needs based on discussion among NCI Program Officers, the Center PI, and the CCNE Coordinating and Governance Committee.

The Center awardees' yearly milestones will be provided to the NCI Program Director and the CCNE Coordinating and Governance Committee. It is expected that the milestones will be adjusted annually at the award anniversary dates to incorporate the group's scientific accomplishments and progress and to reflect any recommendations of the Coordinating and Governance Committee. Following the review of milestones, the NCI may recommend reducing or withholding funds for any Center or specific Center project that substantially fails to meet its milestones or, if the situation warrants, augmenting any Center or specific Center project. However, simply meeting milestones may not be considered sufficient accomplishment for maintaining funding at the initially committed level. Failure to remain at state-of-the-art will also be considered grounds for reduction or cessation of funding.

Section II. Award Information

1. Mechanism of Support

This funding opportunity will use the NIH U54 award mechanism. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

This funding opportunity uses the just-in-time budget concepts. It also uses the non-modular budget format described in the PHS 398 application instructions (see <http://grants.nih.gov/grants/funding/phs398/phs398.html>). A detailed categorical budget for the "Initial Budget Period" and the "Entire Proposed Period of Support" is to be submitted with the application. A categorical budget for each project, along with a summary budget, is required.

The NIH U54 is a cooperative agreement award mechanism. In the cooperative agreement mechanism, the Principal Investigator retains the primary responsibility and dominant role for planning, directing, and executing the proposed project, with NIH staff being substantially involved as a partner with the Principal Investigator, as described under the [Section VI. 2. Administrative Requirements](#), "Cooperative Agreement Terms and Conditions of Award."

2. Funds Available

The NCI intends to commit approximately \$90.8 M in FYs 2005-2009 (approximately \$20M in FY 2005) to fund up to five Centers of Cancer Nanotechnology Excellence. An applicant should request a project period of 5 years. The budget may not exceed \$5 million in total costs per year. Costs for equipment may be included in year 1, up to \$500,000; these costs will not count against the \$5,000,000 total cost limit but should be well justified. Applicants should include travel funds in the budget for the annual site visit, annual CCNE meetings, and CCNE Coordinating and Governance Committee meetings.

This RFA is a one-time solicitation, and plans for this initiative beyond the current funding opportunity are indefinite. The NCI may expand or reduce the scope and direction of the CCNEs by amendment during the course of the 5-year period of set-aside funding, terminate it upon expiration, or extend or expand it prior to expiration by reissuing the RFA soliciting competitive applications for translational research for nanotechnology in oncology. It is anticipated that individual projects of a CCNE will mature, complete aims, add new aims, end, and/or be replaced by other projects. Developments that successfully translate to clinically feasible or research-oriented instruments and methods are expected to stimulate investigator-initiated applications for clinical and basic research grants under other support mechanisms, such as the R01, R21, R21/R33, R33, R41, R42, R43, and R44.

Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size of each award will also vary. Although the financial plans of the NCI provide support for this program, awards pursuant to this funding opportunity are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

You may submit (an) application(s) if your organization has any of the following characteristics:

- For-profit organizations
- Non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State government
- Units of local government
- Eligible agencies of the Federal government
- Domestic Institutions only
- Faith-based or community-based organizations

Foreign institutions may participate only as subcontractors within Centers.

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

An individual can be the PI on only one proposal submitted under this announcement. However, an individual may be listed as a participant in multiple CCNE applications provided that his/her research project activities within those centers are entirely discrete. An individual may not propose overlapping research projects on multiple applications.

2. Cost Sharing

This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part2.htm.

3. Other-Special Eligibility Criteria

Applications must demonstrate a Center composition that meets the criteria and possesses sufficient capabilities as explicitly defined in this RFA to be eligible for merit review of proposed Center projects and activities (see “Organizational Structure of the CCNE,” above).

Programs will be expected to have a Center-specific Steering Committee, including experts outside the project. While a description of the Steering Committee's activities should be included in the application, potential members of the Steering Committee should not be named, contacted, or selected until an award has been made. This stipulation will allow a wider pool of potential reviewers of the application. Costs for activities of the Steering Committee should be included in the budget.

Section IV. Application and Submission Information

1. Address to Request Application Information

The PHS 398 application instructions are available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. For further assistance, contact GrantsInfo, Telephone: (301) 435-0714, Email: GrantsInfo@nih.gov. Applicants are strongly encouraged to reference <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-006.html> which describes the revisions in the PHS 398 form as of 09/2004.

Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the PHS 398 research grant application instructions and forms. Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at <http://www.dnb.com/us/>. The D&B number should be entered on line 11 of the face page of the PHS 398 form.

The title and number of this funding opportunity must be typed on line 2 of the face page of the application form and the YES box must be checked.

Given the multicomponent nature of this RFA, applicants should structure the application as follows:

Part A – Overall CCNE Organizational Framework : Describe composition, leadership, integration, focus, and core structural requirements (see “Organizational Structure of the CCNEs”). Applications should include a face page listing all key personnel (p.2 and continuation page) and level of effort by each team member by project and explicitly identify one or more of the thematic/programmatic areas in the “Objectives” section of this RFA; abstract page; overall budget (including all proposed projects, core support functions, and travel), listing direct and indirect costs separately; and Center-specific milestones. Part A is limited to a maximum of 40 pages.

Part B – CCNE Projects : Number each proposed project (minimum of five) sequentially and include its own face page, abstract page (Form p.2), budget, and project-specific milestones. Each project is limited to a maximum of 25 pages for sections a-d.

Part C – CCNE Core Support Functions : Include capability examples and development plans for education, training, dissemination, technology assessment, and partnership development, with budget details and specific milestones for each. Identify budget and resources set aside for Alliance activities, including CCNE Coordinating and Governance Committee meetings and activities, annual CCNE meeting, and annual CCNE site visits (all participating institutions must be present). Each Core is limited to 10 pages for the description of each Core Support function, with a maximum of 50 pages for Part C.

Appendices should be comprised of unbound materials with separators between documents, collated by project.

3. Submission Dates

Applications must be received on or before the receipt date described below in [Section IV.3.A.](#)

3.A. Receipt, Review and Anticipated Start Dates

Release Date: December 2, 2004

Pre-Application Meeting Date: December 14, 2004

Letters Of Intent Receipt Date: February 25 2005

Application Receipt Date: March 25, 2005

Peer Review Dates: June/July 2005

Council Review Date: September 2005

Earliest Anticipated Start Date: September 2005

3.A.1. Letter of Intent

Prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed research
- Name, address, and telephone number of the Principal Investigator
- Names of other key personnel
- Participating institutions
- Number and title of this funding opportunity.

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document.

The letter of intent should be sent to:

Gregory J. Downing, D.O., Ph.D.
Director, Office of Technology and Industrial Relations
Office of the Director
National Cancer Institute, NIH, DHHS
Building 31, Room 10A-52, MSC 2580
31 Center Drive
Bethesda, MD 20892-2580
Telephone: (301) 496-1550
FAX: (301) 496-7807
E-mail: downingg@mail.nih.gov

Pre-Application Meeting

A pre-application meeting will be held on December 14, 2004, at the Natcher Conference Center on the NIH campus in Bethesda, MD, to help communicate the goals of this RFA and answer questions for potential applicants. Attendance at the pre-application meeting is not required to submit an application in response to this RFA. The meeting will be open to the public and webcast. The specific time and agenda will be posted on the NCI Alliance for Nanotechnology in Cancer web site, <http://nano.cancer.gov>.

3.B. Sending an Application to the NIH

Applications must be prepared using the PHS 398 research grant application instructions and forms as described above. Submit a signed, typewritten original of the application, including the checklist, and three signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

At the time of submission, two additional copies of the application and all five copies of the appendix material must be sent to:

Referral Office
National Cancer Institute
Division of Extramural Activities
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 496-3428
FAX: (301) 402-0275
Email: nciref@dea.nci.nih.gov

Appendices should be comprised of unbound materials with separators between documents.

Using the RFA Label: The RFA label available in the PHS 398 application instructions must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at <http://grants.nih.gov/grants/funding/phs398/labels.pdf>.

3.C. Application Processing

Applications must be received **on or before the application receipt date** listed in the heading of this funding opportunity. If an application is received after that date, it will be returned to the applicant without review.

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NCI. Incomplete and/or non-responsive applications will not be reviewed.

The NCI will not accept any application in response to this funding opportunity that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to a funding opportunity, it is to be prepared as a NEW application. That is, the application for the funding opportunity must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

4. Intergovernmental Review

This initiative is not subject to [intergovernmental review](#).

5. Funding Restrictions

All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm> (see also [Section VI.3. Award Criteria](#)).

6. Other Submission Requirements

It is recognized that the applications in response to this RFA will be longer and more complex than those of many other NIH applications. To ensure effective review, the application should be well organized as described in [Section IV.2.](#) In particular, each of the functions identified earlier in the RFA in the section “Organizational Structure of the CCNEs” must be clearly addressed.

For cooperative agreements, awardees must agree to the "Cooperative Agreement Terms and Conditions of Award" in [Section VI.3 Award Criteria](#). Other submission requirements are described in detail below.

Plan for Sharing Research Data

The precise content of the data-sharing plan will vary, depending on the data being collected and how the investigator is planning to share the data. Applicants who are planning to share data may wish to describe briefly the expected schedule for data sharing, the format of the final dataset, the documentation to be provided, whether or not any analytic tools also will be provided, whether or not a data-sharing agreement will be required and, if so, a brief description of such an agreement (including the criteria for deciding who can receive the data and whether or not any conditions will be placed on their use), and the mode of data sharing (e.g., under their own auspices by mailing a disk or posting data on their institutional or personal web site, through a data archive). Investigators choosing to share under their own auspices may wish to enter into a data-sharing agreement. References to data sharing may also be appropriate in other sections of the application.

All applicants are expected to include a **plan** for sharing research data in their application. The data sharing policy is available at http://grants.nih.gov/grants/policy/data_sharing. All investigators responding to this funding opportunity should include a description of how final research data will be shared, or explain why data sharing is not possible.

The reasonableness of the data sharing **plan** or the rationale for not sharing research data will be assessed by the reviewers. Reviewers will factor the proposed data sharing **plan** into the determination of scientific merit or the priority score.

Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication. See the NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and at http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part7.htm#_Toc54600131. Investigators responding to this funding opportunity are expected to include a **plan** for sharing research resources addressing how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the resources sharing will be considered by Program staff of the NCI when making recommendations about funding applications. The effectiveness of the resource sharing will be

evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590, <http://grants.nih.gov/grants/funding/2590/2590.htm>). See [Section VI.3. Award Criteria](#).

Dissemination of Research Results

This initiative encourages investigators to facilitate translating effective interventions and tools into practice. As part of the NCI's commitment to the rapid translation of research evidence into practice, applicants should include explicit plans to disseminate research results into practice.

Guidance for Preparation of Research Tools Sharing Plan and Intellectual Property Plan.

Restricted availability of unique research resources, upon which further studies are dependent, can impede the advancement of research. The NIH is interested in ensuring that the research resources developed through this grant also become readily available to the broader research community in a timely manner for further research, development, and application, in the expectation that this will lead to products and knowledge of benefit to the public health.

Investigators conducting biomedical research frequently develop unique research resources. The policy of the NIH is to make available to the public the results and accomplishments of the activities that it funds. To address this interest in ensuring research resources are accessible, NIH expects applicants who respond to this RFA to submit a plan: (1) for sharing the research resources generated through the grant (e.g., human biospecimens and novel cancer biomarkers); and (2) addressing how they will exercise intellectual property rights, should any be generated through this grant, while making such research resources available to the broader scientific community consistent with this initiative. Therefore, such research resources tools sharing plan and intellectual property management plans would make unique research resources readily available for research purposes to qualified individuals within the scientific community in accordance with the NIH Grants Policy Statement (<http://grants.nih.gov/grants/policy/> and the Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice, December 1999 <http://ott.od.nih.gov/NewPages/64FR72090.pdf>) ("NIH Research Tools Guidelines Policy"). These documents also: (1) define terms, parties, and responsibilities; (2) prescribe the order of disposition of rights and a chronology of reporting requirements; and (3) delineate the basis for and extent of government actions to retain rights. Patent rights clauses may be found at 37 CFR Part 401.14 and are accessible from the Interagency Edison web page (<http://www.iedison.gov>); see also, 35 USC § 210(c); Executive Order 12591, 52 FR 13414 (Apr. 10, 1987); and Memorandum on Government Patent Policy (Feb. 18, 1983). If applicant investigators plan to collaborate with third parties, the research tools sharing plan would need to address how such collaborations would not restrict their ability to share research materials produced with NIH funding. The applicant's institution should avoid exclusively licensing those inventions that are research tools, unless either: (1) the field of use of the exclusive license is restricted to commercial use, or (2) the exclusive licensee will make the research tool available on reasonable terms.

Intellectual property management plans are a just-in-time requirement; it is not necessary to include the final plan approved by all parties in the grant application, but final, approved plans will be expected before a U54 grant can be awarded. NIH program staff will consider the adequacy of the plans in determining whether to recommend an application for award. The approved plans would become a condition of the grant award and Progress Reports must contain information on activities for the sharing of research resources and intellectual property.

In the development of any research resource sharing and intellectual property management plans, applicants should confer with their institutions' office(s) responsible for handling technology transfer related matters and/or sponsored research. If applicants or their representatives require additional guidance in preparing such plans, they are encouraged to make further inquiries to the appropriate contacts listed above for such matters. Further, applicants may wish to independently research and review examples of approaches considered by other institutions such as those described on the NCI

Technology Transfer Branch web site (<http://ttc.nci.nih.gov/intellectualproperty/>). The foregoing guidance is provided by way of example to assist applicants in preparing the expected research resources sharing and intellectual property management plans in a manner that encourages partnerships with industry. While these approaches will likely suit most situations, these approaches are not exclusive and applicants should feel free to submit alternative versions for consideration.

The majority of transfers to not-for-profit entities should be implemented under terms no more restrictive than the Uniform Biological Material Transfer Agreement (UBMTA). In particular, recipients are expected to use the Simple Letter Agreement (SLA) provided at <http://ott.od.nih.gov/NewPages/SimplLtrAgr.pdf>, or another document with no more restrictive terms, to readily transfer unpatented tools developed with NIH funds to other recipients for use in NIH-funded projects. If the materials are patented or licensed to an exclusive provider, other arrangements may be used, but commercialization option rights, royalty reach-through rights, or product reach-through rights back to the provider are inappropriate. Similarly, when for-profit entities are seeking access to NCI-funded tools for internal use purposes, recipients should ensure that the tools are transferred with the fewest encumbrances possible. The Simple Letter Agreement (SLA) may be expanded for use in transferring tools to for-profit entities, or simple internal use license agreements with execution or annual use fees may be appropriate.

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process. Only those applications demonstrating a Center composition that meets the criteria and possesses sufficient capabilities as explicitly defined in this RFA will continue through review (see “[Organizational Structure of the CCNE](#)”, above).

2. Review and Selection Process

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by NCI in accordance with the review criteria stated below.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
- Receive a written critique
- Receive a second level of review by the National Cancer Advisory Board.

3. Merit Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The scientific review group will address and consider each of these criteria in assigning the application's overall score, weighting them as appropriate for each application.

- Significance

- Approach
- Innovation
- Investigator
- Environment
- Additional Review Criteria

The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

The scientific review group will address and consider each of the above criteria with respect to the proposed **CCNE framework, projects, and core support functions** in assigning the application's overall score, weighting them as appropriate for each application.

CCNE Framework

Significance: Does the CCNE address an important cancer problem with development and application of nanotechnology to cancer? If the milestones of the CCNE are achieved of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive the use of nanotechnology approaches in cancer research?

Approach: Are the conceptual framework, design, methods, and capabilities adequately defined and developed, well integrated, and appropriate to the aims of the overall application, within the limits inherent in an emerging, complex approach to cancer research? Does the applicant acknowledge potential problem areas and consider alternative tactics? Is the governance plan appropriate for a large-scale, highly integrated CCNE of this type? Do the individual components exhibit a high degree of interrelatedness and synergy? Are the proposed core facilities and collaborative capabilities adequate and essential to the proposed focus of the CCNE?

Will the CCNE serve as a model for cross-disciplinary activities? Is there evidence of strong interaction and feedback among the CCNE's collaborating academic or research centers in bioengineering or the physical sciences? Is there an adequate plan to disseminate the nanotechnology products that will be produced by the CCNE?

Innovation: Does the proposed CCNE employ novel concepts, approaches or methods? Are the aims original and innovative? Does the CCNE challenge existing collaborative paradigms and effectively integrate across scientific and clinical disciplines? Does the CCNE demonstrate an adequate plan to identify and attract new nanotechnologies for development?

Investigators: Is the Principal Investigator appropriately trained and well-suited to lead and coordinate a Center program of this size and complexity? Does the overall research team have sufficient expertise in all the critical aspects of this undertaking?

Environment: Does the scientific environment of the proposed CCNE contribute to the probability of success? Is there strong evidence of institutional support and interdisciplinary interactions? Is the CCNE that is being developed recognized as a major element within the organizational structure of the institution?

CCNE Projects

Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

Innovation: Do the proposed projects employ novel concepts, approaches or methods? Are the aims original and innovative? Do the projects challenge existing paradigms or develop new methodologies or technologies? Do projects include clear plans for translation to clinical application?

Investigators: Are the investigators appropriately trained and well suited to carry out this work? Are the projects proposed apposite to the experience and expertise of the principal investigator and other researchers and team members?

Environment: Does the scientific environments of the proposed CCNE in which the project work will be done contribute to the probability of success? Do the proposed projects take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

CCNE Core Support Functions

Significance: Are there examples of and plans identified for translating research advances and knowledge of key technologies across disciplines and particular to clinicians? Will the CCNE establish adequate portals for education, training, and potential input?

Approach: Are the conceptual framework, design, methods, and core support capabilities adequately defined and developed, well integrated, and appropriate to the aims of the overall application, within the limits inherent in an emerging, complex approach to cancer research? Is the training and outreach plan appropriate (i.e., is it likely to meet the needs of the CCNE and the scientific community in cancer and the application of nanotechnologies? Does it integrate well with and leverage existing educational and training resources at the CCNE?

Innovation: Do the proposed education, training and dissemination efforts employ novel concepts, approaches or methods? Are the aims truly cross-disciplinary, original and innovative? Do the projects challenge existing paradigms or develop new methodologies or technologies?

Investigators: Are the investigators directly involved in planning and executing cross-disciplinary training, education, and dissemination of technology development and research results?

Environment: Are there mechanisms in place for the sharing of researchers, students and post doctoral fellows among participating labs and/or institutions in the CCNE?

3.A. Additional Review Criteria:

In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

Protection of Human Subjects from Research Risk: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed.

See also (see the Research Plan, [Section VIII - Other Information](#) on Human Subjects in the PHS Form 398).

Inclusion of Women, Minorities and Children in Research: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated. See also (see the Research Plan, [Section VIII-Other Information](#) on Human Subjects in the PHS Form 398).

Care and Use of Vertebrate Animals in Research: If vertebrate animals are to be used in the project, the five items described under Section F of the PHS Form 398 research grant application instructions will be assessed.

3.B. Additional Review Considerations

Budget: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. The priority score will not be affected by the evaluation of the budget.

3.C. Sharing Research Data

Data Sharing Plan: The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. Reviewers will factor the proposed data sharing plan into the determination of scientific merit or the priority score. A final data sharing plan will be part of the terms and conditions of the award. The funding organization will be responsible for monitoring the data sharing policy (http://grants.nih.gov/grants/policy/data_sharing).

3.D. Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication. See the NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and at http://www.ott.nih.gov/policy/rt_guide_final.html. Investigators responding to this funding opportunity are expected to include a sharing research resources plan addressing how unique research resources will be shared or explain why sharing is not possible

The adequacy of the both the data and resources sharing plans will be considered by Program staff of the funding organization when making recommendations about funding applications. Program staff may negotiate modifications of the data and resource sharing plans with the awardee before recommending funding of an application. The final version of the data and resource sharing plans negotiated by both will become a condition of the award of the grant. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report. (PHS 2590). See [Section VI.3. Award Criteria](#).

Section VI. Award Administration Information

1. Award Notices

After the peer review of the application is completed, the Principal Investigator will also receive a written critique called a Summary Statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and

Conditions of NIH Grant Awards, Subpart A: General
(http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm).

A formal notification in the form of a Notice of Grant Award (NGA) will be provided to the applicant organization. The NGA signed by the grants management officer is the authorizing document.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NGA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

The NGA will be sent via email or postal system to the administrative official whose name is listed in Block 12 on the Face Page of the Form PHS 398.

2. Administrative Requirements

All NIH Grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General at http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities at http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm.

The following Terms and Conditions will be incorporated into the award statement and will be provided to the Principal Investigator as well as to the appropriate institutional official, at the time of award.

2.A. Cooperative Agreement Terms and Conditions of Award

The following special terms of award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, DHHS grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other DHHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement (NIH U54), an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility reside with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

2.A.1. Principal Investigator Rights and Responsibilities

The PI will coordinate project activities scientifically and administratively at the awardee institution, including research design and protocol development, data collection, quality control, interim data and safety monitoring, final data analysis and interpretation, and preparation of publications . The PI will have primary responsibility for defining the details for the projects within the guidelines of this RFA and for performing all scientific activities. The PI will be responsible for collaborations between his/her Center and NCI Comprehensive Cancer Centers and/or SPOREs as appropriate. The PI will agree to accept the close coordination, cooperation, and participation of the NCI Program Director, NCI Project Scientists, and the CCNE Coordinating and Governance Committee in those aspects of scientific and technical management of the project as described below.

Specifically, the PI will:

- Determine experimental approaches, design protocols, set project milestones, and conduct experiments;
- Propose protocol modifications as required;
- Analyze and interpret research data;
- Provide goals for assay optimization, screening throughput, quality, and cost to the NCI Program Director as requested, usually at the outset of the award and in six-month progress reports, but also at other times if requested;
- Release data according to the approved plans for timely sharing of research resources and data generated through the award, and publish results, as agreed upon by the CCNE Coordinating and Governance Committee;
- Ensure that primary and secondary screening data and assay protocols are deposited in a centralized database, caBIG, according to the timeline implemented by the NCI;
- Establish a Center Steering Committee (CSC) consisting of key Center personnel, external scientific advisors, and the NCI Project Scientist (a public advocate/representative is also recommended), and prepare a concise summary of their meeting within 30 days;
- Serve on the CCNE Coordinating and Governance Committee or appoint an appropriate designee to do so;
- Provide information to the NCI Program Director and Project Scientists concerning progress by submitting periodic progress reports in a standard format, as agreed upon by the CCNE Coordinating and Governance Committee;
- Accept and implement all scientific, practical, and policy decisions approved by the CCNE Coordinating and Governance Committee;
- Share with other CCNE facilities research resources, tools, and data of interest to those facilities, as directed by the CCNE Coordinating and Governance Committee; and
- Be prepared for annual administrative site visits by NCI staff.

Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, and NIH policies.

2.A.2. NIH Responsibilities

The NCI Project Scientist will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below. The Project Scientist will:

- Attend CSC meetings and serve as a CSC participant;
- Assist in avoiding unwarranted duplication of effort across Centers;
- Help coordinate collaborative research efforts that involve multiple Centers;
- Review and comment on critical stages in the research program before subsequent stages are implemented;
- Assist in the interaction between the awardee and investigators at other institutions; and

NCI Project Scientist(s) will also assist the NCI Program Director in stimulating broader NCI program interaction to accelerate the translational research efforts of the CCNE towards clinical trial applications of nanotechnologies developed under this initiative.

In order to carry out these duties, the NCI Project Scientist(s) may consult with other NCI and NIH staff as well as non-NIH experts in the field.

One NCI Project Scientist will be designated as the as the NCI voting participant on the CCNE Coordinating and Governance Committee and attend meetings;

The dominant role and prime responsibility for the activity resides with the awardees for the project as a whole, although specific tasks and activities in carrying out the projects/programs will be shared among the awardees and the NCI Project Scientists.

Additionally, an agency program official or IC Program Director will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice. The NCI Program Director may recommend the termination or curtailment of an investigator or project/program (or an individual award) in the event the partnerships fail to evolve within the intent and purpose of this initiative. The NCI Program Director may also serve as a NCI Project Scientist.

A given individual may be the Program Director for more than one Center.

The NCI Program Director will:

- Exercise the normal stewardship responsibilities of an NIH Program Officer;
- Carry out continuous review of all activities to ensure objectives are being met;
- Have the option to recommend, with the advice of the CCNE Coordinating and Governance Committee, the withholding or reduction of support from any center that substantially fails to achieve its goals according to the milestones agreed to at the time of the award, fails to maintain state-of-the-art capabilities, or fails to comply with the Terms and Conditions of the award;
- Retain the option to recommend additional research endeavors within the constraints of the approved research and negotiated budget.

2.A.3. Collaborative Responsibilities

CCNE Coordinating and Governance Committee:

A CCNE Coordinating and Governance Committee will be established to optimize the flow of information between the Centers, as well as provide statistical, logistics and informatics support for the CCNE network. The CCNE Coordinating and Governance Committee will play a key role in standardizing data collection and reporting with respect to nanotechnology use in clinical oncology. Through its central position as a conduit for the CCNE network, the Coordinating and Governance Committee will be instrumental in disseminating research results and accelerating the translation of research discoveries enabled by the CCNEs into clinically-relevant diagnostics and therapeutics. Specific services provided by the CCNE Coordinating and Governance Committee include: 1) prioritizing materials for further characterization and standardization via an evaluation team; 2) monitoring contemporary developments at external nanotechnology programs; 3) matching appropriate technologies to individual Centers; 4) assessing appropriate destinations/areas for export of technologies developed at the CCNEs; 5) integrating programs across CCNEs; 6) coordinating with the NCL to characterize nanodevices and nanomaterials developed at the CCNEs; 7) interfacing with NCI clinical trials programs; 8) maintaining a set of common data elements that coordinate with caBIG to allow pooling and/or comparisons across and among the CCNEs; 9) establishing an interactive web site partitioned for public access and password-protected study access; 10) developing manuals of policies and procedures for the CCNEs; 11) organizing conference calls and investigator meetings; and 12) providing senior biostatistical and bioinformatics expertise.

The CCNE Coordinating and Governance Committee is the operational governing board responsible for overall coordination of the CCNE program and the committee through which the NCI interacts and collaborates with individual Centers. The CCNE Coordinating and Governance Committee membership will include at least one member from each CCNE (the PI or his/her designee, who must be an investigator from the CCNE research team as identified in the application), one NCI Project Scientist and representatives from public advocacy groups and other Federal agencies. The CCNE Coordinating and Governance Committee will oversee the coordination of the activities of the Centers

and disseminate data, protocols, and other materials to the wider scientific community. Before the end of year 1, the Coordinating and Governance Committee will initiate a review process for proposals for developmental projects, either for pilot projects that have the potential to become new primary projects, or to expand the scale and scope of primary projects towards translational research.

Each CCNE representative will have one vote in the CCNE Coordinating and Governance Committee. The NCI (i.e., the CCNE CGC Project Scientist, or, in his/her place, his/her designated NCI Project Scientist.) and the public advocacy representative will also have one vote each. Center membership on the Coordinating and Governance Committee becomes effective upon issuance of the Notice of Grant Award. The Coordinating and Governance Committee may establish additional by-laws, subcommittees, or workgroups for specific tasks. The NCI Project Scientist(s) may not chair any committee or subcommittee and has (have) no voting rights unless a single Project Scientist is designated by the CCNE CGC Project Scientist to vote in his/her place.

The CCNE Coordinating and Governance Committee meetings will be convened at least twice yearly to assess scientific progress, identify new research opportunities, establish priorities, consider policy recommendations, and discuss strategy. CCNE Coordinating and Governance Committee decisions will be made by a majority vote of a quorum, with an attempt for consensus when possible. A quorum is the presence of a majority of the Center representatives and the CCNE CGC Project Scientist. The CCNE Coordinating and Governance Committee can convene through telephone conference or in person. Outside consultants/experts may be asked to participate in these discussions as nonvoting advisors. The CCNE Coordinating and Governance Committee may also be used to endorse methods, standard operating procedures for quality control, validation methods, data analysis, and data deposition formats that will be used across multiple centers.

The CCNE Coordinating and Governance Committee will:

- Recommend the assignment and scheduling of tasks;
- Develop guidelines to standardize the validation of procedures and data storage across Centers;
- Develop uniform procedures and policies for validation and data quality measures, assessment procedures, and annotation conventions for data depositions in conjunction with the NCI caBIG designee;
- Serve as a venue to coordinate improving the state-of-the-art use of nanotechnology in the academic sector by reporting progress, disseminating best practices, and collectively evaluating new procedures, resources, and technologies;
- Monitor, develop, and implement quality control procedures that assure consistency across Centers;
- Develop a plan for terminating projects that become unpromising or unproductive;
- Schedule meetings (at least twice yearly) and telephone conference calls as necessary for conducting business;
- Schedule one annual meeting at which all CCNE investigators will present their scientific progress and future plans;
- Facilitate the timely release of data in the format and on the schedule recommended by the CCNE Coordinating and Governance Committee; and
- Develop and recommend progress report formats for both individual centers and for the CCNE Program as a whole.

2.A.4. Arbitration Process

Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NCI may be brought to arbitration. An Arbitration Panel composed of three members will be convened. It will have three members: a designee of the Coordinating and Governance Committee chosen without NCI staff voting, one NCI designee, and a

third designee with expertise in the relevant area who is chosen by the other two; in the case of individual awardee disagreement, the first member may be chosen by the individual awardee. This special arbitration panel will establish a procedure to arbitrate the dispute and deliver a recommendation. This special arbitration procedure in no way affects the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulations 42 CFR Part 50, Subpart D and HHS regulations 45 CFR Part 16.

3. Award Criteria

The following criteria will be considered in making funding decisions:

- Scientific merit of the proposed projects as determined by peer review
- Availability of funds
- Relevance of program priorities
- Programmatic balance--The purpose of the CCNEs is to develop a network of pilot Centers with complementary capabilities that will allow the network to address a wide range of biological opportunities for nanotechnology in cancer-- therefore, decisions about awards will consider the mix of capabilities offered by the proposed Centers; and
- Adequacy of proposed data and research resource sharing plans (required in application) and intellectual property management plan (just-in-time requirement).

Adequacy of proposed data and research resource sharing plans and intellectual property management plan. The goals of the CCNE program are to create nanotechnology-based tools and products for the prevention, detection, diagnosis, and treatment of cancer that are suitable for testing in clinical trials, to make data publicly available through caBIG, and to identify/generate a diverse set of research tools to explore mechanisms of cancer.

Applicants selected for funding in response to this RFA are expected to include a plan addressing how they will exercise their intellectual property rights, should any intellectual property be generated under a Center award, while making such research resources available to the broader scientific community for research purposes consistent with the goals of the NCI Alliance for Nanotechnology in Cancer. A reasonable time frame for release of materials should be specified in the data sharing plan and will be considered by NCI Program staff. Furthermore, transfers of research resources must be made consistent with the NIH Research Tools Policy (http://www.ott.nih.gov/policy/rt_guide_final.html) and other NIH sharing policies. In the development of any sharing and intellectual property plans, applicants should confer with their own institution's office(s) responsible for handling technology transfer related matters and/or their sponsored research office. If applicants or their representatives require additional guidance in preparing these plans, they are encouraged to make further inquiries to the appropriate contacts listed below for such matters.

NCI program staff, in determining whether the application shall be awarded, will consider the adequacy of the proposed plans. The plans as approved after negotiation with the applicant when necessary will be part of the terms and conditions of the award. Evaluation of non-competing continuation applications will include assessment of the Center awardee's adherence to the proposed plans, and will be a criterion for continued funding of the award.

Applicants also are reminded that the grantee institution is required to disclose each subject invention to NCI within 2 months after the inventor discloses it in writing to grantee institutional personnel responsible for patent matters. The NCI reserves the right to monitor awardee activity in this area to ascertain if patents or patent applications are adversely affecting the goals of this RFA.

Public Domain of Data

All awards made under this RFA are subject to the Final NIH Statement on Sharing Research Data (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>) and the Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources (http://www.ott.nih.gov/policy/rt_guide_final.html). This document also defines terms, parties, responsibilities, prescribes the order of disposition of rights, prescribes a chronology of reporting requirements, and delineates the basis for and extent of government actions to retain rights. Patent rights clauses may be found at 37 CFR Part 401.14 and are accessible from the Interagency Edison web page, <http://www.iedison.gov>. It is expected that research resources generated through the award will be shared by awardees according to these guidelines. The plans for the development of resources for use by the biomedical community will have the appropriate timelines and milestones. NCI program staff will evaluate the compliance with the sharing plan and scientific progress in the non-competing progress report (Form 2590); such compliance will be a criterion for continued funding of the award.

Awardees are expected to comply with the intellectual property guidelines adopted by NCI for the CCNE RFA. In the interim, awardees will comply with their approved plan for addressing if, or how, they will exercise their intellectual property rights, should any intellectual property be generated under a center award, while making such research resources available to the broader scientific community consistent with the goals of the NCI Alliance for Nanotechnology in Cancer. The plan would include a reasonable time frame for release of materials. This plan would also include disclosure of any pre-existing agreements involving intellectual property rights, including options to for-profit research sponsors that are associated with biomaterials and data that may be generated.

NCI program staff will evaluate the compliance with the sharing plan and scientific progress in the non-competing progress report (Form 2590); such compliance will be a criterion for continued funding of the award.

4. Reporting

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 2590 annually (<http://grants.nih.gov/grants/funding/2590/2590.htm>) and financial statements as required in the NIH Grants Policy Statement. The annual progress report for the U54 award will use the standard 2590 form as well as supplementary information that will be more extensive. Additional information in the progress report will include both the progress made in the Center as well as the relationship between the Center and collaborators. Details of the U54 progress report are spelled out in the notice of grant award and in the Terms and Conditions section of this RFA. Applications for U54 centers should contain appropriate personnel to collect the needed information and to prepare this progress report.

Because of the complexity of the CCNEs, NCI program staff will conduct annual administrative site visits. U54 centers should be prepared for annual site visits and should budget appropriately (including travel for collaborators and other necessary costs).

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific/Research Contacts:

Gregory J. Downing, D.O., Ph.D.
Director, Office of Technology and Industrial Relations
Office of the Director
National Cancer Institute, NIH, DHHS
Building 31, Room 10A-52, MSC 2580
31 Center Drive
Bethesda, MD 20892-2580
Telephone: (301) 496-1550
FAX: (301) 496-7807
Email: downingg@mail.nih.gov

2. Peer Review Contacts:

Referral Officer
National Cancer Institute
Division of Extramural Activities
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 496-3428
FAX: (301) 402-0275
E-mail: nciref@dea.nci.nih.gov

3. Financial or Grants Management Contacts:

Kathy Dunn
Grants Management Specialist
Grants Administration Branch
National Cancer Institute
6120 Executive Boulevard, EPS Room 243
Bethesda, MD 20892
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 846-6829
FAX: (301) 846-5720
E-mail: dunnkath@mail.nih.gov

Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:

Recipients of PHS support for activities involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (<http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf>), as mandated by the Health Research Extension Act of 1985 (<http://grants.nih.gov/grants/olaw/references/hrea1985.htm>), and the USDA Animal Welfare Regulations (<http://www.nal.usda.gov/awic/legislat/usdaleg1.htm>), as applicable.

Human Subjects Protection:

Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>).

Data and Safety Monitoring Plan:

Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity, and dose-finding studies (Phase I); efficacy studies (Phase II); and efficacy, effectiveness, and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants. (See the NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts at <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>.)

Sharing Research Data:

Investigators submitting an NIH application seeking \$500,000 or more in direct costs in any single year are expected to include a plan for data sharing (http://grants.nih.gov/grants/policy/data_sharing) or state why this is not possible.

Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, State, and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Sharing of Model Organisms:

NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time, the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh-Dole Act (see the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal beginning with the October 1, 2004, receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Inclusion of Women And Minorities in Clinical Research:

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:

The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at <http://grants.nih.gov/grants/funding/children/children.htm>.

Required Education on The Protection of Human Subject Participants:

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

Human Embryonic Stem Cells (hESC):

Criteria for federal funding of research on hESCs can be found at <http://stemcells.nih.gov/index.asp> and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see <http://escr.nih.gov/>). It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

Public Access to Research Data through the Freedom of Information Act:

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are: (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget

justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Standards for Privacy of Individually Identifiable Health Information:

The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information," the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR web site (<http://www.hhs.gov/ocr>) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>.

URLs in NIH Grant Applications or Appendices:

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople>.

Authority and Regulations:

This program is described in the Catalog of Federal Domestic Assistance at <http://www.cfda.gov/> and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Kirschstein-NRSA Awards are made under the authorization of Section 487 of the Public Health Service Act as amended (42 USC 288) and Title 42 of the Code of Federal Regulations, Part 66. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Loan Repayment Programs:

NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The LRP is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career

award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50% of their time (at least 20 hours per week based on a 40 hour week) for two years to the research. For further information, please see: <http://www.lrp.nih.gov/>.

[Weekly TOC for this Announcement](#)
[NIH Funding Opportunities and Notices](#)



Office of
Extramural
Research
(OER)



National
Institutes of
Health (NIH)
9000 Rockville
Pike
Bethesda,
Maryland
20892



Department of
Health
and Human
Services (HHS)



Note: For help accessing PDF, RTF, MS Word, Excel, PowerPoint, RealPlayer, Video or Flash files, see
[Help Downloading Files](#).

Cancer Nanotechnology Platform Partnerships

RFA Number: RFA-CA-05-026

Part I Overview Information

Department of Health and Human Services

Participating Organizations

National Institutes of Health (NIH), (<http://www.nih.gov/>)

Components of Participating Organizations

National Cancer Institute (NCI), (<http://www.nci.nih.gov/>)

Announcement Type

New

Update: The following update relating to this announcement has been issued:

- [December 2, 2004](#) (NOT-CA-05-006) - NCI will hold a pre-application meeting for investigators planning to submit applications in response to RFA-CA-05-026.

Catalog of Federal Domestic Assistance Numbers

93.393, 93.399

Key Dates

Release Date: November 30, 2004

Letter of Intent Receipt Date: February 25, 2005

Application Receipt Date: March 25, 2005

Peer Review Date: June/July 2005

Council Review Date: September 2005

Earliest Anticipated Start Date: September 2005

Additional Information To Be Available Date (URL Activation Date): Not Applicable

Expiration Date: March 26, 2005

Due Dates for E.O. 12372

Not Applicable

Executive Summary

The National Cancer Institute (NCI) invites applications for research project grants (RPGs) to support development of nanotechnology platforms for basic, applied, and translational multi-disciplinary research that uses nanotechnology (e.g., nanoscale devices or nanomaterials less than 1000 nm in size, although the assembly, synthesis, and/or fabrication of components at dimensions less than 300 nm should be demonstrated) in cancer research. Proposed projects will be eligible for consideration if they address one or more of the following thematic/programmatic areas of focus: molecular imaging and early detection, *in vivo* imaging, reporters of therapeutic efficacy, multifunctional therapeutics, prevention and control of cancer, and research enablers. The NCI intends to commit approximately 7 million dollars in FY 2005 to fund approximately 10 new grants in response to this RFA. An applicant may request a project period of up to 5 years and a budget for total costs up to 1 million dollars per year.

Eligible organizations include for-profit or non-profit organizations, public or private institutions (such as universities, colleges, hospitals, and laboratories), units of State and local governments, eligible agencies of the Federal government, and domestic institutions/organizations. Foreign institutions are not eligible to apply, but an application may include collaborative work at a foreign site when the expertise at the foreign site is not present in the United States. Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with his or her eligible institution to develop an application for support. An applicant may submit one application in response to this RFA. Application materials are available from the NIH Office of Extramural Research (OER; <http://grants.nih.gov/grants/oer.htm>). Telecommunications for the hearing impaired is available at: TTY 301-451-0088.

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

The National Cancer Institute (NCI) invites applications for research project grants (RPGs) to support development of nanotechnology platforms for basic, applied, and translational multi-disciplinary research that uses nanotechnology (e.g., nanoscale devices or nanomaterials less than 1000 nm in size, although the assembly, synthesis, and/or fabrication of components at dimensions less than 300 nm should be demonstrated) in cancer research. In the context of this program, a multi-disciplinary research team must be assembled to apply an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose, or treat cancer. The research team must include appropriate bioengineering or allied physical/computational sciences in combination with biomedical and/or clinical components to address a cancer-related focus. The Principal Investigator (PI) serves as the project manager and must be capable of leading the proposed effort. The research team may propose design-directed, developmental, discovery-driven, or hypothesis-driven research at universities, national laboratories, medical schools, large or small businesses, or other public and private entities or combinations of these entities. It is expected that in the application the team will present a well-defined goal or deliverable that will be achieved based on objective milestones specified for the overall project period. This RFA uses components of team engineering approaches such as Bioengineering Research Partnerships (BRPs; <http://grants2.nih.gov/grants/guide/pa-files/PAR-04-023.html>) and Bioengineering Research Grants (BRGs; <http://grants2.nih.gov/grants/guide/pa-files/PAR-02-011.html>). This RFA supports the NCI's Alliance for Nanotechnology in Cancer, which is detailed below.

Current clinical cancer-related nanotechnology research has demonstrated advances in areas such as laboratory-based diagnostics (e.g., nanowires, quantum dots, “lab-on-a-chip” applications), *in vivo* diagnostic imaging (e.g., contrast agents, implantable biosensors), and therapeutics (e.g., dendrimers, engineered virus particles, multifunctional nanodevices). These developments will provide insight into the understanding and measurement of numerous aspects of the tumor microenvironment, including the production of growth signals, and the regulation of apoptosis, angiogenesis, replication, metastasis, and genomic instabilities. Nanotechnology encompasses a broad range of novel materials, strategies, and devices, and the intent of this RFA is to benefit basic biological and preclinical research by increasing the variety of available nanotechnologies for cancer and to catalyze their development and commercialization by the public or private sector.

It is expected that nanotechnology will enable numerous applications in cancer research and treatment, including (but not limited to):

- Imaging agents and diagnostics that will allow clinicians to detect cancer in its earliest stages;
- Systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation;
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents directly to cancer cells and those tissues in the microenvironment that play a critical role in the growth and metastasis of cancer;
- Agents that can monitor predictive molecular changes and prevent precancerous cells from becoming malignant;
- Novel methods to manage the symptoms of cancer that adversely impact quality of life; and
- Research tools that will enable rapid identification and validation of new targets for clinical development and predict drug resistance.

The NCI Alliance for Nanotechnology in Cancer. Nanotechnology's dimensions and multifunctional capabilities enable investigators to study and interact with normal and cancer cells in real time, at the molecular and cellular scales, and during the earliest stages of the cancer process. Nanotechnology will be a mission-critical tool to meet the NCI's Challenge Goal of eliminating the suffering and death due to cancer. To enable nanotechnology to become a fundamental driver of advances in oncology and cancer research, the NCI has developed a series of directed programmatic mechanisms known collectively as the Alliance for Nanotechnology in Cancer (<http://nano.cancer.gov>). The Alliance is an integrated 5-year initiative to develop and apply nanotechnology to cancer prevention, detection, diagnosis, and treatment. The ultimate goal of the Alliance is to benefit the cancer patient through the delivery of novel therapeutics and enhanced diagnostic tools.

The three core elements of the Alliance for Nanotechnology in Cancer are:

- The establishment of **Centers for Cancer Nanotechnology Excellence** (CCNEs), which will serve as hubs to develop and apply nanotechnology solutions to the diagnosis, prevention, and treatment of cancer; (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-024.html>)
- Support for the **career development** of investigators for multi-disciplinary nano-oncology research; (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-025.html>) and
- Support for individual **investigator-initiated projects** in cancer nanotechnology platform development and applications through partnerships.

NCI Resources. The Alliance is designed to integrate nanotechnology research and development (R&D) with existing NCI resources that includes Comprehensive Cancer Centers (<http://www3.cancer.gov/cancercenters/>), Specialized Programs of Research Excellence (<http://spores.nci.nih.gov/>), and the Early Detection Research Network (<http://www3.cancer.gov/prevention/cbrg/edrn/>). CCNEs will also engage with relevant NCI initiatives such as the Developmental Therapeutics program (http://dtp.nci.nih.gov/docs/raid/raid_index.html), the Academic Public Private Partnership Program (<http://grants2.nih.gov/grants/guide/rfa-files/RFA-CA-04-005.html>), the Development of Clinical Imaging Drug Enhancers program (<http://www3.cancer.gov/bip/dcide.htm>), the Integrative Cancer Biology Program (<http://dcib.nci.nih.gov/branchdetail.cfm?branch=1>), the Innovative Molecular Analysis Technologies program (<http://otir.nci.nih.gov/tech/imat.html>), Unconventional Innovations Program (<http://otir.nci.nih.gov/tech/uip.html>), the Fundamental Technologies for Biomolecular Sensors program (<http://otir.nci.nih.gov/tech/ftbs.html>), and the Mouse Models of Human Cancer Consortium (<http://emice.nci.nih.gov/>). These linkages will increase the visibility and availability of nanomaterials and nanoscale device technology within the cancer research and development communities, and they will promote further collaboration with other Federal agencies. Respondents to this RFA will be expected to integrate scientific approaches, collaborate in design and testing of nanotechnology

platforms, and share common resources and data with the Steering and Governance Committee of the Cancer Centers of Nanotechnology Excellence.

Objectives

Successful application of nanotechnology to cancer research requires an understanding of how synthetic materials developed from the atomic-level interface with biological systems that are relevant to genetic, cellular, and molecular features of cancer. Thus, the success of the Alliance initiatives hinges upon the breakthroughs of multidisciplinary research teams whose combined expertise extends beyond the individual disciplines of traditional biological and clinical sciences.

Bioengineering integrates principles from a diversity of technical and biomedical fields and crosses the boundaries of many scientific disciplines represented throughout academia, laboratories, and industry. The creativity of these interdisciplinary teams will be a central component of cancer nanotechnology, as it results in new basic understandings and in innovative platform technologies that lead to diagnostic and therapeutic delivery systems.

The primary objective of this RFA is to encourage basic, applied, and translational scientific and engineering methods through multidisciplinary team approaches to create new nanoscale platform technologies that are relevant to cancer processes. A nanotechnology platform is characterized in the following section (see below). By integrating physical, engineering, and computational science principles with biological and clinical applications, bioengineering research can advance fundamental concepts, create knowledge from the molecular to the organ systems level, and develop innovative materials, devices, and informatics approaches to prevent, detect, diagnose, and treat cancer. Applicants for this RFA may propose research that leads to novel devices, and partnerships with companies that have relevant expertise or that may eventually be involved in commercialization are appropriate under this program.

A second objective is to encourage collaborations and partnerships among the allied quantitative and biomedical disciplines that interface with cancer research. An applicant must bring together the necessary physical, engineering, and computational science expertise with biological or clinical expertise and resources to address a significant area of targeted cancer research in one or more of six thematic areas (see below). In addition to the benefits to be derived from the research, the collaborations and partnerships can create opportunities for trans-disciplinary communication and training for a new generation of scientists capable of interacting across traditional technical boundaries. As such, applicants for this RFA will be expected to collaborate with researchers at the NCI Centers of Cancer Nanotechnology Excellence and utilize all appropriate collaborative opportunities catalyzed by the Alliance.

Nanotechnology Platforms. The National Nanotechnology Initiative (NNI; <http://nano.gov/html/facts/whatisNano.html>) characterizes “nanotechnology” as meeting the following criteria: 1) Research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1 - 100 nanometers; 2) Creating and using structures, devices, and systems that have novel properties and functions because of their small and/or intermediate size; and 3) Having the ability to control or manipulate on the atomic scale. For the purposes of this application, applicants are encouraged to use the NNI definition as a guideline, with the following addenda: 1) Applicants must propose research platforms or base materials that are less than 1000 nm in size, although the assembly, synthesis, and/or fabrication of components at dimensions less than 300 nm should be demonstrated ; and 2) Projects must incorporate synthetic or engineered materials or biomaterials that have been engineered to become nanomaterials (e.g., carbon nanotubes). Projects that propose only the use of unmodified, naturally-occurring materials (e.g., carbohydrates, proteins, baculovirus) will be considered not responsive and will be returned to the applicant without review.

For reference purposes, nanotechnology platforms that are appropriate for this RFA include but are not limited to base particles such as: dendrimers, carbon-based nanostructures (e.g., nanotubes,

nanopores), perfluorooctylbromide (PFOB), Polyacrylamide/Sol-Gel Silica, peptide nucleic acids/PNA-peptides, immunoliposomes, SiO₂/pS and polymer micelles, and virus- and carbohydrate-based hydrogels. Contrast agents based on gadolinium, iron, gold, technetium, indium or copper, as well as engineered fluorophores, are also appropriate. Applicants are encouraged to consider new biomaterial composites as their physicochemical properties address problems of biological significance such as biofouling, protein aggregation, etc. Examples of base platforms include but are not limited to: nanowires, cantilevers, quantum dots, biomolecular sensors, nanoshells, nanoparticles, nanoscale harvesters, nanochannels, imaging agents and methods, and integrated, "lab-on-a-chip" diagnostic tools.

Cancer Focus Areas. In accordance with the principles of the Alliance, the NCI has identified six thematic/programmatic areas of focus for directed nanotechnology-based research platforms where nanotechnology can have a pronounced impact in the short- and long-terms. These areas of interest are described below :

- 1) Molecular imaging and the early detection of cancer - Novel nanotechnologies can complement and augment existing genomic and proteomic techniques to analyze variations across different tumor types, thus offering the potential to distinguish between normal and malignant cells. Sensitive biosensors constructed of nanoscale components (e.g., nanocantilevers, nanowires, and nanochannels) can recognize genetic and molecular events and have reporting capabilities, thereby offering the potential to detect rare molecular signals associated with malignancy. Such signals may then be collected for analysis by nanoscale harvesters that selectively isolate cancer-related molecules from tissues. Another area with near-term potential for early detection is the identification of mutations and genomic instability *in situ*.
- 2) *In vivo* imaging - A pressing need in clinical oncology is for imaging methods (e.g., optical, magnetic resonance-based, ultrasound) that can identify tumors that are orders of magnitude smaller than those detected with current technology. When utilized in conjunction with powerful contrast agents, coupled with nanoparticles such as dendrimers, these methods can improve targeting capability and increase signal intensity. In the future, implantable nanoscale biomolecular sensors may enable clinicians to more carefully monitor the disease-free status of patients who have undergone treatment or individuals susceptible to cancer because of various risk factors. Furthermore, imaging agents that target changes in the environment surrounding a tumor, such as angiogenesis, will further augment methodologies and will be invaluable to obtain optimal benefit from therapeutics that target such specific cancer-related processes.
- 3) Reporters of therapeutic efficacy - Nanotechnology offers the potential to develop highly sensitive imaging-based devices and *ex vivo* diagnostics that can determine whether a therapeutic agent is reaching its intended target and whether that agent is killing malignant or support cells. Optical imaging devices that use nanoscale agents may also enable surgeons to more readily detect the margins of a tumor prior to resection or to detect micrometastases in lymph nodes or tissues distant from the primary tumor. Nanoparticle-based systems to detect apoptosis or reactivation of the p53 system and targeted nanoparticles that can bind to a tumor and be re-released into the bloodstream as tumor cells undergo apoptosis following therapy represent another potential application of nanotechnologies as reporters of efficacy.
- 4) Multifunctional therapeutics - Because of their multifunctional capabilities, nanoscale devices can contain both targeting agents and therapeutic payloads, particularly in areas of the body that are difficult to access because of a variety of biological barriers, including those developed by tumors. Multifunctional nanoscale devices also offer the opportunity to utilize new approaches to therapy, such as localized heating or reactive oxygen generation, and to combine a diagnostic or imaging agent with a therapeutic and/or a reporter of therapeutic efficacy. "Smart" nanotherapeutics may provide clinicians with the ability to time the release of an anticancer drug or deliver multiple drugs sequentially in a timed manner or at several locations in the body, potentially ushering in an era of sustained therapy for cancers that must be treated chronically. Such nanotherapeutics could also

house engineered cellular “factories” that make and secrete proteins and other antigrowth factors that impact a tumor and/or its immediate environment. Many nanotherapeutics (e.g., nanoparticulate hydrogels, nanoparticles, and quantum dots) can also double as imaging agents.

5) Prevention and control of cancer - Many of the advances that nanotechnology will enable in each of the four preceding areas will also find widespread applicability in efforts to prevent and control cancer. Once specific biomarkers of cancer susceptibility and precancerous lesions have been identified, nanotechnology can enable devices that signal their presence and deliver targeted therapy. Nanoscale devices may also prove valuable for delivering polyepitope cancer vaccines that engage the immune system or for delivering cancer-preventing nutraceuticals or other chemopreventive agents in a sustained, time-release and targeted manner.

6) Research enablers - Nanotechnology offers a wide range of tools, from chip-based nanolabs capable of monitoring and manipulating individual cells to nanoscale probes that can track the movements of cells, and even individual molecules, as they move about in their environment. Using such tools will enable cancer biologists to study, monitor, and alter the multiple systems that are implicated in cancer processes and identify key biochemical and genetic targets for future molecular therapies. As such, nanotechnology can complement other technology platforms, such as proteomics and bioinformatics. Another near-term application of nanotechnology to accelerate basic research is to use molecular-size nanoparticles with a wide range of optical properties (e.g., quantum dots) to track individual molecules or cells as they move through local environments, thereby monitoring multiplexed cellular and molecular events in real time. When combined with mouse models that reproduce the genetic, biochemical, and physiological properties of human cancers, these nanolabels will be useful for integrative, systems biology research. Finally, nanoscale devices that enable simultaneous biochemical measurements (e.g., time, size, dynamic events) on multiple cells, particularly those grown in such a way as to mimic tissue development *in vivo*, will bring new dimensionality to basic cancer research.

While the NCI has identified these specific programmatic research areas, the Institute recognizes the breadth and scope of current cancer nanotechnology projects. The specific cancer nanotechnology applications described under each thematic/programmatic area are provided only as examples to highlight the diverse tools and strategies of cancer nanotechnology research supported by this RFA.

Quantitative Milestones. All applications for nanotechnology platform awards must include a specific section labeled “Milestones.” Milestones should be submitted annually (at a minimum) and should be well-described, quantitative, scientifically justified and not simply a restatement of the specific aims. Rather, the milestones should offer a timeline and a pathway for the development of the proposed technology. These milestones will be used to judge the success of the proposed research and to evaluate the criteria for the program. Applications that lack quantitative milestones as determined by the NCI program staff will be returned to the applicant without review.

Section II. Award Information

1. Mechanism of Support

This funding opportunity will use the R01 award mechanism. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

This funding opportunity uses just-in-time concepts. It also uses the modular as well as the non-modular budget formats (see <http://grants.nih.gov/grants/funding/modular/modular.htm>). Specifically, if you are submitting an application with direct costs in each year of \$250,000 or less, use the modular budget format described in the PHS 398 application instructions. Otherwise, follow the instructions for non-modular research grant applications.

2. Funds Available

The NCI intends to commit approximately 7 million dollars in FY 2005 to fund ten new grants in response to this RFA. An applicant may request a project period of up to 5 years and a budget for total costs up to 1 million dollars per year.

Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. The NCI will look to fund a variety of proposals in terms of scale and scope. Although the financial plans of the IC(s) provide support for this program, awards pursuant to this funding opportunity are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. The RFA may be reissued in the future, contingent upon the availability of funds.

For new grants, the maximum total (direct plus facilities and administrative [F&A] costs) budget to be awarded in any year is \$1 million.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

You may submit (an) application(s) if your organization has any of the following characteristics:

- For-profit organizations
- Non-profit organizations
- Public or private institutions such as universities, colleges, hospitals, and national laboratories
- Units of State government
- Units of local governments
- Eligible agencies of the Federal government
- Domestic institutions
- Faith-based or community-based organizations

Foreign institutions are not eligible to apply as Principal Investigators. However, collaborative projects may include work at a foreign site when the expertise at the foreign site is not present in the United States.

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

Applications for renewal or supplementation of existing projects are not eligible to compete with applications for new awards supported by this RFA.

2. Cost Sharing

This program does not require cost sharing.

3. Other-Special Eligibility Criteria

Research Focus Areas: Applicants must state how their proposed project(s) support one or more of the six thematic/programmatic areas of focus for directed nanotechnology-based research platforms listed in the RESEARCH OBJECTIVES section of this RFA. Applicants should clearly describe how their proposed projects will address fundamental principles of cancer biology (e.g., apoptosis, metastasis, protein folding and assembly, DNA repair, recognition of mutational deletions in lymphocytes, cell cycle regulation, loss of heterozygosity) at the molecular and/or sub-cellular levels in terms of the biology and chemistry involved (e.g., energy transfer and cellular thermodynamics, surface properties and phenomena, molecular self-assembly). Emphasis should be placed on why the approach is revolutionary within the context of related research and how it will overcome biological barriers and interfere with the biological processes involved in carcinogenesis.

Section IV. Application and Submission Information

1. Address to Request Application Information

The PHS 398 application instructions are available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. For further assistance, contact GrantsInfo, Telephone: (301) 435-0714, Email: GrantsInfo@nih.gov.

Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the PHS 398 research grant application instructions and forms. Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at <http://www.dnb.com>. The D&B number should be entered on line 11 of the face page of the PHS 398 form.

The title and number of this funding opportunity must be typed on line 2 of the face page of the application form and the YES box must be checked.

1. Page limitations for both new and competing continuation applications have been increased to a maximum of 40 pages from the usual 25-page limit for sections A-D of the "Research Plan." Applicants are encouraged to be concise and use fewer pages.
2. Description page - In addition to the information requested on Form Page 2, identify in the Description the name(s) of the institution(s) leading the project and other participating institutions. The Description should clearly indicate the area(s) of cancer nanotechnology research that will be the focus of the application, the planned multi-disciplinary approach, and the specific objective of the project.

To provide recognition of the essential contributions of partners who provide significant intellectual leadership to the nanotechnology platform project, applicants are strongly encouraged to include information about Lead Investigators in the Description, which becomes publicly accessible. Lead Investigators are those who provide essential scientific, engineering, technical, and visionary leadership to the effort. In the past, applications might have listed such individuals as Key Personnel. Include in the Description the following information about each Lead Investigator: name, institution if different from the applicant organization, and one sentence about the leadership role. The description

of the roles of Lead Investigators should be provided in greater detail in the narrative for personnel in the budget section.

The Lead Investigators will usually include the Principal Investigator and a subset of the Key Personnel. The following information is provided to clarify the roles of the various individuals who are to be named on this page. NIH grants policy requires that each application designate a single Principal Investigator (PI) who: (1) is responsible for the overall scientific and technical direction of the effort; and (2) serves as the contact person with whom NIH staff will interact. Lead Investigators provide essential scientific, engineering, technical, and visionary leadership to the effort. Key Personnel are those individuals who contribute in a substantive way to the scientific or engineering development or execution of the project.

3. An organization chart (OC) that clearly defines the partnership and relationships among its various components must be included with the application. A project plan (PP) should accompany the OC and list major tasks with a timeline of quantitative milestones for the entire project period. The OC and PP must not exceed one page each. This information should be included along with the Research, Design, and Methods section of the application.

4. Nanotechnology Platform Budget Items - A separate budget for each partner at a subcontract/consortium institution, and when appropriate for clarity, for each partner within the grantee institution must be included. Include a summary budget for all research team participants with partners at non-grantee institutions shown as consortium arrangements. It is understood that this is an initial budget, and that the PI has the responsibility to reallocate funds during the project to accomplish the platform development goals. Rebudgeting of funds must be done in accordance with the NIH Grants Policy Statement found at http://grants.nih.gov/grants/policy/nihgps_2003/index.htm.

The NCI will not provide annual support in excess of \$1 million total cost for any year for new applications. Direct cost inflationary increases following the first year may be included, but the maximum total cost request level of \$1 million per year must be observed. Negotiated costs assessed by partnering organizations do not need to be included in direct costs.

The PI is expected to devote a minimum of 25 percent effort to the proposed project. The percent effort requested for all personnel should be limited to time devoted specifically to project activities and not to other research projects. Information documenting the level of effort on project-related activities should be included in the application. The need for all requested personnel costs should be thoroughly justified.

There will be an annual meeting of the Alliance for Cancer Nanotechnology at a date and location to be determined by NIH staff. Applicants should include travel funds specifically for these meetings in the budget request.

Applicants may request and justify additional travel funds. Travel funds could be used to promote collaboration among partners at different institutions or at a distant site, for travel of external advisors to the collaborating site, and/or for partners to attend scientific meetings essential to the progress of the project and for which other funds are not available.

Other expenses can be requested including costs necessary for the central administration and fiscal management of the research team including relevant and reasonable costs for reprints, graphics, and publications.

With regard to projected funding by source, some applicants may anticipate or receive commitments for significant funding from sources other than the NIH (e.g., from a collaborating company). Applicants are responsible to verify that terms and conditions under other funding from non-NIH

sources, if any, must not conflict with the terms and conditions under any NIH funding agreement, if awarded.

5. Resources - The application should describe the equipment and facilities available for the proposed research project.

If the project entails an institutional commitment of resources across boundaries in the institution or anticipates the provision of institutional resources, letters from appropriate senior-level individuals describing their agreements to support those commitments must be included.

Where appropriate, describe the shared facilities to be established including specific major research instruments and plans for the development of instruments. Describe plans for maintaining and operating the facilities including staffing, provisions for user fees, and plans for ensuring access to outside users. Distinguish between existing facilities and those still to be developed.

6. Research Plan

A. Specific Aims – A research team may propose design-directed, developmental, discovery-driven, or hypothesis-driven research focused on yielding nanotechnology platforms. Thus, the application should state the hypotheses, designs, problems, and/or needs that will drive the proposed research. Describe the specific aims in the appropriate area of cancer research and the quantitative milestones for the nanotechnology development project period. The quantitative milestones should occupy a separate section and be consistent with the requirements under the section above on Objectives. Describe the expected cancer applications of the nanotechnology platform that will improve human health. One page is recommended.

B. Background and Significance - Briefly describe the area of cancer research that is the focus of the nanotechnology development project. Critically evaluate existing knowledge and approaches that have been or are being applied in the area and specifically describe how the proposed approach will advance the field. State concisely the importance and health relevance of the research proposed to achieve the Specific Aims.

C. Preliminary Studies and Rationale - Preliminary studies that support the proposed research should be described in the application.

D. Research Design and Methods - A research project should focus on developing nanotechnology platforms as previously described to address a specific area or problem in cancer research within the six areas previously described, with the direct goal of enabling cancer research and clinical application. The research plan should be sufficiently long term and comprehensive to justify organizing a research team and adaptable enough to permit change as the research proceeds. The integrative systems approach and its appropriateness for the proposed project should be described including plans for collecting, analyzing, and interpreting data. A timetable of events including quantitative milestones or other evaluative criteria should be included. The contributions of each partner and how these will be integrated and organized to accomplish the specific aims of the project should be described. Potential technical challenges and possible alternative approaches to achieve the aims of the project should be discussed. Plans for enhancing the abilities and opportunities for investigators and trainees to work across disciplinary boundaries should also be included. If the proposed research and technology development is closely related to ongoing research and technology development, explain how the research activities of the proposed team will complement but not overlap the existing research.

7. NIH expects applications to include a plan for making available to the research community any technologies developed or enhanced by work conducted as part of the request for applications. The plan should include ordering of authors and provision for publication/recognition of the contributions of each essential co-author. This plan should be described in the Research Design and Methods

section of the application. Investigators using PHS funds are required to make unique research resources readily available for research purposes to qualified individuals within the scientific community when the results have been published. The intent of this policy is not to discourage, impede, or prohibit the organization that develops the unique research resources or intellectual property from commercializing the products. Refer to [Section IV.6.](#) for details of required data and research resource sharing plans as well as the just-in-time requirements for intellectual property management plans.

3. Submission Dates

Applications must be received on or before the receipt date described in [Section IV.3.A..](#)

3.A. Receipt, Review and Anticipated Start Dates

Release Date: November 30, 2004

Letter-of-Intent Receipt Date: February, 2005

Application Receipt Date: March 25, 2005

Peer Review Date: June/July 2005

Council Review Date: September 2005

Earliest Anticipated Start Date: September 2005

3.A.1. Letter of Intent

Prospective applicants are asked to submit a letter-of-intent that includes the following information:

- Descriptive title of proposed research
- Name, address, and telephone number of the Principal Investigator
- Names of other key personnel
- Participating institutions
- Number and title of this funding opportunity

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document.

The letter of intent should be sent to:

Gregory J. Downing, D.O., Ph.D.
Director, Office of Technology and Industrial Relations
Office of the Director
National Cancer Institute, NIH, DHHS
Building 31, Room 10A-52, MSC 2580
31 Center Drive
Bethesda, MD 20892-2580
Telephone: (301) 496-1550
FAX: (301) 496-7807
Email: downingg@mail.nih.gov

3.B. Sending an Application to the NIH

Applications must be prepared using the PHS 398 research grant application instructions and forms as described above. Submit a signed, typewritten original of the application, including the checklist, and three signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

At the time of submission, two additional copies of the application and all five copies of the appendix material must be sent to:

National Cancer Institute
Division of Extramural Activities
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 496-3428
FAX: (301) 402-0275
Email: ncirefof@dea.nci.nih.gov

Appendices should be comprised of unbound materials with separators between documents.

Using the RFA Label: The RFA label available in the PHS 398 application instructions must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at <http://grants.nih.gov/grants/funding/phs398/labels.pdf>.

3.C. Application Processing

Applications must be **received on or before the application receipt date** listed in the heading of this funding opportunity. If an application is received after that date, it will be returned to the applicant without review.

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NCI. Incomplete and/or non-responsive applications will not be reviewed.

The NIH will not accept any application in response to this funding opportunity that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to a funding opportunity, it is to be prepared as a NEW application. That is, the application for the funding opportunity must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

4. Intergovernmental Review

This initiative is not subject to [intergovernmental review](#).

5. Funding Restrictions

All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm> (see also [Section VI.3. Award Criteria](#)).

6. Other Submission Requirements

RESEARCH TEAM ORGANIZATIONAL STRUCTURE, LEADERSHIP, AND MANAGEMENT: An organizational structure that clearly defines the partnership and relationships among the various components must be developed and described in the application; the size, structure, and mode of operation should match the needs and scope of the proposed research. NIH policy requires that a single PI be designated on the face page of all applications. While this individual is responsible for the scientific and technical aspects, as well as the proper conduct of the project, the structure of the proposed nanotechnology platform project may involve more than one individual in developing the application and in making decisions concerning planning, management, staffing, and resource allocation. In recognition of the essential intellectual and/or technical contributions of the lead scientists responsible for developing and implementing the goals of the proposal, the organizational structure must include a “Leadership Statement” that specifies the roles of the individuals that provide major intellectual and/or technical contributions. The PI has the responsibility and authority to use funds in the most productive way to achieve the goals defined at the time of the award. To accomplish these tasks, the PI in collaboration with other individuals identified in the “Leadership Statement” can adjust funding among research team participants to support new partners or to reduce support to existing partners as needed. Please note the use of funds is governed by NIH Grants Policy Statement (http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). The research proposal should establish a Scientific Steering Group that consists of representatives from each of the partnering organizations and meets regularly to discuss project status, problems, and directions. Those individuals identified in the “Leadership Statement,” who together would have the intellectual and leadership responsibilities normally attributed to the PI, would likely be members of the Scientific Steering Group.

NANOTECHNOLOGY PLATFORM PI MEETING: PIs will meet annually to share results, to ensure that the NIH has a coherent view of the advances in these fields, and to have an opportunity for collective problem solving among the PIs. The cost of participating in this annual meeting should be included in the budget.

Plan for Sharing Research Data

The precise content of the data-sharing plan will vary, depending on the data being collected and how the investigator is planning to share the data. Applicants who are planning to share data may wish to describe briefly the expected schedule for data sharing, the format of the final dataset, the documentation to be provided, whether or not any analytic tools also will be provided, whether or not a data-sharing agreement will be required and, if so, a brief description of such an agreement (including the criteria for deciding who can receive the data and whether or not any conditions will be placed on their use), and the mode of data sharing (e.g., under their own auspices by mailing a disk or posting data on their institutional or personal website, through a data archive or enclave). Investigators choosing to share under their own auspices may wish to enter into a data-sharing agreement. References to data sharing may also be appropriate in other sections of the application.

All applicants are expected to include a plan for sharing research data in their application. The data sharing policy is available at http://grants.nih.gov/grants/policy/data_sharing. All investigators responding to this funding opportunity should include a description of how final research data will be shared, or explain why data sharing is not possible.

Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication. See the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and at http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part7.htm#_Toc54600131. Investigators responding to this funding opportunity are expected to include a **plan** for sharing research resources addressing how unique research resources will be shared or explain why sharing is not possible.

Intellectual Property Management Plan

Guidance for Preparation of Research Tools Sharing Plan and Intellectual Property Plan.

Restricted availability of unique research resources, upon which further studies are dependent, can impede the advancement of research. The NIH is interested in ensuring that the research resources developed through this grant also become readily available to the broader research community in a timely manner for further research, development, and application, in the expectation that this will lead to products and knowledge of benefit to the public health.

Investigators conducting biomedical research frequently develop unique research resources. The policy of the NIH is to make available to the public the results and accomplishments of the activities that it funds. To address this interest in ensuring research resources are accessible, NIH expects applicants who respond to this RFA to submit a plan: (1) for sharing the research resources generated through the grant (e.g., human biospecimens and novel cancer biomarkers); and (2) addressing how they will exercise intellectual property rights, should any be generated through this grant, while making such research resources available to the broader scientific community consistent with this initiative. Therefore, such research resources tools sharing plan and intellectual property management plans would make unique research resources readily available for research purposes to qualified individuals within the scientific community in accordance with the NIH Grants Policy Statement (<http://grants.nih.gov/grants/policy/>) and the Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice, December 1999 <http://ott.od.nih.gov/NewPages/64FR72090.pdf> ("NIH Research Tools Guidelines Policy"). These documents also: (1) define terms, parties, and responsibilities; (2) prescribe the order of disposition of rights and a chronology of reporting requirements; and (3) delineate the basis for and extent of government actions to retain rights. Patent rights clauses may be found at 37 CFR Part 401.14 and are accessible from the Interagency Edison web page (<http://www.edison.gov>); url not working see also, 35 USC § 210(c); Executive Order 12591, 52 FR 13414 (Apr. 10, 1987); and Memorandum on Government Patent Policy (Feb. 18, 1983). If applicant investigators plan to collaborate with third parties, the research tools sharing plan would need to address how such collaborations would not restrict their ability to share research materials produced with NIH funding. The applicant's institution should avoid exclusively licensing those inventions that are research tools, unless either: (1) the field of use of the exclusive license is restricted to commercial use, or (2) the exclusive licensee will make the research tool broadly available on reasonable terms.

Intellectual property management plans are a just-in-time requirement; it is not necessary to include the final plan approved by all parties in the grant application, but final, approved plans will be expected before a U54 grant can be awarded. NIH program staff will consider the adequacy of the plans in determining whether to recommend an application for award. The approved plans would become a condition of the grant award and Progress Reports must contain information on activities for the sharing of research resources and intellectual property.

In the development of any research resource sharing and intellectual property management plans, applicants should confer with their institutions' office(s) responsible for handling technology transfer related matters and/or sponsored research. If applicants or their representatives require additional guidance in preparing such plans, they are encouraged to make further inquiries to the appropriate

contacts listed above for such matters. Further, applicants may wish to independently research and review examples of approaches considered by other institutions such as those described on the NCI Technology Transfer Branch web site (<http://ttc.nci.nih.gov/intellectualproperty/>). The foregoing guidance is provided by way of example to assist applicants in preparing the expected research resources sharing and intellectual property management plans in a manner that encourages partnerships with industry. While these approaches will likely suit most situations, these approaches are not exclusive and applicants should feel free to submit alternative versions for consideration.

The majority of transfers to not-for-profit entities should be implemented under terms no more restrictive than the Uniform Biological Materials Transfer Agreement (UBMTA) (<http://ott.od.nih.gov/NewPages/UBMTA.pdf>). In particular, recipients are expected to use the Simple Letter Agreement (SLA) provided at <http://ott.od.nih.gov/NewPages/SimplLtrAgr.pdf>, or another document with no more restrictive terms, to readily transfer unpatented tools developed with NIH funds to other recipients for use in NIH-funded projects. If the materials are patented or licensed to an exclusive provider, other arrangements may be used, but commercialization option rights, royalty reach-through rights, or product reach-through rights back to the provider are inappropriate. Similarly, when for-profit entities are seeking access to NCI-funded tools for internal use purposes, recipients should ensure that the tools are transferred with the fewest encumbrances possible. The Simple Letter Agreement (SLA) may be expanded for use in transferring tools to for-profit entities, or simple internal use license agreements with execution or annual use fees may be appropriate.

Section V. Application Review Information

1. Criteria

Only the criteria described below will be considered in the review process.

2. Review and Selection Process

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by NCI in accordance with the review criteria stated below.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score;
- Receive a written critique; and
- Receive a second level of review by the National Cancer Advisory Board.

3. Merit Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, to improve the control of disease, and to enhance health. In their written critiques, reviewers will be asked to comment on each of the following criteria in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field? Is the research likely to have a significant impact on other areas of research? Will the technological advances have a significant impact on clinical care of cancer patients?

Approach: Are the engineering, scientific, and clinical approaches of the research team partnership integrated on the proposed project? Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics? Is a timetable with adequate, quantitative milestones for the research proposed? Are appropriate specifications and evaluation procedures provided for assessing technological progress? Is the plan for sharing or disseminating technologies developed or enhanced under this program announcement adequate?

Is the plan for technology transfer involving each partnering organization adequate? Does the application describe arrangements that facilitate the fruitful participation of a partner at a distant site? If partnership with industry or small business is included, does this positively affect the research goals and technology dissemination?

Innovation: Does the project employ novel concepts, approaches or methods that combine engineering, physical, and clinical sciences? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies? Will the proposed approaches or concepts solve current scientific or technical problems in novel ways?

Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Is the PI capable of coordinating and managing the proposed research team partnership? Are the investigators (partners) appropriately trained in their disciplines and capable of conducting and contributing to the management of the proposed interdisciplinary work?

Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support? Does the partnership create potential opportunities to foster trans-disciplinary communication and training across traditional boundaries between cancer biology and physical sciences and engineering?

3.A. Additional Review Criteria:

In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

Partnership and leadership: Is the proposed research team partnership adequate for the research? Is there evidence that the partnership will be effectively managed by the PI or project manager? Is the partnership strategy well planned and documented? Is there evidence that the partners from academia or industry can work together effectively, have an impact on achieving the research goals, and disseminate the developed technology?

Protection of Human Subjects from Research Risk: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Inclusion of Women, Minorities and Children in Research: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate

for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Care and Use of Vertebrate Animals in Research: If vertebrate animals are to be used in the project, the five items described under Section F of the PHS Form 398 research grant application instructions will be assessed.

3.B. Additional Review Considerations

Budget: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. The priority score will not be affected by the evaluation of the budget.

3.C. Sharing Research Data

Data Sharing Plan: The reasonableness of the data sharing **plan** or the rationale for not sharing research data **will** be assessed by the reviewers. Reviewers will factor the proposed data sharing plan into the determination of scientific merit or the priority score. A final data sharing **plan** will be part of the terms and conditions of the award. The NCI will be responsible for monitoring the data sharing policy.

3.D. Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication. See the NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and at http://www.ott.nih.gov/policy/rt_guide_final.html. Investigators responding to this funding opportunity are expected to include a sharing research resources **plan** addressing how unique research resources will be shared or explain why sharing is not possible

The adequacy of the resources sharing plan will be considered by Program staff of the NCI when making recommendations about funding applications. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590, <http://grants.nih.gov/grants/funding/2590/2590.htm>). See [Section VI.3. Award Criteria](#).

Section VI. Award Administration Information

1. Award Notices

After the peer review of the application is completed, the Principal Investigator will also receive a written critique called a Summary Statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm).

A formal notification in the form of a Notice of Grant Award (NGA) will be provided to the applicant organization. The NGA signed by the grants management officer is the authorizing document.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NGA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

The NGA will be sent via email or the via postal system to the administrative official whose name is listed in Block 12 on the Face Page of the Form PHS 398.

2. Administrative Requirements

All NIH Grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm) and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm).

The following Terms and Conditions will be incorporated into the award statement and will be provided to the Principal Investigator as well as to the appropriate institutional official, at the time of award.

2.A. Cooperative Agreement Terms and Conditions of Award

Not Applicable

3. Award Criteria

The following will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review;
- Availability of funds; and
- Relevance of program priorities.

4. Reporting

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 2590 annually: <http://grants.nih.gov/grants/funding/2590/2590.htm> and financial statements as required in the NIH Grants Policy Statement.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific/Research Contacts:

Gregory J. Downing, D.O., Ph.D.
Director, Office of Technology and Industrial Relations
Office of the Director
National Cancer Institute, NIH, DHHS
Building 31, Room 10A-52, MSC 2580
31 Center Drive
Bethesda, MD 20892-2580
Telephone: (301) 496-1550
FAX: (301) 496-7807
Email: downingg@mail.nih.gov

2. Peer Review Contacts:

Referral Officer
National Cancer Institute
Division of Extramural Activities
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 496-3428
FAX: (301) 402-0275
E-mail: nciref@dea.nci.nih.gov

3. Financial or Grants Management Contacts:

Kathy Dunn
Grants Management Specialist
Grants Administration Branch
National Cancer Institute
6120 Executive Boulevard, EPS Room 243
Bethesda, MD 20892 (for regular mail)
Rockville, MD 20852 (for express mail)
Telephone: (301) 846-6829
FAX: (301) 846-5720
E-mail: dunnkath@mail.nih.gov

Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:

Recipients of PHS support for activities involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (<http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf>), as mandated by the Health Research Extension Act of 1985 (<http://grants.nih.gov/grants/olaw/references/hrea1985.htm>), and the USDA Animal Welfare Regulations (<http://www.nal.usda.gov/awic/legislat/usdaleg1.htm>), as applicable.

Human Subjects Protection:

Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>).

Data and Safety Monitoring Plan:

Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity, and dose-finding studies (Phase I); efficacy studies (Phase II); and efficacy, effectiveness, and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants. (See the NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts at <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>.)

Sharing Research Data:

Investigators submitting an NIH application seeking \$500,000 or more in direct costs in any single year are expected to include a plan for data sharing (http://grants.nih.gov/grants/policy/data_sharing) or state why this is not possible.

Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, State, and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Sharing of Model Organisms:

NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time, the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh-Dole Act (see the NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal beginning with the October 1, 2004, receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Inclusion of Women And Minorities in Clinical Research:

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling

justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:

The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at <http://grants.nih.gov/grants/funding/children/children.htm>.

Required Education on The Protection of Human Subject Participants:

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

Human Embryonic Stem Cells (hESC):

Criteria for federal funding of research on hESCs can be found at <http://stemcells.nih.gov/index.asp> and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see <http://escr.nih.gov/>). It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

Public Access to Research Data through the Freedom of Information Act:

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at

http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Standards for Privacy of Individually Identifiable Health Information:

The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information," the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR web site (<http://www.hhs.gov/ocr>) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>.

URLs in NIH Grant Applications or Appendices:

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople>.

Authority and Regulations:

This program is described in the Catalog of Federal Domestic Assistance at <http://www.cfda.gov/> and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Kirschstein-NRSA Awards are made under the authorization of Section 487 of the Public Health Service Act as amended (42 USC 288) and Title 42 of the Code of Federal Regulations, Part 66. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Loan Repayment Programs:

NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The LRP is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50% of their time (at least 20 hours per week based on a 40 hour week) for two years to the research. For further information, please see: <http://www.lrp.nih.gov/>.

[Weekly TOC for this Announcement](#)
[NIH Funding Opportunities and Notices](#)



Office of
Extramural
Research
(OER)



National
Institutes of
Health (NIH)
9000 Rockville
Pike
Bethesda,
Maryland
20892



Department of
Health
and Human
Services (HHS)



Note: For help accessing PDF, RTF, MS Word, Excel, PowerPoint, RealPlayer, Video or Flash files, see
[Help Downloading Files](#).

Multidisciplinary Career Development in Cancer Nanotechnology Research

RFA Number: RFA-CA-05-025

Part I Overview Information

Department of Health and Human Services

Participating Organizations

National Institutes of Health (NIH), (<http://www.nih.gov/>)

Components of Participating Organizations

National Cancer Institute (NCI), (<http://www.nci.nih.gov/>)

Announcement Type

New

Update: The following update relating to this announcement has been issued:

- [September 17, 2007](#) - This RFA has been reissued as (RFA-CA-08-003).

Catalog of Federal Domestic Assistance Number(s)

93.393, 93.399

Key Dates

Release Date: December 1, 2004

Letters Of Intent Receipt Date: Not Applicable

Application Receipt Date: March 25, 2005

Peer Review Date: June/July 2005

Council Review Date: September 2005

Earliest Anticipated Start Date: September 2005

Additional Information to Be Available Date (URL Activation Date): Not Applicable

Expiration Date: March 26, 2005

Due Dates for E.O. 12372

Not Applicable

Executive Summary

This RFA supports the career development of individuals from the basic, biomedical, clinical, and information sciences and engineering who are pursuing research that applies nanotechnology development and application for the prevention, detection, diagnosis, or treatment of cancer. This funding opportunity will use Ruth L. Kirschstein National Research Service Awards (Kirschstein-NRSA) to support individual postdoctoral fellowships (F32) and senior fellowships (F33). The NCI intends to commit approximately \$15.5M dollars over three years to fund a total of 36 new grants in response to this RFA (approximately 18 for each mechanism). The total amount of funds committed for F32 awards for FY 2005 is approximately \$0.75 M. The total for F33 awards and supplements for FY 2005 is approximately \$4.42M. An applicant may request a project period of up to 3 years for F32 (stipend levels depend on full years of post-degree experience at the time of award, and include an Institutional allowance; both amounts are determined yearly by Congress) and 2 years for F33 awards (stipend not to exceed the level of NRSA stipend support for individuals with more than 7 years

experience). An applicant may request a project period of up to 3 years for F32 and 2 years for F33 awards. The anticipated start date for awards is September 2005, and funding will terminate no later than September 2008.

Eligible supporting organizations include for-profit or non-profit organizations, public or private institutions (such as universities, colleges, hospitals, and laboratories), units of State and local governments, eligible agencies of the Federal government, and domestic (or foreign) institutions/organizations. Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with his or her institution and mentor to develop an application for support. By the time of award, candidates for the F32 or F33 fellowship award must be citizens or non-citizen nationals of the United States or must have been lawfully admitted to the United States for Permanent Residence (i.e., possess a currently valid Alien Registration Receipt Card I-551 or other legal verification of such status). Before a Kirschstein-NRSA F32 postdoctoral fellowship or F33 senior fellowship award can be activated, the individual must have received a Ph.D., M.D., D.O., D.C., D.D.S., D.V.M., O.D., D.P.M., Sc.D., Eng.D., Dr. P.H., D.N.S., N.D., Pharm.D., D.S.W., Psy.D., or equivalent doctoral degree from an accredited domestic or foreign institution. Certification by an authorized official of the degree-granting institution that all degree requirements have been met is also acceptable. In addition, applicants for an F33 NRSA senior fellowship must be at least 7 years beyond one of the above qualifying degrees, have had at least 7 years of post-degree relevant research or professional experience, and have established an independent research career.

An applicant may submit only one application for this one-time RFA.

Application materials are available at <http://grants.nih.gov/grants/funding/416/phs416.htm>. Telecommunications for the hearing impaired is available at: TTY 301-451-0088.

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

This RFA supports the career development of individuals from the basic, biomedical, clinical, and information sciences and engineering who are pursuing research that applies nanotechnology development and application for the prevention, detection, diagnosis, or treatment of cancer. Nanotechnology offers an unprecedented opportunity to study and interact with normal and cancer cells in real time, at the molecular and cellular scales, and during the earliest stages of the cancer process. As a result, nanotechnology will be a mission-critical tool to meet the NCI's Challenge Goal of eliminating death and suffering from cancer by 2015. To achieve this vision, the NCI will support the training of a cadre of researchers who can work as members of multidisciplinary teams to apply the tools of nanotechnology to critical problems in cancer research and clinical oncology.

The elucidation of the human genome, combined with many remarkable advances in cancer biology, has offered great potential for researchers to address complex biological systems using innovative tools and strategies. The use of integrative biology (combining experimental and computational approaches towards the understanding of cancer biology to study cancer systems) is fostering novel nanoscale engineering and design applications to prevent, detect, diagnose, and treat various types of cancers. Although nanotechnology offers great potential to yield important information on the fundamental processes of cancer, there are few formal opportunities to train scientists and engineers who wish to develop and test nanomaterials and nanodevices for cancer-related applications. This RFA is a component of the NCI Alliance for Nanotechnology in Cancer (<http://nano.cancer.gov>), an integrated 5-year initiative to develop and apply nanotechnology to cancer prevention, detection, diagnosis, and treatment, thereby enabling nanotechnology to become a fundamental driver of advances in cancer research and clinical oncology.

This announcement specifically aims to encourage applications for F32 individual postdoctoral fellowships from promising candidates with the potential to become productive, independent investigators in cancer nanotechnology research. It also aims to encourage applications for F33 senior fellowships from experienced scientists who wish to change the direction of their research or broaden their scientific background by acquiring new capabilities in cancer nanotechnology research. This training opportunity supports career development in numerous research disciplines, and it is expected that trainees will gain expertise in the computational, physical, and biological aspects of technology development at the nanoscale for cancer treatment. As part of the NCI Alliance for Nanotechnology in Cancer, awardees will be required to attend the annual scientific meeting of the NCI Centers of Cancer Nanotechnology Excellence (CCNEs).

The goal of this Fellowship Program in cancer nanotechnology research is to train highly skilled research scientists to develop and test nanomaterials and nanodevices and to apply these advances to address cancer-related issues. Awardees are expected to work as productive members of multidisciplinary research teams, assembled to address critical nanotechnology platform needs in cancer. It is expected that these individuals will pursue research that includes, but is not limited to, one or more of the following areas:

- Imaging agents and diagnostic tools that will enable clinicians to detect cancer in its earliest stages;
- Systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation;
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents directly to cancer cells and those tissues in the tumor microenvironment that play critical roles in the growth and metastasis of cancer;
- Agents that can monitor predictive molecular changes and prevent pre-cancerous cells from becoming malignant;
- Novel methods to manage the symptoms of cancer that adversely impact quality of life; and/or
- Research tools that will enable rapid identification of new targets for clinical development and predict drug resistance.

See [Section VIII, Other Information - Required Federal Citations](#), for policies related to this announcement.

Section II. Award Information

1. Mechanisms of Support

This funding opportunity will use the Kirschstein-NRSA F32 and F33 award mechanisms. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation.

2. Funds Available

The NCI intends to commit approximately \$15.5M dollars over 3 years to fund a total of 36 new grants in response to this RFA (approximately 18 for each mechanism). The total amount of funds committed for F32 awards for FY 2005 is approximately \$0.75 M. The total for F33 awards and supplements for FY 2005 is approximately \$4.42M.. An applicant may request a project period of up to 3 years for F32 (stipend levels depend on full years of postdegree experience at the time of award, and include an Institutional allowance; both amounts are determined yearly by Congress) and 2 years for F33 awards (stipend not to exceed the level of NRSA stipend support for individuals with more than 7 years experience). This funding is commensurate with current guidelines specified for Kirschstein-NRSA Awards (<http://grants.nih.gov/grants/funding/416/phs416.htm>). The anticipated start date for awards is September 2005, and funding will terminate no later than September 2008. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of the NCI provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

Stipends. Kirschstein-NRSA awards provide stipends to postdoctoral fellows as a subsistence allowance to help defray living expenses during the research training experience. The awards are not provided as a condition of employment with either the Federal government or the sponsoring institution. The stipend level for the first year of Kirschstein-NRSA support is determined by the number of full years of relevant postdoctoral experience at the time the award is issued (not at the time of activation, see below). Fellows with less than one full year of postdoctoral experience at the time of award will receive initial support at the zero level. Relevant experience may include research (including research in industry), teaching, internship, residency, clinical duties, or other time spent in full-time studies in a health-related field beyond that of the qualifying doctoral degree. The stipend schedule is updated nearly every year, and applicants are advised to check for the posting of the current stipend schedule on the NIH web site at <http://grants.nih.gov/training/nrsa.htm>. The awarding NIH Institute or Center will adjust awards on the anniversary date of the fellowship award to ensure consistency with the stipend schedule in effect at that time. The stipend for each subsequent year of Kirschstein-NRSA support is the next level of experience using the stipend schedule in effect at that time. Stipends will be adjusted on the anniversary date of the award and will not be changed mid-year to accommodate an increase in the level of experience. No departure from the published Kirschstein-NRSA stipend schedule may be negotiated between the institution and the fellow. For fellows sponsored by domestic non-federal institutions, the stipend will be paid through the sponsoring institution. For fellows sponsored by Federal or foreign institutions, the monthly stipend payment will be deposited in the fellow's U.S. bank account or paid directly to the fellow by U.S. Department of Treasury check. Stipends for Kirschstein senior fellows are determined individually at the time of award. The amount of the stipend is based on the salary or remuneration from their home institution on the date of award. However, in no case shall the NIH contribution to the stipend during the fellowship exceed the NRSA stipend provided for individuals with more than 7 years of experience. For fellows on sabbatical, the level of the NRSA stipend award will take into account concurrent sabbatical salary support provided by the home institution and any other supplementation. The stipend is not provided as a condition of employment with either the Federal Government or the institution.

Tuition and Fees. The NIH will offset the combined cost of tuition and fees at the following rate: 100 percent of all costs up to \$3,000 and 60 percent of costs above \$3,000. Costs associated with tuition and fees are allowable only if they are required for specific courses in support of the research training experience supported by the fellowship. A full description of the tuition policy is contained within the NRSA section of the Grants Policy Statement at <http://grants.nih.gov/grants/policy/policy.htm>.

Institutional Allowance. At the time of publication, fellows receive an institutional allowance of \$5,500 per 12-month period to nonfederal, nonprofit, or foreign sponsoring institutions to help defray such awardee expenses as research supplies, equipment, health insurance (either self-only or family as appropriate), and travel to scientific meetings. Support for health insurance is allowable only if it is applied consistently for all individuals in a similar research training status regardless of the source of support. This allowance is intended to cover training related expenses for the individual awardee. The allowance is not available until the fellow officially activates the award. If an individual fellow is enrolled or engaged in training for less than 6 months of the award year, only one-half of that year's allowance may be charged to the grant. The Notice of Research Fellowship Award will be revised and the balance must be refunded to NIH. NIH will provide an institutional allowance of up to \$4,400 for fellows sponsored by Federal laboratories or for-profit institutions for expenses associated with travel to scientific meetings, health insurance, and books. For fellows at for-profit institutions, the \$4,400 will be paid to the institution for disbursement to the fellow. Funds for fellows at Federal laboratories will be disbursed from the NIH awarding Institute. The Institutional Allowance is adjusted from time-to-time. Prospective applicants are advised to check for the current Institutional Allowance in the most recent documentation related to Kirschstein-NRSA stipends at <http://grants.nih.gov/training/nrsa.htm>.

Other Training Costs. Additional funds may be requested by the institution when the training of a fellow involves extraordinary costs for travel to field sites remote from the sponsoring institution or accommodations for fellows who are disabled, as defined by the Americans With Disabilities Act. The funds requested for costs of this nature must be reasonable in relationship to the total dollars awarded under the fellowship and must be directly related to the approved research training experience. Such additional funds shall be provided only in exceptional circumstances that are fully justified and explained by the sponsoring institution. Awards for training at a foreign site may include a single economy or coach round-trip travel fare. No allowance is provided for dependents. U.S. flag air carriers must be used to the maximum extent possible when commercial air transportation is available for travel between the United States and a foreign country or between foreign countries. Funds are not provided to cover the cost of travel between the fellow's place of residence and a domestic training institution. However, in cases of extreme need or hardship, a one-way travel allowance may be authorized by the sponsoring institution. Such travel must be paid from the institutional allowance. Institutions hosting senior fellowship (F33) awardees may be eligible for research support supplements. Details and restrictions will be available at the program website <http://nano.cancer.gov>.

Facilities and Administrative Costs. F&A (indirect) costs are not allowed on individual fellowship awards.

Supplementation of Stipends, Compensation, and Other Income The sponsoring institution is allowed to provide funds to the fellow in addition to the stipends paid by the NIH. Such additional amounts either may be in the form of augmented stipends (supplementation) or in the form of compensation, such as salary or tuition remission for services such as teaching or serving as a laboratory assistant, provided the conditions described below are met. Under no circumstances may the conditions of stipend supplementation or the services provided for compensation interfere with, detract from, or prolong the fellow's approved Kirschstein-NRSA training program.

Stipend Supplementation: Supplementation or additional support to offset the cost of living may be provided by the sponsoring institution. Supplementation does not require additional effort from the fellow. DHHS funds may not be used for supplementation under any circumstances. Additionally, no funds from other Federal agencies may be used for supplementation unless specifically authorized by the NIH and the other Federal Agency.

Compensation: The sponsoring institution may provide additional funds to a fellow in the form of compensation (as salary and/or tuition remission) for services such as teaching or serving as a research assistant. A fellow may receive compensation for services as a research assistant or in some other position on a Federal research grant, including a DHHS research grant. However, compensated services should occur on a limited, part-time basis apart from the normal research training activities, which require a minimum of 40 hours per week. In addition, compensation may not be paid from a research grant that supports the same research that is part of the fellow's research training experience as approved in the application.

Educational Loans or G.I. Bill: An individual may make use of Federal educational loan funds and assistance under the Veterans Readjustment Benefits Act (G.I. Bill). Such funds are not considered supplementation or compensation. Postdoctoral fellows may also be eligible to participate in the NIH Extramural Loan Repayment Program. Information on this program is available at <http://www.lrp.nih.gov/>.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Supporting Institutions

You may submit (an) application(s) if your supporting organization has any of the following characteristics:

- For-profit organizations
- Non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State government
- Units of local governments
- Eligible agencies of the Federal government
- Domestic institutions/organizations
- Foreign institutions/organizations

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs. Fellowship awardees are required to pursue their research training on a full-time basis, devoting at least 40 hours per week to the training program. Women, minorities, and individuals with disabilities are encouraged to apply. Further details of the Kirschstein-NRSA F32 award mechanism can be found at <http://grants.nih.gov/grants/guide/pa-files/RFA-03-067.html>; details of the Kirschstein-NRSA F33 award mechanism can be found at <http://grants.nih.gov/grants/guide/pa-files/RFA-00-131.html>.

Citizenship. By the time of award, candidates for the F32 or F33 fellowship award must be citizens or non-citizen nationals of the United States or must have been lawfully admitted to the United States for Permanent Residence (i.e., possess a currently valid Alien Registration Receipt Card I-551 or other legal verification of such status). Non-citizen nationals are generally persons born in outlying possessions of the United States (i.e., American Samoa and Swains Island). Individuals on temporary or student visas are not eligible. Individuals may apply for the F32 in advance of admission to the United States as a Permanent Resident recognizing that no award will be made until legal verification of Permanent Resident status is provided.

Degree Requirements. Before a Kirschstein-NRSA F32 postdoctoral fellowship or F33 senior fellowship award can be activated, the individual must have received a Ph.D., M.D., D.O., D.C., D.D.S., D.V.M., O.D., D.P.M., Sc.D., Eng.D., Dr. P.H., D.N.S., N.D., Pharm.D., D.S.W., Psy.D., or equivalent doctoral degree from an accredited domestic or foreign institution. Certification by an authorized official of the degree-granting institution that all degree requirements have been met is also acceptable. In addition, applicants for an F33 NRSA senior fellowship must be at least 7 years beyond one of the above qualifying degrees, have had at least 7 years of post-degree relevant research or professional experience, and have established an independent research career.

Duration of Support. F32 awardees may receive up to 3 years of aggregate Kirschstein-NRSA support at the postdoctoral level, including any combination of support from institutional training grants (T32) and individual fellowship awards (F32). F33 senior fellowship awards may be requested for up to 2 years. Applicants must consider any prior Kirschstein-NRSA postdoctoral research training in determining the duration of fellowship support requested. Training beyond the 3-year aggregate limit may be possible under certain exceptional circumstances, but a waiver from the NIH awarding component is required. Individuals seeking additional Kirschstein-NRSA support beyond the 3rd year are strongly advised to consult with relevant NIH staff before preparing a justification. Any waiver will require a detailed justification of the need for additional research training.

2. Cost Sharing

Cost sharing is not required.

3. Other-Special Eligibility Criteria

Sponsor (Mentor). The applicant's sponsor should be an active investigator in the area of the proposed research who will directly supervise the candidate's research. The sponsor should either have expertise in the development and/or application of nanotechnology to cancer or have specific plans to obtain the requisite training, and must document the availability of research support and facilities for high-quality nanotechnology research training. In most cases, the F32 and F33 fellowship awards support research training experiences in new settings in order to maximize the acquisition of new skills and knowledge. However, in unusual circumstances, an applicant may propose postdoctoral training experiences at his/her doctoral institution or at the institution where he or she has been training for more than a year. In such cases, the applicant must carefully document the opportunities for new research training experiences specifically designed to broaden training involving nanotechnology research.

In most cases, the F33 senior fellowship award is used to support sabbatical experiences for established independent scientists who wish to take time from regular professional responsibilities to receive training to expand their research capabilities.

Foreign Sponsorship. Applicants requesting fellowship support for foreign research training must justify in the application that the foreign institution and sponsor offer unique opportunities and clear scientific advantages that are not currently available in the United States.

Section IV. Application and Submission Information

1. Address to Request Application Information

The PHS 416-1 is available at <http://grants.nih.gov/grants/funding/416/phs416.htm> in an interactive format. For further assistance, contact GrantsInfo, Telephone: (301) 435-0714, Email: GrantsInfo@nih.gov. Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the PHS 416-1 research grant application instructions and forms (rev. 06/02). Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at <http://www.dnb.com/us/>. The D&B number should be entered on line 12 of the face page of the PHS 416-1 form.

The title and number of this funding opportunity must be typed on line 3 of the face page of the application form.

APPLICATIONS MUST INCLUDE AT LEAST THREE SEALED LETTERS OF REFERENCE. APPLICATIONS WITHOUT AT LEAST THREE LETTERS OF REFERENCE WILL BE RETURNED OR DELAYED IN REVIEW. If the applicant has been lawfully admitted to the United States for permanent residence, the appropriate item should be checked on the Face Page of the application. Applicants who have applied for and have not yet been granted admission as a permanent resident should check the Permanent Resident block on the Face Page of the application, and also write in the word "pending." A notarized statement documenting legal admission for permanent residence must be submitted prior to the issuance of an award.

Concurrent Applications. An individual may not have more than one individual NRSA fellowship or comparable application pending review or award at the NIH or other DHHS agencies at the same time.

Instructions in the Responsible Conduct of Research:

Applications must include the candidate's plans for obtaining instruction in the responsible conduct of research, including the rationale, subject matter, appropriateness, format, frequency and duration of instruction. The amount and nature of faculty participation must be described. No award will be made if an application lacks this component.

3. Submission Dates

3.A. Receipt, Review and Anticipated Start Dates

Letters Of Intent Receipt Date: Not Applicable
Application Receipt Date: March 25, 2005
Peer Review Date: June/July 2005
Council Review Date: September 2005
Earliest Anticipated Start Date: September 2005

3.A.1 Letter of Intent

Not applicable.

3.B. Sending an Application to the NIH

Applications must be prepared using the PHS 416-1 research grant application instructions and forms as described above. Submit a signed, typewritten original of the application, including the checklist, and one signed photocopy in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

At the time of submission, one additional copy of the application and all copies of the appendix material must be sent to:

Referral Officer
National Cancer Institute
Division of Extramural Activities
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 496-3428
FAX: (301) 402-0275
Email: nciref@dea.nci.nih.gov

Appendices should be comprised of unbound materials with separators between documents.

Using the RFA Label: The RFA label available in the PHS 416-1 application instructions must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 3 of the face page of the application. The RFA label is also available at <http://grants.nih.gov/grants/funding/phs398/labels.pdf>.

All applications submitted to the Center for Scientific Review must come via United States Postal Service or a recognized delivery/courier service. Individuals may not personally deliver packages to the building on Rockledge Drive. For further information please see <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-012.html>.

Certification Procedure: No application will be accepted without the applicant signing the certification block on the face page of the application. Individuals admitted to the United States as Permanent Residents must submit notarized evidence of legal admission prior to award.

Incomplete applications will not be reviewed.

3.C. Application Processing

Applications must be received **on or before the application receipt date** listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NCI. Incomplete and non-responsive applications will not be reviewed.

The NIH will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is, the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

4. Intergovernmental Review

This initiative is not subject to [intergovernmental review](#).

5. Funding Restrictions

All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm> (See also [Section VI.3. Award Criteria](#)).

Concurrent Awards: A Kirschstein-NRSA fellowship may not be held concurrently with another federally sponsored fellowship or similar Federal award that provides a stipend or otherwise duplicates provisions of this award.

Tax Liability Section 117 of the Internal Revenue Code applies to the tax treatment of all scholarships and fellowships. Under that section, non-degree candidates are required to report as gross income any monies paid on their behalf for stipends, or any course tuition and fees required for attendance. Degree candidates may exclude from gross income (for tax purposes) any amount used for tuition and related expenses such as fees, books, supplies, and equipment required for courses of instruction at a qualified educational organization. The taxability of stipends, however, in no way alters the relationship between Kirschstein-NRSA trainees or fellows and their institutions. Kirschstein-NRSA stipends are not considered salaries. In addition, any trainee supported under the Kirschstein-NRSA is not considered to be in an employee-employer relationship with the NIH or the awardee institution. It is therefore inappropriate and unallowable for institutions to charge costs associated with employment (such as FICA, workman's compensation, or unemployment insurance) to the fellowship award. It must be emphasized that the interpretation and implementation of the tax laws are the domain of the Internal Revenue Service (IRS) and the courts. The NIH takes no position on the status of a particular taxpayer, and it does not have the authority to dispense tax advice. Individuals should consult their local IRS office about the applicability of the law to their situation and for information on their tax obligations.

Section V. Application Review Information

1. Criteria

This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part2.htm.

2. Review and Selection Process

Upon receipt, applications will be reviewed for completeness by the CSR and for responsiveness by the NCI. Incomplete and/or non-responsive applications will not be reviewed.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the Division of Extramural Activities at the NCI in accordance with the review criteria stated below.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
- Receive a written critique
- Receive a second level of review by the National Cancer Advisory Board.

3. Merit Review Criteria

Applications submitted in response to a funding opportunity will compete for available funds with all other recommended applications.

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The scientific review group will address and consider each of these criteria in assigning the application's overall score, weighting them as appropriate for each application.

The review criteria focus on four main components:

- Candidate: An assessment of the candidate's previous academic and research performance and the potential to become (F32) or continue (F33) as an important contributor to biomedical, behavioral, or clinical science.
- Sponsor and Training Environment: An assessment of the quality of the training environment and the qualifications of the sponsor as a mentor for the proposed research training experience. Familiarity with the use of nanotechnology, or proposed training to acquire such expertise, will be relevant.
- Research Proposal: The merit of the scientific proposal and its relationship to the candidate's career plans.
- Training Potential: An assessment of the value of the proposed fellowship experience as it relates to the candidate's needs in preparation for a career as an independent researcher (F32) or to the candidate's capabilities as an independent researcher (F33). The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

3.A. Additional Review Criteria:

In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

Nanotechnology Expertise: The sponsor's laboratory should either have expertise in the use of nanotechnology or describe plans for the sponsor and the fellow to obtain such expertise.

Protection of Human Subjects from Research Risk : The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. See also [Section VIII - Other Information](#).

Inclusion of Women, Minorities and Children in Research: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated. See also [Section VIII-Other Information](#).

Care and Use of Vertebrate Animals in Research: If vertebrate animals are to be used in the project, the five items described in section 30b of subsection 6 of the instructions for the PHS 416-1(rev.06/02) will be assessed.

3.B. Additional Review Considerations

Budget: The reasonableness of the requested budget in relation to the proposed training period of support. An F33 applicant must provide detailed budget information when requesting additional research support funds.

Responsible Conduct of Research: Every NRSA fellow must receive instruction in the responsible conduct of research (<http://grants.nih.gov/grants/guide//notice-files/not92-236.html>) Applications must include the applicant's plans for obtaining instruction in the responsible conduct of research, including the rationale, subject matter, appropriateness, format, frequency and duration of instruction. The amount and nature of faculty participation must be described. No award will be made if an application lacks this component.

3.C. Sharing Research Data

Not applicable.

3.D. Sharing Research Resources

Not applicable.

Section VI. Award Administration Information

1. Award Notices

After the peer review of the application is completed, the applicant will also receive a written critique called a Summary Statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm).

A formal notification in the form of a Notice of Grant Award (NGA) will be provided to the applicant by email or postal mail. The NGA signed by the grants management officer is the authorizing document.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NGA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

2. Administrative Requirements

All NIH Grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General

(http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm) and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm).

Service Payback

As required by the NIH Revitalization Act of 1993, postdoctoral fellows incur a service obligation of 1 month for each month of support during the first 12 months of the Kirschstein-NRSA postdoctoral support. The 13th and subsequent months of Kirschstein-NRSA support are acceptable postdoctoral payback service. Thus, individuals who continue under the award for 2 years will have paid off their first year obligation by the end of the 2nd year.

Applicants accepting an award for the first 12 months of Kirschstein-NRSA postdoctoral support must sign a payback agreement (PHS Form 6031) in which they agree to engage in health-related research training, research, and/or teaching for 12 months.

Those who do not pay back their obligation through continued Kirschstein-NRSA supported training may satisfy their obligation by serving in a position in which health-related research, research training, or teaching are the primary activities. Such individuals must engage in research, research training, or teaching at a rate of 20 or more hours per week averaged over a full work-year. Payback service may be conducted in an academic, governmental, commercial, or nonacademic environment, in the United States or in a foreign country. Examples of acceptable payback service include research associateships/assistantships, postdoctoral research fellowships, and college or high school science teaching positions. Examples of unacceptable payback service include clinical practice and administrative responsibilities not directly related to scientific research.

Payback service positions are arranged by the individual, not by the NIH. The NIH will review and approve the activity at the end of the year in which it occurs. Service to satisfy any outstanding obligation must be initiated within 2 years after termination of Kirschstein-NRSA support and must be performed on a continuous basis. For individuals who fail to fulfill their service obligations, the United States is entitled to recover the total amount of Kirschstein-NRSA funds paid to the individual for the obligated period plus interest at a rate determined by the Secretary of the U.S. Department of Treasury. Financial payback must be completed within 3 years, beginning on the date the United States becomes entitled to recover such amount.

Under certain conditions, the Secretary, DHHS, may extend the period for starting service, permit breaks in service, extend the period of repayment, or otherwise waive the payback obligation when compliance would constitute a substantial hardship against equity and good conscience. Policies regarding the Kirschstein-NRSA payback obligation are explained in the Kirschstein-NRSA Section of the NIH Grants Policy Statement available at <http://grants.nih.gov/grants/policy/policy.htm>. Specific questions may appear in a list of Frequently Asked Questions that appears on the Web at http://grants.nih.gov/training/faq_fellowships.htm. Other questions on payback should be directed to the appropriate NIH Institute contact.

Leave Policies

In general, fellows may receive stipends during the normal periods of vacation and holidays observed by individuals in comparable training positions at the sponsoring institution. For the purpose of these awards, however, the period between the Spring and Fall semesters is considered to be an active time of research and research training and is not considered to be a vacation or holiday. Fellows may receive stipends for up to 15 calendar days of sick leave per year. Sick leave may be used for the medical conditions related to pregnancy and childbirth. Fellows may also receive stipends for up to 30 calendar days of parental leave per year for the adoption or the birth of a child when those in comparable training positions at the grantee institution have access to paid leave for this purpose and the use of parental leave is approved by the program director.

A period of terminal leave is not permitted and payment may not be made from fellowship funds for leave not taken. Fellows requiring periods of time away from their research training experience longer than specified here must seek approval from the NIH awarding component for an unpaid leave of absence.

Part-Time Training

While NRSA awardees are required to pursue research training full time, devoting at least 40 hours per week to the training program, under... unusual and pressing personal circumstances, a fellow may submit a written request to the awarding component to permit less than full-time training. Such requests will be considered on a case-by-case basis. They must be approved by the awarding NIH Institute or Center in advance for each budget period. The nature of the circumstances requiring the part-time training might include medical conditions, disability, or pressing personal or family situations such as child or elder care. Permission for part-time training will not be approved to accommodate other sources of funding, job opportunities, clinical practice, clinical training, or for other responsibilities associated with the fellow's position at the institution. In each case, the fellow must submit a written request countersigned by the sponsor and an appropriate institutional business official that includes documentation supporting the need for part-time training. The written request also must include an estimate of the expected duration of the period of part-time training, an assurance that the fellow intends to return to full-time training when that becomes possible, and an assurance that the trainee intends to complete the proposed research training program. In no case will it be permissible for the fellow to be engaged in Kirschstein-NRSA supported research training for less than 50 percent effort. Individuals who must reduce their commitment to less than 50 percent effort must take a leave-of-absence from Kirschstein-NRSA fellowship support. The fellowship notice of award will be reissued and the stipend will be pro-rated during the period of any approved part-time training. Part-time training may affect the rate of accrual or repayment of the service obligation for postdoctoral fellows.

2.A. Cooperative Agreement Terms and Conditions of Award

Not applicable.

3. Award Criteria

NIH staff use the following criteria in making awards: (1) eligibility of the applicant; (2) the SRG recommendation of the overall merit of the application; (3) the relevance of the application to the Institute's research training priorities and program balance; and (4) the availability of funds.

4. Reporting

Fellowships must be administered in accordance with the current NRSA section of the Grants Policy Statement at <http://grants.nih.gov/grants/policy/policy.htm> and any terms and conditions specified on the award notice.

Reporting Procedures. Fellowship Activation. No funds may be disbursed until the fellow has started training under the award and an Activation Notice (PHS 416-5) and (when appropriate) a Payback Agreement (PHS 6031) has been submitted to the NIH. An awardee has up to 6 months from the issue date on the

award notice to activate the award. Under unusual circumstances, an NIH institute may grant an extension of the activation period upon receipt of a specific request from the fellow.

A payback Agreement Form (PHS 6031) must accompany the Activation Notice for any award that occurs during the individual's initial 12 months of Kirschstein-NRSA postdoctoral support. When support ends, the fellow must submit a Termination Notice (PHS 416-7) to the NIH. If the fellow has a

payback obligation, he or she must notify the NIH of any change in address and submit Annual Payback Activities Certification Forms (PHS 6031-1) until the payback service obligation is satisfied. Forms will be provided to awardees by the NIH awarding component. Forms may also be found on the NIH Web site at <http://grants.nih.gov/grants/forms.htm>.

Inventions and Publications. Fellowships made primarily for educational purposes are exempted from the PHS invention requirements. F32 awards will not contain any provision giving PHS rights to inventions made by the awardee.

Copyrights. Except as otherwise provided in the terms and conditions of the award, the recipient is free to arrange for copyright without approval when publications, data, or other copyrightable works are developed in the course of work under a PHS grant-supported project or activity. Any such copyrighted or copyrightable works shall be subject to a royalty-free, nonexclusive, and irrevocable license to the Government to reproduce, publish, or otherwise use them, and to authorize others to do so for Federal Government purposes.

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 416-9 annually (<http://grants.nih.gov/grants/funding/416-9/phs416-9.htm>) and financial statements as required in the NIH Grants Policy Statement.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific/Research Contacts:

Gregory J. Downing, D.O., Ph.D.
Director, Office of Technology and Industrial Relations
Office of the Director
National Cancer Institute
Building 31, Room 10A-52, MSC 2580
31 Center Drive
Bethesda, MD 20892-2580
Telephone: (301) 496-1550
FAX: (301) 496-7807
Email: downingg@mail.nih.gov

2. Peer Review Contacts:

Referral Officer
National Cancer Institute
Division of Extramural Activities
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 496-3428
FAX: (301) 402-0275
E-mail: nciref@dea.nci.nih.gov

3. Financial or Grants Management Contacts:

Kathy Dunn
Grants Management Specialist
Grants Administration Branch
National Cancer Institute
6120 Executive Boulevard, EPS Room 243
Bethesda, MD 20892
Rockville, MD 20852 (for express mail)
Telephone: (301) 846-6829
FAX: (301) 846-5720
E-mail: dunnkath@mail.nih.gov

Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:

Recipients of PHS support for activities involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (<http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf>), as mandated by the Health Research Extension Act of 1985 (<http://grants.nih.gov/grants/references/hrea1985.htm>), and the USDA Animal Welfare Regulations (<http://www.nal.usda.gov/awic/legislat/usdaleg1.htm>), as applicable.

Human Subjects Protection:

Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>).

Data and Safety Monitoring Plan:

Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity, and dose-finding studies (Phase I); efficacy studies (Phase II); and efficacy, effectiveness and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants. (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts at <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>.)

Sharing Research Data:

Investigators submitting an NIH application seeking \$500,000 or more in direct costs in any single year are expected to include a plan for data sharing (http://grants.nih.gov/grants/policy/data_sharing) or state why this is not possible.

Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, State, and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Sharing of Model Organisms:

NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time, the NIH

recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh-Dole Act (see the NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal beginning with the October 1, 2004 receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Inclusion of Women And Minorities in Clinical Research:

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research" (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:

The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at <http://grants.nih.gov/grants/funding/children/children.htm>.

Required Education on The Protection of Human Subject Participants:

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

Human Embryonic Stem Cells (hESC):

Criteria for federal funding of research on hESCs can be found at <http://stemcells.nih.gov/index.asp> and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see <http://escr.nih.gov/>). It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

Public Access to Research Data through the Freedom of Information Act:

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Standards for Privacy of Individually Identifiable Health Information:

The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information," the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR web site (<http://www.hhs.gov/ocr/>) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>.

URLs in NIH Grant Applications or Appendices:

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople>.

Authority and Regulations:

This program is described in the Catalog of Federal Domestic Assistance at <http://www.cfda.gov/> and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Kirschstein-NRSA Awards are made under the authorization of Section 487 of the Public Health Service Act as amended (42 USC 288) and Title 42 of the Code of Federal Regulations, Part 66. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided

to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Loan Repayment Programs:

NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The Loan Repayment Program (LRP) is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50 percent of their time (at least 20 hours per week based on a 40 hour week) for two years to the research. For further information, please see: <http://www.lrp.nih.gov/>.

[Weekly TOC for this Announcement](#)

[NIH Funding Opportunities and Notices](#)



Office of
Extramural
Research
(OER)



National
Institutes of
Health (NIH)
9000 Rockville
Pike
Bethesda,
Maryland
20892



Department of
Health
and Human
Services (HHS)



Note: For help accessing PDF, RTF, MS Word, Excel, PowerPoint, RealPlayer, Video or Flash files, see [Help Downloading Files](#).

Part I Overview Information

Department of Health and Human Services

Participating Organizations

National Institutes of Health (NIH), (<http://www.nih.gov/>)

Components of Participating Organizations

National Cancer Institute (NCI), (<http://www.nci.nih.gov/>)

Title: Ruth L. Kirschstein NRSA Fellowships in Cancer Nanotechnology Research

Announcement Type

New

Request For Applications (RFA) Number: RFA-CA-06-010

Catalog of Federal Domestic Assistance Number(s)

93.393, 93.399

Key Dates

Release Date: July 13, 2005

Letters Of Intent Receipt Date: Not Applicable

Application Receipt Date: November 16, 2005

Peer Review Date: February 2006

Council Review Date: May/June 2006

Earliest Anticipated Start Date: July 2006

Additional Information to Be Available Date (URL Activation Date): Not Applicable

Expiration Date: November 17, 2005

Due Dates for E.O. 12372

Not applicable

Additional Overview Content

Executive Summary

- This RFA supports the training of individuals from the basic, biomedical, clinical, and information sciences and engineering who are pursuing research that applies nanotechnology development and application for the prevention, detection, diagnosis, or treatment of cancer.
- This funding opportunity will use Ruth L. Kirschstein National Research Service Awards (Kirschstein-NRSA) to support individual postdoctoral fellowships (F32) and senior fellowships (F33).
- The NCI intends to commit approximately \$15.5M dollars over 3 years to fund a total of 36 new fellowships in response to this RFA (approximately 18 for each mechanism). The total amount of funds committed for F32 fellowships for FY 2006 is approximately \$0.75 M. The total for F33 fellowships and supplements for FY 2006 is approximately \$4.42M. An applicant may request a project period of up to 3 years for F32 (stipend levels depend on full years of post-degree experience at the time of award, and include an institutional allowance; both amounts are determined yearly by Congress) and 2 years for F33 fellowships (stipend not to exceed the level of Kirschstein-NRSA stipend support for individuals with more than 7 years experience).

An applicant may request a project period of up to 3 years for F32 and 2 years for F33 fellowships.

- The anticipated start date for fellowship awards is July 2006, and funding will terminate no later than September 2009.
- Eligible supporting organizations include for-profit or non-profit organizations, public or private institutions (such as universities, colleges, hospitals, and laboratories), units of State government, units of local government, eligible agencies of the Federal government, and domestic or foreign institutions/organizations.
- Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with his or her institution and mentor to develop an application for support. By the time of award, candidates for the F32 or F33 fellowship must be citizens or non-citizen nationals of the United States or must have been lawfully admitted to the United States for Permanent Residence (i.e., possess a currently valid Alien Registration Receipt Card I-551 or other legal verification of such status). Before a Kirschstein-NRSA F32 postdoctoral fellowship or F33 senior fellowship can be activated, the individual must have received a Ph.D., M.D., D.O., D.C., D.D.S., D.V.M., O.D., D.P.M., Sc.D., Eng.D., Dr. P.H., D.N.S., N.D., Pharm.D., D.S.W., Psy.D., or equivalent doctoral degree from an accredited domestic or foreign institution. Certification by an authorized official of the degree-granting institution that all degree requirements have been met is also acceptable. In addition, applicants for a Kirschstein-NRSA F33 senior fellowship must be at least 7 years beyond one of the above qualifying degrees, have had at least 7 years of post-degree relevant research or professional experience, and have established an independent research career.
- An applicant may submit only one application for this one-time RFA.
- See [Section IV.1](#) for application and submission information.
- Telecommunications for the hearing impaired is available at: TTY 301-451-0088.

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

This RFA supports the training of individuals from the basic, biomedical, clinical, and information sciences and engineering who are pursuing research that applies nanotechnology development and application for the prevention, detection, diagnosis, or treatment of cancer. Nanotechnology offers an unprecedented opportunity to study and interact with normal and cancer cells in real time, at the molecular and cellular scales, and during the earliest stages of the cancer process. As a result, nanotechnology will be a mission-critical tool to meet the NCI's Challenge Goal of eliminating death and suffering from cancer by 2015. To achieve this vision, the NCI will support the training of a cadre of researchers who can work as members of multidisciplinary teams to apply the tools of nanotechnology to critical problems in cancer research and clinical oncology.

The elucidation of the human genome, combined with many remarkable advances in cancer biology, has offered great potential for researchers to address complex biological systems using innovative tools and strategies. The use of integrative biology (combining experimental and computational approaches towards the understanding of cancer biology to study cancer systems) is fostering novel nanoscale engineering and design applications to prevent, detect, diagnose, and treat various types of cancers. Although nanotechnology offers great potential to yield important information on the fundamental processes of cancer, there are few formal opportunities to train scientists and engineers who wish to develop and test nanomaterials and nanodevices for cancer-related applications. This RFA is a component of the NCI Alliance for Nanotechnology in Cancer (<http://nano.cancer.gov>), an integrated 5-year initiative to develop and apply nanotechnology to cancer prevention, detection, diagnosis, and treatment, thereby enabling nanotechnology to become a fundamental driver of advances in cancer research and clinical oncology.

This announcement specifically aims to encourage applications for F32 individual postdoctoral fellowships from promising candidates with the potential to become productive, independent investigators in cancer nanotechnology research. It also aims to encourage applications for F33 senior fellowships from experienced scientists who wish to change the direction of their research or broaden their scientific background by acquiring new capabilities in cancer nanotechnology research. This training opportunity supports training in numerous research disciplines, and it is expected that trainees (fellows) will gain expertise in the computational, physical, and biological aspects of technology development at the nanoscale for cancer treatment. As part of the NCI Alliance for Nanotechnology in Cancer, fellows will be required to attend the annual scientific meeting of the NCI Centers of Cancer Nanotechnology Excellence (CCNEs).

The goal of this fellowship program in cancer nanotechnology research is to train highly skilled research scientists to develop and test nanomaterials and nanodevices and to apply these advances to address cancer-related issues. Fellows are expected to work as productive members of multidisciplinary research teams, assembled to address critical nanotechnology platform needs in cancer. It is expected that these individuals will pursue research that includes, but is not limited to, one or more of the following areas:

- Imaging agents and diagnostic tools that will enable clinicians to detect cancer in its earliest stages;
- Systems that will provide real-time assessments of therapeutic and surgical efficacies for accelerating clinical translation;
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents directly to cancer cells and those tissues in the tumor microenvironment that play critical roles in the growth and metastasis of cancer;
- Agents that can monitor predictive molecular changes and prevent pre-cancerous cells from becoming malignant;
- Novel methods to manage the symptoms of cancer that adversely impact quality of life; and/or
- Research tools that will enable rapid identification of new targets for clinical development and predict drug resistance.

See [Section VIII, Other Information - Required Federal Citations](#), for policies related to this announcement.

Section II. Award Information

1. Mechanism(s) of Support

This funding opportunity will use the Kirschstein-NRSA F32 and F33 fellowship mechanisms.

As an applicant, you will work with your institution and mentor to plan, direct, and execute the proposed project. This RFA is a one-time solicitation.

2. Funds Available

The NCI intends to commit approximately \$15.5M dollars over 3 years to fund a total of 36 new fellowships in response to this RFA (approximately 18 for each mechanism). The total amount of funds committed for F32 fellowships for FY 2006 is approximately \$0.75 M. The total for F33 fellowships and supplements for FY 2006 is approximately \$4.42M. An applicant may request a project period of up to 3 years for an F32 fellowship (stipend levels depend on full years of post-degree experience at the time of award, and include an Institutional allowance; both amounts are determined yearly by Congress) or 2 years for an F33 fellowship (stipend not to exceed the level of Kirschstein-NRSA stipend

support for individuals with more than 7 years experience). This funding is commensurate with current guidelines specified for Kirschstein-NRSA Awards (<http://grants.nih.gov/grants/funding/416/phs416.htm>). The anticipated start date for fellowship awards is April 2006, and funding will terminate no later than September 2009. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each fellowship award will also vary. Although the financial plans of the NCI provide support for this program, fellowships pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

Stipends. Kirschstein-NRSA fellowships provide stipends to postdoctoral fellows as a subsistence allowance to help defray living expenses during the research training experience. The fellowships are not provided as a condition of employment with either the Federal government or the sponsoring institution. The stipend level for the first year of Kirschstein-NRSA support is determined by the number of full years of relevant postdoctoral experience at the time the award is issued (not at the time of activation, see below). Fellows with less than one full year of postdoctoral experience at the time of award will receive initial support at the zero level. Relevant experience may include research (including research in industry), teaching, internship, residency, clinical duties, or other time spent in full-time studies in a health-related field beyond that of the qualifying doctoral degree. The stipend schedule is updated nearly every year, and applicants are advised to check for the posting of the current stipend schedule on the NIH web site at <http://grants.nih.gov/training/nrsa.htm>. The awarding NIH Institute or Center will adjust awards on the anniversary date of the fellowship award to ensure consistency with the stipend schedule in effect at that time. The stipend for each subsequent year of Kirschstein-NRSA support is the next level of experience using the stipend schedule in effect at that time. Stipends will be adjusted on the anniversary date of the award and will not be changed mid-year to accommodate an increase in the level of experience. No departure from the published Kirschstein-NRSA stipend schedule may be negotiated between the institution and the fellow. For fellows sponsored by domestic non-federal institutions, the stipend will be paid through the sponsoring institution. For fellows sponsored by Federal or foreign institutions, the monthly stipend payment will be deposited in the fellow's U.S. bank account or paid directly to the fellow by U.S. Department of Treasury check. Stipends for Kirschstein senior fellows are determined individually at the time of award. The amount of the stipend is based on the salary or remuneration from their home institution on the date of award. However, in no case shall the NIH contribution to the stipend during the fellowship exceed the Kirschstein-NRSA stipend provided for individuals with more than 7 years of experience. For fellows on sabbatical, the level of the Kirschstein-NRSA stipend award will take into account concurrent sabbatical salary support provided by the home institution and any other supplementation. The stipend is not provided as a condition of employment with either the Federal Government or the institution.

Tuition and Fees. The NIH will offset the combined cost of tuition and fees at the following rate: 100 percent of all costs up to \$3,000 and 60 percent of costs above \$3,000. Costs associated with tuition and fees are allowable only if they are required for specific courses in support of the research training experience supported by the fellowship. A full description of the tuition policy is contained within the Kirschstein-NRSA section of the NIH Grants Policy Statement at <http://grants.nih.gov/grants/policy/policy.htm>.

Institutional Allowance. At the time of publication, fellows receive an institutional allowance of \$5,500 per 12-month period to nonfederal, nonprofit, or foreign sponsoring institutions to help defray such expenses as research supplies, equipment, health insurance (either self-only or family as appropriate), and travel to scientific meetings. Support for health insurance is allowable only if it is applied consistently for all individuals in a similar research training status regardless of the source of support. This allowance is intended to cover training related expenses for the individual awardee. The allowance is not available until the fellow officially activates the award. If an individual fellow is enrolled or engaged in training for less than 6 months of the award year, only one-half of that year's allowance may be charged to the grant. The Notice of Research Fellowship Award will be revised and the balance must be refunded to NIH. NIH will provide an institutional allowance of up to \$4,400 for

fellows sponsored by Federal laboratories or for-profit institutions for expenses associated with travel to scientific meetings, health insurance, and books. For fellows at for-profit institutions, the \$4,400 will be paid to the institution for disbursement to the fellow. Funds for fellows at Federal laboratories will be disbursed from the NIH awarding Institute. The Institutional Allowance is adjusted from time-to-time. Prospective applicants are advised to check for the current Institutional Allowance in the most recent documentation related to Kirschstein-NRSA stipends at <http://grants.nih.gov/training/nrsa.htm>.

Other Training Costs. Additional funds may be requested by the institution when the training of a fellow involves extraordinary costs for travel to field sites remote from the sponsoring institution or accommodations for fellows who are disabled, as defined by the Americans with Disabilities Act. The funds requested for costs of this nature must be reasonable in relationship to the total dollars awarded under the fellowship and must be directly related to the approved research training experience. Such additional funds shall be provided only in exceptional circumstances that are fully justified and explained by the sponsoring institution. Awards for training at a foreign site may include a single economy or coach round-trip travel fare. No allowance is provided for dependents. U.S. flag air carriers must be used to the maximum extent possible when commercial air transportation is available for travel between the United States and a foreign country or between foreign countries. Funds are not provided to cover the cost of travel between the fellow's place of residence and a domestic training institution. However, in cases of extreme need or hardship, a one-way travel allowance may be authorized by the sponsoring institution. Such travel must be paid from the institutional allowance. Institutions hosting senior fellowship (F33) awardees may be eligible for research support supplements. Details and restrictions will be available at the program website (<http://nano.cancer.gov>).

Facilities and Administrative (F&A) Costs. F&A (indirect) costs are not allowed on individual fellowship awards.

Supplementation of Stipends, Compensation, and Other Income The sponsoring institution is allowed to provide funds to the fellow in addition to the stipends paid by the NIH. Such additional amounts either may be in the form of augmented stipends (supplementation) or in the form of compensation, such as salary or tuition remission for services such as teaching or serving as a laboratory assistant, provided the conditions described below are met. Under no circumstances may the conditions of stipend supplementation or the services provided for compensation interfere with, detract from, or prolong the fellow's approved Kirschstein-NRSA training program.

Stipend Supplementation: Supplementation or additional support to offset the cost of living may be provided by the sponsoring institution. Supplementation does not require additional effort from the fellow. U.S. Department of Health and Human Services (DHHS) funds may not be used for supplementation under any circumstances. Additionally, no funds from other Federal agencies may be used for supplementation unless specifically authorized by the NIH and the other Federal Agency.

Compensation: The sponsoring institution may provide additional funds to a fellow in the form of compensation (as salary and/or tuition remission) for services such as teaching or serving as a research assistant. A fellow may receive compensation for services as a research assistant or in some other position on a Federal research grant, including a DHHS research grant. However, compensated services should occur on a limited, part-time basis apart from the normal research training activities, which require a minimum of 40 hours per week. In addition, compensation may not be paid from a research grant that supports the same research that is part of the fellow's research training experience as approved in the application.

Educational Loans or G.I. Bill: An individual may make use of Federal educational loan funds and assistance under the Veterans Readjustment Benefits Act (G.I. Bill). Such funds are not considered supplementation or compensation. Postdoctoral fellows may also be eligible to participate in the NIH Extramural Loan Repayment Program. Information on this program is available at <http://www.lrp.nih.gov>.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

You may submit (an) application(s) if your organization has any of the following characteristics:

- For-profit organizations
- Non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State government
- Units of local government
- Eligible agencies of the Federal government
- Foreign Institutions
- Domestic Institutions

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Women, minorities (individuals from underrepresented racial and ethnic groups), and individuals with disabilities are always encouraged to apply for NIH programs.

Fellows are required to pursue their research training on a full-time basis, devoting at least 40 hours per week to the training program.

Further details of the Kirschstein-NRSA F32 fellowship mechanism can be found at <http://grants.nih.gov/grants/guide/pa-files/RFA-03-067.html>; details of the Kirschstein-NRSA F33 fellowship mechanism can be found at <http://grants.nih.gov/grants/guide/pa-files/RFA-00-131.html>.

Citizenship. By the time of award, candidates for the F32 or F33 fellowship must be citizens or non-citizen nationals of the United States or must have been lawfully admitted to the United States for Permanent Residence (i.e., possess a currently valid Alien Registration Receipt Card I-551 or other legal verification of such status). Non-citizen nationals are generally persons born in outlying possessions of the United States (i.e., American Samoa and Swains Island). Individuals on temporary or student visas are not eligible. Individuals may apply for the F32 fellowship in advance of admission to the United States as a Permanent Resident recognizing that no award will be made until legal verification of Permanent Resident status is provided.

Degree Requirements. Before a Kirschstein-NRSA F32 postdoctoral fellowship or F33 senior fellowship can be activated, the individual must have received a Ph.D., M.D., D.O., D.C., D.D.S., D.V.M., O.D., D.P.M., Sc.D., Eng.D., Dr. P.H., D.N.S., N.D., Pharm.D., D.S.W., Psy.D., or equivalent doctoral degree from an accredited domestic or foreign institution. Certification by an authorized official of the degree-granting institution that all degree requirements have been met is also acceptable. In addition, applicants for an F33 Kirschstein-NRSA senior fellowship must be at least 7 years beyond one of the above qualifying degrees, have had at least 7 years of post-degree relevant research or professional experience, and have established an independent research career.

Duration of Support. F32 fellows may receive up to 3 years of aggregate Kirschstein-NRSA support at the postdoctoral level, including any combination of support from institutional training grants (T32) and individual fellowship awards (F32). F33 senior fellowships may be requested for up to 2 years.

Applicants must consider any prior Kirschstein-NRSA postdoctoral research training in determining the duration of fellowship support requested. Training beyond the 3-year aggregate limit may be possible under certain exceptional circumstances, but a waiver from the NIH awarding component is required. Individuals seeking additional Kirschstein-NRSA support beyond the 3rd year are strongly advised to consult with relevant NIH staff before preparing a justification. Any waiver will require a detailed justification of the need for additional research training.

2. Cost Sharing or Matching

Cost sharing is not required.

3. Other-Special Eligibility Criteria

Sponsor (Mentor). The applicant's sponsor should be an active investigator in the area of the proposed research who will directly supervise the candidate's research. The sponsor should either have expertise in the development and/or application of nanotechnology to cancer or have specific plans to obtain the requisite training, and must document the availability of research support and facilities for high-quality nanotechnology research training. In most cases, the F32 and F33 fellowship awards support research training experiences in new settings in order to maximize the acquisition of new skills and knowledge. However, in unusual circumstances, an applicant may propose postdoctoral training experiences at his/her doctoral institution or at the institution where he or she has been training for more than a year. In such cases, the applicant must carefully document the opportunities for new research training experiences specifically designed to broaden training involving nanotechnology research.

In most cases, the F33 senior fellowship is used to support sabbatical experiences for established independent scientists who wish to take time from regular professional responsibilities to receive training to expand their research capabilities.

Foreign Sponsorship. Applicants requesting fellowship support for foreign research training must justify in the application that the foreign institution and sponsor offer unique opportunities and clear scientific advantages that are not currently available in the United States.

Section IV. Application and Submission Information

1. Address to Request Application Information

The PHS 416-1 is available at <http://grants.nih.gov/grants/funding/416/phs416.htm> in an interactive format. For further assistance, contact GrantsInfo, Telephone: (301) 435-0714, Email: GrantsInfo@nih.gov.

Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the PHS 416-1 research grant application instructions and forms (rev. 06/02). Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at <http://www.dnb.com/us/>. The D&B number should be entered on line 12 of the face page of the PHS 416-1 form.

The title and number of this funding opportunity must be typed on line 3 of the face page of the application form.

APPLICATIONS MUST INCLUDE AT LEAST THREE SEALED LETTERS OF REFERENCE. APPLICATIONS WITHOUT AT LEAST THREE LETTERS OF REFERENCE WILL BE RETURNED OR DELAYED IN REVIEW. If the applicant has been lawfully admitted to the United States for permanent residence, the appropriate item should be checked on the Face Page of the application. Applicants who have applied for and have not yet been granted admission as a permanent resident should check the Permanent Resident block on the Face Page of the application, and also write in the word "pending." A notarized statement documenting legal admission for permanent residence must be submitted prior to the issuance of an award.

Concurrent Applications. An individual may not have more than one individual Kirschstein-NRSA fellowship or comparable application pending review or award at the NIH or other DHHS agencies at the same time.

Instructions in the Responsible Conduct of Research:

Applications must include the candidate's plans for obtaining instruction in the responsible conduct of research, including the rationale, subject matter, appropriateness, format, frequency and duration of instruction. The amount and nature of faculty participation must be described. No award will be made if an application lacks this component.

Foreign Organizations

Several special provisions apply to applications submitted by foreign organizations:

- Charge back of customs and import fees is not allowed.
- Format: every effort should be made to comply with the format specifications, which are based upon a standard US paper size of 8.5" x 11."
- Funds for up to 8% administrative costs (excluding equipment) can now be requested (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-028.html>)
- Organizations must comply with federal/NIH policies on human subjects, animals, and biohazards.
- Organizations must comply with federal/NIH biosafety and biosecurity regulations. See [Section VI.2. Administrative Requirements, "Cooperative Agreement Terms and Conditions of Award"](#)

Proposed research should provide a unique research opportunity not available in the U.S.

3. Submission Dates and Times

Applications must be received on or before the receipt date described below ([Section IV.3.A](#)).
Submission times N/A.

3.A. Receipt, Review, and Anticipated Start Dates

Letters Of Intent Receipt Date: Not Applicable
Application Receipt Date: November 16, 2005
Peer Review Date: February 2006
Council Review Date: May/June 2006
Earliest Anticipated Start Date: July 2006

3.A.1. Letter of Intent

Not applicable

3.B. Sending an Application to the NIH

Applications must be prepared using the PHS 416-1 research grant application instructions and forms as described above. Submit a signed, typewritten original of the application, including the checklist, and one signed photocopy in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

Personal deliveries of applications are no longer permitted (see <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-040.html>).

At the time of submission, one additional copy of the application and all copies of the appendix material must be sent to:

Referral Officer
National Cancer Institute
Division of Extramural Activities
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 496-3428
FAX: (301) 402-0275
Email: nciref@dea.nci.nih.gov

Appendices should be comprised of unbound materials with separators between documents.

Using the RFA Label: The RFA label available in the PHS 416-1 application (and in the PHS 398 application) instructions must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 3 of the face page of the application form. The RFA label is also available at <http://grants.nih.gov/grants/funding/phs398/labels.pdf>.

United States as Permanent Residents must submit notarized evidence of legal admission prior to award.

3.C. Application Processing

Applications must be **received on or before the application receipt date(s)** described above ([Section IV.3.A.](#)). If an application is received after that date, it will be returned to the applicant without review. Upon receipt, applications will be evaluated for completeness by the CSR and responsiveness by the NCI. Incomplete and non-responsive applications will not be reviewed. If the application is not responsive to the RFA, NIH staff may contact the applicant to determine whether to return the application to the applicant or submit it for review in competition with unsolicited applications at the next appropriate NIH review cycle.

The NIH will not accept any application in response to this funding opportunity that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to a funding opportunity, it is to be prepared as a NEW

application. That is, the application for the funding opportunity must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

4. Intergovernmental Review

This initiative is not subject to [intergovernmental review](#).

5. Funding Restrictions

All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm> (see also [Section VI.3. Reporting](#)).

Concurrent Awards: A Kirschstein-NRSA fellowship may not be held concurrently with another federally sponsored fellowship or similar Federal award that provides a stipend or otherwise duplicates provisions of this award.

Taxability of Stipends: Internal Revenue Code Section 117 applies to the tax treatment of all scholarships and fellowships. The Tax Reform Act of 1986, Public Law 99-514, impacts on the tax liability of all individuals supported under the Kirschstein-NRSA program. Under that section, non-degree candidates are now required to report as gross income all stipends and any monies paid on their behalf for course tuition and fees required for attendance. Degree candidates may exclude from gross income (for tax purposes) any amount used for tuition and related expenses such as fees, books, supplies, and equipment required for courses of instruction at a qualified educational organization.

The IRS and Treasury Department released regulations in January 2005 (Revenue Procedure 2005-11) clarifying the student exception to the FICA (Social Security and Medicare) taxes for students employed by a school, college, or university where the student is pursuing a course of study. Our understanding is that these final regulations do not apply to or impact Kirschstein-NRSA programs or awards. A Kirschstein-NRSA stipend is provided by the NIH as a subsistence allowance for Kirschstein-NRSA fellows and trainees to help defray living expenses during the research training experience. NRSA recipients are not considered employees of the Federal government or the grantee institution for purposes of the award. We must note that NIH takes no position on the status of a particular taxpayer, nor does it have the authority to dispense tax advice. The interpretation and implementation of the tax laws are the domain of the IRS.

Individuals should consult their local IRS office about the applicability of the tax laws to their situation and for information on their tax obligations.

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process.

The following items will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review
- Availability of funds

- Relevance of program priorities

2. Review and Selection Process

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the Division of Extramural Activities at the NCI in accordance with the review criteria stated below. Incomplete and/or non-responsive applications will not be reviewed.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
- Receive a written critique
- Receive a second level of review by the National Cancer Advisory Board.

The goals of NIH supported research are to advance our understanding of biological systems, to improve the control of disease, and to enhance health. In their written critiques, reviewers will be asked to comment on each of the following criteria in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application:

Candidate: An assessment of the candidate's previous academic and research performance and the potential to become (F32) or continue (F33) as an important contributor to biomedical, behavioral, or clinical science.

Sponsor and Training Environment: An assessment of the quality of the training environment and the qualifications of the sponsor as a mentor for the proposed research training experience. The sponsor's laboratory should either have expertise in the use of nanotechnology or describe plans for the sponsor and the fellow to obtain such expertise.

Research Proposal: The merit of the scientific proposal and its relationship to the candidate's career plans.

Training Potential: An assessment of the value of the proposed fellowship experience as it relates to the candidate's needs in preparation for a career as an independent researcher (F32) or to the candidate's capabilities as an independent researcher (F33). The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

2.A. Additional Review Criteria:

In addition to the above criteria, the following items will continue to be considered in the determination of scientific merit and the priority score:

Protection of Human Subjects from Research Risk: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Inclusion of Women, Minorities and Children in Research: The adequacy of plans to include subjects from both gender groups, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Care and Use of Vertebrate Animals in Research: If vertebrate animals are to be used in the project, the five items described under Section F of the PHS Form 398 research grant application instructions will be assessed.

Biohazards: The investigator and the sponsoring institution are responsible for protecting the environment and research personnel from hazardous conditions. If materials or procedures are proposed that are potentially hazardous to research personnel and/or the environment, please describe the procedures to be taken in order to ensure adequate protection.

2.B. Additional Review Considerations

Budget : The reasonableness of the requested budget in relation to the proposed training period of support. An F33 applicant must provide detailed budget information when requesting additional research support funds.

2.C. Sharing Research Data

Not applicable

2.D. Sharing Research Resources

Not applicable

3. Anticipated Announcement and Award Dates

Not applicable

Section VI. Award Administration Information

1. Award Notices

After the peer review of the application is completed, the Principal Investigator will also receive a written critique called a Summary Statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm).

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization. The NoA signed by the grants management officer is the authorizing document. Once all administrative and programmatic issues have been resolved, the NoA will be generated via e-mail notification from the awarding component to the grantee business official (designated in item 14 on the Application Face Page). If a grantee is not e-mail enabled, a hard copy of the NoA will be mailed to the business official.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs. See also [Section IV.5. Funding Restrictions](#).

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm) and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm).

Service Payback

As required by the NIH Revitalization Act of 1993, postdoctoral fellows incur a service obligation of 1 month for each month of support during the first 12 months of the Kirschstein-NRSA postdoctoral support. The 13th and subsequent months of Kirschstein-NRSA support are acceptable postdoctoral payback service. Thus, individuals who continue under the award for 2 years will have paid off their first year obligation by the end of the 2nd year.

Applicants accepting an award for the first 12 months of Kirschstein-NRSA postdoctoral support must sign a payback agreement (PHS Form 6031) in which they agree to engage in health-related research training, research, and/or teaching for 12 months.

Those who do not pay back their obligation through continued Kirschstein-NRSA supported training may satisfy their obligation by serving in a position in which health-related research, research training, or teaching are the primary activities. Such individuals must engage in research, research training, or teaching at a rate of 20 or more hours per week averaged over a full work-year. Payback service may be conducted in an academic, governmental, commercial, or nonacademic environment, in the United States or in a foreign country. Examples of acceptable payback service include research associateships/assistantships, postdoctoral research fellowships, and college or high school science teaching positions. Examples of unacceptable payback service include clinical practice and administrative responsibilities not directly related to scientific research.

Payback service positions are arranged by the individual, not by the NIH. The NIH will review and approve the activity at the end of the year in which it occurs. Service to satisfy any outstanding obligation must be initiated within 2 years after termination of Kirschstein-NRSA support and must be performed on a continuous basis. For individuals who fail to fulfill their service obligations, the United States is entitled to recover the total amount of Kirschstein-NRSA funds paid to the individual for the obligated period plus interest at a rate determined by the Secretary of the U.S. Department of Treasury. Financial payback must be completed within 3 years, beginning on the date the United States becomes entitled to recover such amount.

Under certain conditions, the Secretary, DHHS, may extend the period for starting service, permit breaks in service, extend the period of repayment, or otherwise waive the payback obligation when compliance would constitute a substantial hardship against equity and good conscience. Policies regarding the Kirschstein-NRSA payback obligation are explained in the Kirschstein-NRSA Section of the NIH Grants Policy Statement available at <http://grants.nih.gov/grants/policy/policy.htm>. Specific questions may appear in a list of Frequently Asked Questions that appears on the Web at http://grants.nih.gov/training/faq_fellowships.htm. Other questions on payback should be directed to the appropriate NIH Institute contact.

Leave Policies

In general, fellows may receive stipends during the normal periods of vacation and holidays observed by individuals in comparable training positions at the sponsoring institution. For the purpose of these awards, however, the period between the Spring and Fall semesters is considered to be an active time

of research and research training and is not considered to be a vacation or holiday. Fellows may receive stipends for up to 15 calendar days of sick leave per year. Sick leave may be used for the medical conditions related to pregnancy and childbirth. Fellows may also receive stipends for up to 30 calendar days of parental leave per year for the adoption or the birth of a child when those in comparable training positions at the grantee institution have access to paid leave for this purpose and the use of parental leave is approved by the program director.

A period of terminal leave is not permitted and payment may not be made from fellowship funds for leave not taken. Fellows requiring periods of time away from their research training experience longer than specified here must seek approval from the NIH awarding component for an unpaid leave of absence.

Part-Time Training

While Kirschstein-NRSA awardees are required to pursue research training full time, devoting at least 40 hours per week to the training program, under unusual and pressing personal circumstances, a fellow may submit a written request to the awarding component to permit less than full-time training. Such requests will be considered on a case-by-case basis. They must be approved by the awarding NIH Institute or Center in advance for each budget period. The nature of the circumstances requiring the part-time training might include medical conditions, disability, or pressing personal or family situations such as child or elder care. Permission for part-time training will not be approved to accommodate other sources of funding, job opportunities, clinical practice, clinical training, or for other responsibilities associated with the fellow's position at the institution. In each case, the fellow must submit a written request countersigned by the sponsor and an appropriate institutional business official that includes documentation supporting the need for part-time training. The written request also must include an estimate of the expected duration of the period of part-time training, an assurance that the fellow intends to return to full-time training when that becomes possible, and an assurance that the trainee intends to complete the proposed research training program. In no case will it be permissible for the fellow to be engaged in Kirschstein-NRSA supported research training for less than 50 percent effort. Individuals who must reduce their commitment to less than 50 percent effort must take a leave-of-absence from Kirschstein-NRSA fellowship support. The fellowship notice of award will be reissued and the stipend will be pro-rated during the period of any approved part-time training. Part-time training may affect the rate of accrual or repayment of the service obligation for postdoctoral fellows.

3. Reporting

Fellowships must be administered in accordance with the current Kirschstein-NRSA section of the Grants Policy Statement at <http://grants.nih.gov/grants/policy/policy.htm> and any terms and conditions specified on the award notice.

Reporting Procedures. Fellowship Activation. No funds may be disbursed until the fellow has started training under the award and an Activation Notice (PHS 416-5) and (when appropriate) a Payback Agreement (PHS 6031) has been submitted to the NIH. An awardee has up to 6 months from the issue date on the award notice to activate the award. Under unusual circumstances, an NIH institute may grant an extension of the activation period upon receipt of a specific request from the fellow. A payback Agreement Form (PHS 6031) must accompany the Activation Notice for any award that occurs during the individual's initial 12 months of Kirschstein-NRSA postdoctoral support. When support ends, the fellow must submit a Termination Notice (PHS 416-7) to the NIH. If the fellow has a payback obligation, he or she must notify the NIH of any change in address and submit Annual Payback Activities Certification Forms (PHS 6031-1) until the payback service obligation is satisfied. Forms will be provided to awardees by the NIH awarding component. Forms may also be found on the NIH Web site at <http://grants.nih.gov/grants/forms.htm>.

Inventions and Publications. Fellowships made primarily for educational purposes are exempted from the PHS invention requirements. F32 awards will not contain any provision giving PHS rights to inventions made by the awardee.

Copyrights. Except as otherwise provided in the terms and conditions of the award, the recipient is free to arrange for copyright without approval when publications, data, or other copyrightable works are developed in the course of work under a PHS grant-supported project or activity. Any such copyrighted or copyrightable works shall be subject to a royalty-free, nonexclusive, and irrevocable license to the Government to reproduce, publish, or otherwise use them, and to authorize others to do so for Federal Government purposes.

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 416-9, annually (<http://grants.nih.gov/grants/funding/416-9/phs416-9.htm>) and financial statements as required in the NIH Grants Policy Statement.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific/Research Contacts:

Gregory J. Downing, D.O., Ph.D.
Director, Office of Technology and Industrial Relations
Office of the Director
National Cancer Institute
Building 31, Room 10A-52, MSC 2580
31 Center Drive
Bethesda, MD 20892-2580
Telephone: (301) 496-1550
FAX: (301) 496-7807
Email: downingg@mail.nih.gov

2. Peer Review Contacts:

Referral Officer
National Cancer Institute
Division of Extramural Activities
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 496-3428
FAX: (301) 402-0275
E-mail: ncirefof@dea.nci.nih.gov

3. Financial or Grants Management Contacts:

Dena Solomon
Grants Management Specialist
Grants Administration Branch
National Cancer Institute
6120 Executive Boulevard, EPS Room 243, MSC 7150
Bethesda, MD 20892-7150
Rockville, MD 20852 (for express mail)
Telephone: (301) 496-7208
FAX: (301) 496-8601
E-mail: solomond@gab.nci.nih.gov

Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:

Recipients of PHS support for activities involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (<http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf>) as mandated by the Health Research Extension Act of 1985 (<http://grants.nih.gov/grants/olaw/references/hrea1985.htm>), and the USDA Animal Welfare Regulations (<http://www.nal.usda.gov/awic/legislat/usdaleg1.htm>) as applicable.

Human Subjects Protection:

Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>).

Data and Safety Monitoring Plan:

Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity and dose-finding studies (phase I); efficacy studies (Phase II); and efficacy, effectiveness, and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>).

Sharing Research Data:

Investigators submitting an NIH application seeking \$500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible (http://grants.nih.gov/grants/policy/data_sharing).

Investigators should seek guidance from their institutions, on issues related to institutional policies and local IRB rules, as well as local, State, and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Access to Research Data through the Freedom of Information Act:

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited

publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this funding opportunity in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Sharing of Model Organisms:

NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh-Dole Act (see the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal, beginning with the October 1, 2004, receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Inclusion of Women And Minorities in Clinical Research:

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:

The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects (<http://grants.nih.gov/grants/funding/children/children.htm>).

Required Education on the Protection of Human Subject Participants:

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

Human Embryonic Stem Cells (hESC):

Criteria for federal funding of research on hESCs can be found at <http://stemcells.nih.gov/index.asp> and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (<http://escr.nih.gov>). It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

NIH Public Access Policy:

NIH-funded investigators are requested to submit to the NIH manuscript submission (NIHMS) system (<http://www.nihms.nih.gov>) at PubMed Central (PMC) an electronic version of the author's final manuscript upon acceptance for publication, resulting from research supported in whole or in part with direct costs from NIH. The author's final manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process.

NIH is requesting that authors submit manuscripts resulting from 1) currently funded NIH research projects or 2) previously supported NIH research projects if they are accepted for publication on or after May 2, 2005. The NIH Public Access Policy applies to all research grant and career development award mechanisms, cooperative agreements, contracts, Institutional and Individual Ruth L. Kirschstein National Research Service Awards, as well as NIH intramural research studies. The Policy applies to peer-reviewed, original research publications that have been supported in whole or in part with direct costs from NIH, but it does not apply to book chapters, editorials, reviews, or conference proceedings. Publications resulting from non-NIH-supported research projects should not be submitted.

For more information about the Policy or the submission process, please visit the NIH Public Access Policy Web site at <http://www.nih.gov/about/publicaccess/> and view the Policy or other Resources and Tools including the Authors' Manual (http://www.nih.gov/about/publicaccess/publicaccess_Manual.htm).

Standards for Privacy of Individually Identifiable Health Information:

The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information," the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (<http://www.hhs.gov/ocr/>) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>.

URLs in NIH Grant Applications or Appendices:

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to

view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:

The U.S. Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople>.

Authority and Regulations:

This program is described in the Catalog of Federal Domestic Assistance at <http://www.cfda.gov/> and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Section 487 of the Public Health Service Act as amended (42 USC 288) and under Federal Regulations 42 CFR 66. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Loan Repayment Programs:

NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The LRP is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50 percent of their time (at least 20 hours per week based on a 40 hour week) for two years to the research. For further information, please see: <http://www.lrp.nih.gov>.

[Weekly TOC for this Announcement](#)
[NIH Funding Opportunities and Notices](#)



Office of
Extramural
Research
(OER)



National
Institutes of
Health (NIH)
9000 Rockville
Pike
Bethesda,
Maryland
20892



Department of
Health
and Human
Services (HHS)



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Fellowships in Cancer Nanotechnology Research Renewal Request

Background

Nanotechnology offers the unprecedented and paradigm-changing opportunity to study and interact with normal and cancer cells in real time, at the molecular and cellular scales, and during the earliest stages of the cancer process. Nanotechnology encompasses a broad range of disciplines including physics, engineering, toxicology, chemistry, physical chemistry, organic chemistry, biology, mathematics, and clinical medicine. It represents the science of creating and using new materials with dimensions of one to hundred nanometers and exhibiting novel properties not found in bulk dimensions. Harnessing the power of nanotechnology will radically change the current state of cancer prevent, detection, diagnosis, and treatment. Recognizing the need to facilitate such integration, and based on the strategies outlined in the NCI Cancer Nanotechnology Plan, the NCI Alliance for Nanotechnology in Cancer (the Alliance) initiative was launched in the Fall of 2005. This initiative enables technologies for:

- Imaging agents and diagnostics that will allow clinicians to detect cancer in its earliest stages
- Systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents directly to cancer cells and those tissues in the microenvironment that play a critical role in the growth and metastasis of cancer
- Agents that can monitor predictive molecular changes and prevent precancerous cells from becoming malignant
- Novel methods to manage the symptoms of cancer that adversely impact quality of life
- Research tools that will enable rapid identification of new targets for clinical development and predict drug resistance

Based on the strategies outlined in the NCI Cancer Nanotechnology Plan, the Alliance for Nanotechnology in Cancer (the Alliance) builds on the Institute's successes in developing nanotechnologies and facilitates their integration into translational research. The Alliance supports the development of consortia of laboratories collectively identified as a "center" that consists of multidisciplinary teams of biological and physical scientists working together on specific projects that meet one of the 6 programmatic areas of emphasis. The centers will provide a nexus of interactions aimed at the assembly of components from materials sciences that with interface with biological systems that provide unique capabilities for conducting scientific explorations of the cancer cell at atomic level. Other components of the Alliance include individual investigator initiated projects and career development initiatives to accelerate the translation of nanotechnology platforms in clinical research. Collectively, these programs will facilitate the detailed examination and rigorous validation necessary to prepare promising agents and diagnostics for clinical trials. The ultimate goal of the Alliance is to benefit the cancer patient through the delivery of novel therapeutics and enhanced diagnostic tools. The Multidisciplinary Training and Team Development Program presented here consist of award for postdoctoral (F32) and senior (F33) fellowships in cancer nanotechnology research. Formulation of the program was conducted in collaboration with the Cancer Training Branch as it constitutes a core element of the NCIs Alliance for Nanotechnology in Cancer program. While the program currently is managed within the Office of Technology and Industrial Relations (OTIR), there have been continued interactions with the Office of Centers, Training, and Resources (OCTR), including the Cancer Training Branch (CTB) to ensure both the success of program and its awardees such as providing Alliance program materials for distribution at training events held by OCTR. In addition, contacts within OCTR will assist in promoting the program, pending successful RFA reissuance.

Purpose of Award

As part of the NCI Alliance for Nanotechnology in Cancer, this RFA reissuance aims to continue supporting the career development of investigators for multi-disciplinary nano-oncology research and provide career development initiatives to accelerate the translation of nanotechnology platforms in clinical research. Outcome objectives (performance measures) are represented by institutions with training programs and scientists and engineers who are trained in cancer nanotechnology. The goal of this programmatic initiative is to support the entry of qualified scientists over the next three to five years with formal training in the application of nanotechnology to cancer biology who can lead new programs in technology development through the cancer research enterprise towards clinical applications.

Given the multidisciplinary nature of nanotechnology research, investigators with basic science and clinical backgrounds will require specific training to translate nanotechnologies toward clinical oncology applications. To help build this vital workforce, the NCI will support career development for individual researchers through F33 National Research Service Awards for Senior Fellows (estimate up to 3 awards) and F32 Ruth L. Kirschstein National Research Service Awards for postdoctoral training in biomedical, behavioral, or clinical research that serves health-related sciences (estimate up to 10 awards).

The NCI will initially use existing training and career development mechanisms to direct talent to this area as quickly as possible and to incentivize cross-disciplinary research through training. When necessary, the NCI will investigate innovative policy considerations, such as naming multiple principal investigators per project, as incentives for conducting team science. The NCI will also encourage programs to be developed with interfaces to the training programs of other Federal agencies as components of the National Nanotechnology Initiative (NNI). The advantages are to translate knowledge rapidly from fundamental nanotechnology sciences to directed application in cancer biology.

Outcome objectives (performance measures) are represented by institutions with training programs and scientists and engineers who are trained in cancer nanotechnology. A 3- to 5-year benchmark is to support the entry of 20–30 scientists with formal training experiences in nanotechnology applied to cancer biology who can lead new programs in technology development through the cancer research enterprise in the next five years and beyond.

Current Program Structure and Portfolio Analysis

Career development has utilized the following mechanisms for the training of individual researchers: the F33 National Research Service Awards for Senior Fellows and the F32 Ruth L. Kirschstein National Research Service Awards (for postdoctoral training in biomedical, behavioral, or clinical research that serves health-related sciences). As part of a larger collective of funding opportunities within the NCI Alliance for Nanotechnology, this funding opportunity announcement will continue to catalyze a research environment wherein a variety of trained researchers can use nanotechnology to solve mission-critical problems in cancer research. It is also expected that these RFAs will continue to and support the translational research and development that will provide advances in cancer diagnostics and therapy, in both the and short terms.

An analysis of two prior RFAs for the program, 05-025 and CA-06-010, clearly indicates a trend of growth in both applications and

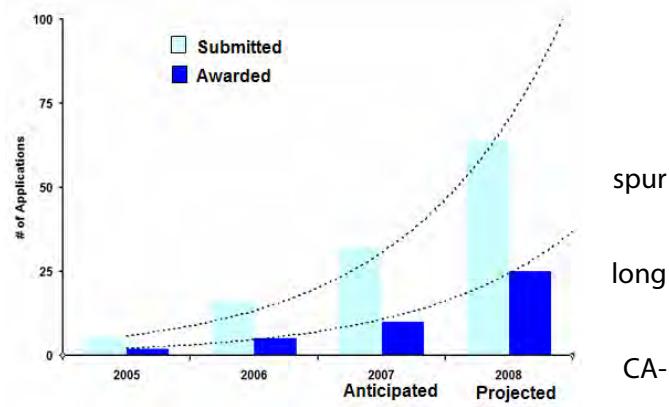


Figure 1

awards (Fig 1). For CA-05-025, five F32 applications were received and two were awarded. In comparison, CA-06-010 received fourteen F32 applications and 2 F33 applications, with five F32 applications receiving awards. Based on these trends and interest we are receiving from the investigators and their students, we anticipate over thirty applications this year and hope that up to 13 additional investigators may be supported under this extended program component. It should be pointed out that at our recent annual NCI Alliance for Nanotechnology in Cancer Investigators' Meeting, 70 of 215 attendees (~33%) were either postdoctoral or graduate researchers, evidence to a strong engagement of the young cadre in the field and the need for their multi-disciplinary training. At the meeting, current F32 recipients were allotted poster presentations, which provided further program awareness and dissemination. In addition, F32 recipients from CA-05-025 would be eligible and well qualified applicants for F33 awards.

The current seven awardees are summarized in table below followed by two specific case studies. Cross-disciplinary training is evident as chemists are training in the fields of biophysics and pharmacology, while engineers and material scientists are training in the fields of polymer chemistry and radiology. As a further testament of success, in 2006 alone, over seven publications have been co-authored by these current awardees, with two more in the pipeline for 2007.

Investigator	Project Title	PhD Field	Postdoc Field
Ivo P. Doudevski	Nanoscale mechanisms of Hsp90 and its co-chaperones	Chemistry	Biophysics
Rena J. May	Single Walled Carbon Nanotube Based Tumor Vaccines	Cell Biology	Pharmacology
Sofi Bin-Salamon	Nanoparticle-Bioconjugates As Cancer-Treating Agents	Mat. Sci	Chemistry
Mark D. Lim	Nanolabels of active proteases for cancer detection	Chemistry	Pharmacology
Ashley L. Galloway	Targeted Delivery Via Protein-Carbohydrate Interactions	Organic Chem	Mat. Sci
Yah-El Har-El	Liposomal Delivery of High LET Emitters to Cell Nuclei	Chem Eng.	Radiology
Giselle M. Knudsen	Geldanamycin-Mediated Uptake of Nanoparticle Probes	Chemistry	Pharmacology

Case Study I: Ashley L. Galloway

Background

Originally trained in synthetic bioorganic chemistry at Emory University, Ashley wanted to broaden her knowledge of chemistry at the interface of biology and biomaterials. By training in a well-renowned polymer chemistry lab, she planned to assist in functionalizing nanoparticles generated by Joseph DeSimone's patented technique, PRINT (Particle Replication in Non-wetting Templates), for novel therapeutic applications. Ashley proposes to enhance efficacy of gene therapy by encapsulated siRNA in PRINT particles and targeting with conjugated lectins. To complete the project, she would receive training not only in polymer chemistry, but also in molecular biology and cell biology.

Accomplishments

- Preliminary in vitro experiments were conducted on HeLa -globin 705 cells. In this cell line, a mutation at intron 2 of the -globin gene has caused an aberrant splicing of the pre-mRNA leading to -globin deficiency. (-thalassemia model). Successful in vitro delivery was monitored by measuring the production of -globin mRNA by RT-PCR.
- Antisense oligonucleotide that will block the aberrant splice site at intron 2, thus restoring -globin production, was successfully encapsulated in both disulfide nanoparticles (active release) and PEG nanoparticles (passive release).

- Preliminary results indicate that both nanoparticles restored correct splicing in vitro. Conjugation of lectin targeting moieties is currently underway and should significantly increase efficacy.

Case Study II: Mark D. Lim

Background

The main goal of Mark's training is to exploit the boundaries between chemistry and biology, where he will utilize his previous training in chemistry (UCSB) to explore how a chemical approach could be used to develop methods that would expand what is available in a medical clinicians' toolbox. Charles Craik at UCSF is noted for work in the field of analysis of proteolytic enzymes and their inhibitors using genetic, biochemical and biophysical methods. Mark proposed to create a novel method of imaging early stage cancer cells by targeting upregulated cell surface proteases. From this project, he would expand his existing training to encompass both the fields of biochemistry and biophysics.

Accomplishments

- Successful prototype design of activity based probe (ABP). Quantum dots are Quantum dots are functionalized to detect upregulated cell surface proteases such as MT-SP1, which have been found to have upregulated activity in breast cancer.
- Preliminary results presented at Annual Alliance Investigators Meeting indicate that probes can detect upregulated activity in vitro.
- Based upon interactions at the Alliance meeting, Mark is serving as liaison between his project and Project 6 at Stanford CCNE, headed by Sam Gambhir, to share functionalization techniques and to use NIRF QDs developed at Stanford.
- A manuscript detailing the results is currently in preparation.

As shown above, it is clear that the ultimate goal of this program is to help build the pipeline of qualified scientists with formal training experiences in nanotechnology applied to cancer biology who can lead new programs in technology development through the cancer research enterprise in the next five years and beyond.

Justification for Use of FOA

The proposed program continuance would best be served through the continuing use of a modest set aside due to the fact that the career development of investigators for multidisciplinary nanotechnology and nano-oncology specific technologies to address the many needs of the cancer community is essential. As part of a larger initiative to train specific investigators in the development, application, and/or translational use of these technologies, these fellowships will support many aspects of the cancer nanotechnology program as well as broader technology development and integration initiatives across NCI and across the cancer research enterprise. The use of a set-aside to attract such high-risk, interdisciplinary trainee proposals is therefore critical to successfully supporting interdisciplinary investigator development vital for cancer nanotechnology research.

Program Contact

Piotr Grodzinski, Ph.D.
Program Director, Alliance for Nanotechnology in Cancer
Office of Technology and Industrial Relations
Telephone: (301) 496-1550
E-mail: grodzinp@mail.nih.gov

Part I Overview Information

Department of Health and Human Services

Participating Organizations

National Institutes of Health (NIH), (<http://www.nih.gov>)

Components of Participating Organizations

National Cancer Institute (NCI), (<http://www.nci.nih.gov>)

Title: Multidisciplinary Fellowships in Cancer Nanotechnology Research (F32 and F33)

Announcement Type

This is a reissue of [RFA-CA-05-025](#), which was previously released on December 1, 2004.

Request For Applications (RFA) Number: RFA-CA-08-003

Catalog of Federal Domestic Assistance Number(s)

93.398, 93.393, 93.399, 93.395, 93.396

Key Dates

Release Date: September 17, 2007

Application Receipt Date: December 20, 2007

Peer Review Date(s): February/March 2008

Council Review Date: May 2008

Earliest Anticipated Start Date: July 2008

Additional Information To Be Available Date (URL Activation Date): Not Applicable

Expiration Date: December 21, 2007

Due Dates for E.O. 12372

Not Applicable.

Additional Overview Content

Executive Summary

- This Funding Opportunity Announcement (FOA) is designed to support the multidisciplinary training of individuals with background in the basic, biomedical, clinical, and information sciences and/or engineering who are pursuing research that applies the development and application of nanotechnology to the prevention, detection, diagnosis, and/or treatment of cancer.
- This FOA will use Ruth L. Kirschstein National Research Service Awards (Kirschstein-NRSAs) to support individual postdoctoral fellowships (F32) and senior fellowships (F33).
- The NCI intends to commit approximately \$2.25M over 3 years to fund a total of 10 new fellowships in response to this FOA. The total amount of funds committed for FY2008 fellowships is \$0.75 M.
- An applicant may request a support period of up to 3 years for F32 fellowships (stipend levels depend on full years of post-doctoral degree experience at the time of award, and include an institutional allowance; both amounts are determined yearly by Congress). An applicant may request a support period of up to 2 years for F33 fellowships. However, no individual may receive no more than 3 years of aggregate NRSA support at the postdoctoral level, including any combination of support from institutional training grants (T32) and individual awards.
- The anticipated start date for these fellowship awards is July 2008.
- Eligible supporting organizations include: Public/State Controlled Institutions of Higher Education; Private Institutions of Higher Education; Nonprofit with 501(c)(3) IRS Status (Other than Institution of Higher Education); Nonprofit without 501(c)(3) IRS Status (Other than Institution of Higher Education); Regional Organizations; U.S. Territory or Possession; Non-domestic (non-U.S.) Entity (Foreign Organization); and eligible agencies of the Federal government.
- **Eligibility for F32 postdoctoral fellowships:** Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with his or her institution and sponsor to develop an application for support. By the time of award, candidates for the F32 fellowship must be citizens or non-citizen nationals of the United States (U.S.) or must have been lawfully admitted to the U.S. for Permanent Residence (i.e., possess a currently valid Alien Registration Receipt Card I-551 or other legal verification of such status). Before a Kirschstein-NRSA F32 postdoctoral fellowship can be activated, the individual must have received a Ph.D., M.D., D.O., D.C., D.D.S., D.V.M., O.D., D.P.M., Sc.D., Eng.D., Dr. P.H., D.N.S., N.D., Pharm.D., D.S.W., Psy.D., or equivalent doctoral degree from an accredited Domestic or Foreign institution. Certification by an authorized official of the degree-granting institution that all degree requirements have been met is also acceptable.
- **Eligibility for F33 senior fellowships:** Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with his or her institution and sponsor to develop an application for support. By the time of award,

candidates for the F33 fellowship must be citizens or non-citizen nationals of the United States (U.S.) or must have been lawfully admitted to the U.S. for Permanent Residence (i.e., possess a currently valid Alien Registration Receipt Card I-551 or other legal verification of such status). To be eligible for a Kirschstein-NRSA F33 senior fellowship, the candidate must have received a Ph.D., M.D., D.O., D.C., D.D.S., D.V.M., O.D., D.P.M., Sc.D., Eng.D., Dr. P.H., D.N.S., N.D., Pharm.D., D.S.W., Psy.D., or equivalent doctoral degree from an accredited Domestic or Foreign institution. Applicants for a Kirschstein-NRSA F33 senior fellowship must have completed at least 7 subsequent years beyond one of the above listed qualifying degrees of relevant research or professional experience and have established an independent research career.

- Only new applications are allowed. Neither competing continuation nor resubmission applications will be accepted.
- An applicant may submit only one application for this one-time FOA.
- See [Section IV.1](#) for application and submission information.
- Telecommunications for the hearing impaired is available at: TTY 301-451-0088.

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

Purpose

This Funding Opportunity Announcement (FOA) is designed to support the multidisciplinary training of individuals from the basic, biomedical, clinical, and information sciences and/or engineering who are pursuing research on nanotechnology tools and/or applications for the prevention, detection, diagnosis, and/or treatment of cancer.

This FOA solicits applications for **postdoctoral fellowships** from recent doctoral level graduates as well as applications for **senior fellowships** from candidates with at least 7 years of research experience beyond the doctorate and established independent research positions.

The term “nanotechnology”, as used in this FOA, refers to devices or base materials that are less than 1000 nm in size (although the assembly, synthesis, and/or fabrication of components at dimensions less than 300 nm should be demonstrated) and may incorporate synthetic materials or biomaterials engineered to provide novel properties or modified functions based on nanoscale size, i.e., nanomaterials.

Nanotechnology broadens in an unprecedented way the opportunities to study normal and cancer cells and to collect (often in real time) relevant information on cancer emergence and progression at the molecular and cellular levels. The NCI regards nanotechnology as one of the critically important and innovative tools in attempts to reduce the burden of cancer. The goal of this FOA is to train a cadre of researchers who would become competent in applying the tools and approaches of nanotechnology to critical problems in cancer research and clinical oncology while working as members of multidisciplinary teams.

This FOA is a component of the NCI Alliance for Nanotechnology in Cancer (<http://nano.cancer.gov/>), an integrated 5-year-long initiative to develop and apply nanotechnology to cancer prevention, detection, diagnosis, and treatment, thereby enabling nanotechnology to become a fundamental driver of advances in cancer research and clinical oncology.

Training Scope and Specific Goals

The elucidation of the human genome, combined with many remarkable advances in cancer biology, has offered great potential for researchers to address complex biological systems using innovative tools and strategies. The use of integrative biology (combining experimental and computational approaches towards the understanding of cancer biology to study cancer systems) is fostering novel nanoscale systems to prevent, detect, diagnose, and treat various types of cancers. Although nanotechnology offers great potential to yield important information on the fundamental processes of cancer, there are few formal opportunities to train scientists and engineers who wish to develop and test nanomaterials and nanodevices for cancer-related applications.

The goal of this fellowship program is to provide research scientists with an opportunity to train outside of their current field of expertise and develop multidisciplinary skill sets that can be applied in the development and testing of nanomaterials and nanodevices in cancer-related applications.

Through this FOA, the NCI specifically intends to encourage:

1. Applications for **F32 individual postdoctoral fellowships** from promising candidates with the potential to become productive, independent investigators in cancer nanotechnology research; and
2. Applications for **F33 senior fellowships** from experienced scientists who wish to change the direction of their research or broaden their scientific background by acquiring new capabilities in cancer nanotechnology research, including translations of such research to clinical applications.

The scope of both training opportunities spans various research disciplines. Specifically, it is expected that trainees (fellows) will gain expertise in and pursue active research work in one or more fields outside of their current field of expertise. This may include, but is not limited to, computational, physical, or biological aspects of technology development benefiting applications of nanotechnology in cancer. Thus, for the duration of support, F32/F33 fellows should be members of multidisciplinary teams assembled to address critical nanotechnology platform needs in cancer.

As members of multidisciplinary research teams, fellowship candidates are expected to pursue nanotechnology applications pertinent to one or more areas of high priority to cancer research. Examples of such areas include, but are not limited to:

- Imaging agents and diagnostic tools for cancer detection at the earliest stages;
- Systems for real-time assessments of therapeutic and/or surgical efficacies;

- Multifunctional, targeted devices capable of crossing biological barriers to deliver various therapeutic agents directly to cancer cells and/or those tissues in the tumor microenvironment that play critical roles in the growth and metastasis of cancer;
- Tools to monitor cancer-predictive molecular changes to prevent pre-cancerous cells from becoming malignant;
- Novel methods to manage the symptoms of cancer that adversely impact patients' quality of life; and/or
- Tools to enable rapid identification of new therapeutic targets for clinical development and/or predict drug resistance.

As part of the NCI Alliance for Nanotechnology in Cancer, fellows will be required to attend every year the annual scientific principal investigators' meeting of the NCI Centers of Cancer Nanotechnology Excellence (CCNEs) and Cancer Nanotechnology Platform Partnerships (CNPPs).

See [Section VIII, Other Information - Required Federal Citations](#), for policies related to this announcement.

Section II. Award Information

1. Mechanism(s) of Support

This FOA will use both the Ruth L. Kirschstein National Research Service Award (Kirschstein-NRSA) for Individual Postdoctoral Fellows (F32) and the Kirschstein-NRSA for Individual Senior Fellows (F33) mechanisms. As an applicant, the candidate and his/her sponsor are jointly responsible for planning, directing, and executing the proposed project.

This mechanism is intended for candidates that will have received a Ph.D., M.D., D.O., D.C., D.D.S., D.V.M., O.D., D.P.M., Sc.D., Eng.D., Dr. P.H., DNSc., N.D. (Doctor of Naturopathy), Pharm.D., D.S.W., Psy.D., or equivalent doctoral degree from an accredited Domestic or Foreign institution prior to activation of the award. Additional information and detailed requirements for this NRSA award mechanism can be found at <http://grants.nih.gov/training/nrsa.htm>.

2. Funds Available

The NCI intends to commit approximately \$2.25M over 3 years (\$750,000 dollars in FY08) to fund approximately eight to ten F32 awards and one to two F33 awards.

Although the financial plans of the NCI provide support for this program, awards pursuant to this funding opportunity are contingent upon the receipt of a sufficient number of meritorious applications, the program priorities, and the availability of funds.

Stipends

Ruth L. Kirschstein-National Research Service Awards provide stipends to postdoctoral fellows as a subsistence allowance to help defray living expenses during the research training experience. The awards are not provided as a condition of employment with either the Federal government or the sponsoring institution. The stipend level for the first year of Ruth L. Kirschstein-NRSA support is determined by the number of full years of relevant postdoctoral experience at the time the award is issued (not at the time of activation, see below). Fellows with less than one full year of postdoctoral experience at the time of award will receive initial support at the zero level. Relevant experience may include research (including research in industry), teaching, internship, residency, clinical duties, or other time spent in full-time studies in a health-related field beyond that of the qualifying doctoral degree. The current stipend schedule is on the NIH web site at <http://grants.nih.gov/training/nrsa.htm> and the NIH Guide Notice released on January 9, 2006, located at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-026.html>. The NCI will adjust awards on the anniversary date of the fellowship award to ensure consistency with the stipend schedule in effect at that time.

The stipend for each subsequent year of Ruth L. Kirschstein-NRSA support is the next level of experience using the stipend schedule in effect at that time. Stipends will be adjusted on the anniversary date of the award and will not be changed mid-year to accommodate an increase in the level of experience. No departure from the published Ruth L. Kirschstein-NRSA stipend schedule may be negotiated between the institution and the fellow.

For fellows sponsored by Domestic non-Federal institutions, the stipend will be paid through the sponsoring institution. For fellows sponsored by Federal or Foreign institutions, the monthly stipend payment will be deposited in the fellow's U.S. bank account or paid directly to the fellow by U. S. Department of Treasury check.

Tuition and Fees

The NIH will offset the combined cost of tuition and fees at the rate in place at the time of award. The rate currently in place, as indicated in the NIH Guide announcement NOT-OD-06-093 released August 18, 2006, will provide an amount per fellow equal to 60% of the level requested by the applicant institution, up to \$4,500 per year. Costs associated with tuition and fees are allowable only if they are required for specific courses in support of the research training experience supported by the fellowship. A full description of the current tuition policy is located at: <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-06-093.html>

Institutional Allowance

The NIH provides an institutional allowance to help offset expenses such as research supplies, equipment, health insurance (either self-only or family as appropriate), and travel to scientific meetings. At the time of publication of this FOA (and as indicated in NIH Guide Notice [NOT-OD-06-093](#)), fellows receive an institutional allowance of \$7,850 per 12-month period to non-Federal, nonprofit, or Foreign sponsoring institutions. Support for health insurance is allowable only if it is applied consistently for all individuals in a similar research training status regardless of the source of support. This allowance is intended to cover training related expenses for the individual fellow, and is not available until the fellow officially activates the award. If an individual fellow is enrolled or engaged in training for less than 6 months of the award year, only one-half of that year's allowance may be charged to the grant. The Notice of Research Fellowship Award will be revised and the balance must be returned to the NIH.

NIH will currently provide an institutional allowance of up to \$6,750 for fellows sponsored by Federal laboratories or for-profit institutions for expenses associated with travel to scientific meetings, health insurance, and books. For fellows at for-profit institutions, the \$6,750 will be paid to the institution for disbursement to the fellow. Funds for fellows at Federal laboratories will be disbursed from the awarding NIH institute or center (IC).

The Institutional Allowance is adjusted from time-to-time. Prospective applicants are advised to check for the current Institutional Allowance in the most recent documentation related to Ruth L. Kirschstein-NRSA stipends at <http://grants.nih.gov/training/nrsa.htm>.

Other Training Costs

Additional funds may be requested by the institution when the training of a fellow involves exceptional circumstances. In all cases, the additional funds requested must be reasonable in relationship to the total dollars awarded under the fellowship and must be directly related to the approved research training experience. Such additional funds shall be provided only in exceptional circumstances that are fully justified and explained by the sponsoring institution in the application.

- Reasonable accommodations – As part of this award, additional funds may be requested by the sponsoring institution to make changes or adjustments in the academic or research environment that will make it possible for an otherwise qualified individual with disabilities to perform the work necessary to meet the requirements of the degree program in which he/she is enrolled. Individuals with disabilities are defined as those with a physical or mental impairment that substantially limits one or more major life activities. The accommodations requested under this program must be directly related to the work required to meet the requirements as regards to both course work and laboratory

experience, and must be appropriate to the special needs of the applicant. Some types of accommodations that might be provided under this award include, but are not limited to: specialized equipment, assistive devices, and personnel, such as readers, interpreters, or assistants. This award is not meant to relieve the sponsoring institution of its obligation to provide reasonable accommodations as defined by the Americans with Disabilities Act. NIH will not provide funds for infrastructure alterations such as lowering countertops, widening doorways, etc.

- Off-site research training – As part of this award, additional funds may be requested by the sponsoring institution if the research training of a fellow involves extraordinary costs for travel to field sites remote from the sponsoring institution.
- Foreign site research training – As part of this award, applications that include training at a Foreign site may include a single economy or coach round-trip travel fare. No allowance is provided for dependents. U.S. flag carriers must be used to the maximum extent possible when commercial air transportation is available for travel between the U.S. and a Foreign country or between Foreign countries.

Facilities and Administrative (F&A) Costs

Facilities and administrative (F&A) costs are not allowed on individual fellowship awards.

Supplementation of Stipends, Compensation, and Other Income

The sponsoring institution is allowed to provide funds to the fellow in addition to the stipends paid by the NIH in accordance with its own formally established policies governing stipend support. These policies must be consistently applied to all individuals in a similar status, regardless of the source of funds. Such additional amounts either may be in the form of augmented stipends (supplementation) or in the form of compensation, such as salary or tuition remission for services such as teaching or serving as a laboratory assistant, provided the conditions described below are met. Under no circumstances may the conditions of stipend supplementation or the services provided for compensation interfere with, detract from, or prolong the fellow's approved Ruth L. Kirschstein-NRSA training program.

Stipend Supplementation

Supplementation or additional support to offset the cost of living may be provided by the sponsoring institution. Supplementation does not require additional effort from the fellow. U.S. Department of Health and Human Services (DHHS) funds may not be used for supplementation under any circumstances. Additionally, no funds from other Federal agencies may be used for supplementation unless specifically authorized by the NIH and the other Federal agency.

Compensation

The sponsoring institution may provide additional funds to a fellow in the form of compensation (as salary and/or tuition remission) for services such as teaching or serving as a research assistant. A fellow may receive compensation for services as a research assistant or in some other position on a Federal research grant, including a DHHS research grant. However, compensated services should occur on a limited, part-time basis apart from the normal full time research training activities. In addition, compensation may not be paid from a research grant supporting the fellow's research training experience.

A full description of the policy for stipend supplementation and compensation is located in the NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part10.htm.

Educational Loans or G.I. Bill

An individual may make use of Federal educational loan funds and assistance under the Veterans Readjustment Benefits Act (G.I. Bill). Such funds are not considered supplementation or compensation. Postdoctoral fellows may also be eligible to participate in the NIH Extramural Loan Repayment Program. Information on this program is available at <http://www.lrp.nih.gov/>.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

You may submit (an) application(s) if your organization has any of the following characteristics:

- Public/State Controlled Institutions of Higher Education;
- Private Institutions of Higher Education;
- Nonprofit with 501(c)(3) IRS Status (Other than Institution of Higher Education);
- Nonprofit without 501(c)(3) IRS Status (Other than Institution of Higher Education);
- Regional Organizations;
- U.S. Territory or Possession;
- Non-domestic (non-U.S.) Entity (Foreign Organization);
- Eligible agencies of the Federal government

The sponsoring institution must have staff and facilities available on site to provide a suitable environment for performing high-quality research training. An applicant must include in the application the name of his/her sponsor who will supervise the training and research experience.

Applicants requesting fellowship support for Foreign research training must demonstrate in the application that the Foreign institution and sponsor offer unique opportunities and clear scientific advantages over positions currently available in the U.S. Only if there is a clear scientific advantage will training at a Foreign site be supported.

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

Fellows are required to pursue their research training on a full-time basis, devoting at least 40 hours per week, or as specified by the sponsoring institution in accordance with its own policies, to the training program and its related research activities.

Citizenship

By the time of award, the individual applying for the Kirschstein-NRSA fellowship award must be a citizen or a non-citizen national of the United States or have been lawfully admitted for permanent residence (i.e., possess a currently valid Alien Registration Receipt Card I-551, or other legal verification of such status). Non-citizen nationals are generally persons born in outlying possessions of the United States (i.e., American Samoa and Swains Island). Individuals on temporary or student visas are not eligible. Individuals may apply for the F32 in advance of admission to the United States as a Permanent Resident recognizing that no award will be made until legal verification of Permanent Resident status is provided.

Degree Requirements

Before a Ruth L. Kirschstein-NRSA postdoctoral fellowship award can be activated, the individual must have received a Ph.D., M.D., D.O., D.C., D.D.S., D.V.M., O.D., D.P.M., Sc.D., Eng.D., Dr. P.H., DNSc., N.D. (Doctor of Naturopathy), Pharm.D., D.S.W., Psy.D., or equivalent doctoral degree from an accredited Domestic or Foreign institution. Certification by an authorized official of the degree-granting institution that all degree requirements have been met is also acceptable.

2. Cost Sharing or Matching

Cost sharing is not required.

The current NIH Grants Policy Statement can be found at

http://grants.nih.gov/grants/policy/nihgps_2003/nihgps_Part2.htm#matching_or_cost_sharing.

3. Other-Special Eligibility Criteria

An individual may not have two or more competing NIH fellowship applications pending review concurrently. In addition, CSR will not accept for review any application that is essentially the same as one already reviewed.

Duration of Support

Individuals may receive up to 3 years of aggregate Ruth L. Kirschstein-NRSA support at the postdoctoral level, including any combination of support from institutional training grants (T32) and individual fellowship awards (F32). Senior fellowship (F33) support may be requested for a period of up to 2 years. However, no individual may receive more than 3 years of aggregate Ruth L. Kirschstein-NRSA support at the postdoctoral level, including any combination of support from institutional training grants (T32) and individual fellowship awards. Applicants must consider any prior Ruth L. Kirschstein-NRSA postdoctoral research training in determining the duration of fellowship support requested. Training beyond the 3-year aggregate limit may be possible under certain exceptional circumstances, but a waiver from the NIH awarding component is required. Individuals seeking additional Ruth L. Kirschstein-NRSA support beyond the third year are strongly advised to consult with relevant NIH staff before preparing a justification. Any waiver will require a detailed justification of the need for additional research training.

Sponsor

Before submitting a fellowship application, the applicant must identify a sponsoring institution and an individual who will serve as a **sponsor (also referred to as mentor or supervisor)** and will supervise the training and research experience. The sponsor should be an active investigator in the area of the proposed research who is committed to the research training of the individual and will directly supervise the candidate's research. The sponsor should document the availability of sufficient research support, facilities, and didactic coursework, if appropriate, for a high-quality research training experience. Opportunities for the fellow to obtain additional guidance from other subject matter experts during the research training experience are encouraged. In some instances, it may be advisable for a co-sponsor to complement the primary sponsor's experience.

Sponsoring Institution

The sponsoring institution must have appropriate faculty and facilities available on site to provide a suitable environment for high-quality research training. In most cases, the F32 supports research training experiences in new settings in order to maximize the acquisition of new skills and knowledge. However, in unusual circumstances, applicants may propose postdoctoral training experiences at their doctorate institution or at the institution where they have been training for more than 1 year. In such cases, the applicant must carefully document the opportunities for new research training experiences specifically designed to broaden his/her scientific background.

Applicants requesting training at a Foreign venue are required to provide detailed justification for the Foreign training, including the reasons why the facilities, the sponsor, and/or other aspects of the proposed experience are more appropriate than training in a domestic setting. The justification is evaluated in terms of the scientific advantages of the Foreign training as compared to the training available domestically. Foreign training will be considered for funding only when the scientific advantages are clear. Applicants seeking training abroad are encouraged to contact the NCI prior to preparing an application (see Section VII.1).

Foreign Organizations

Several special provisions apply to applications submitted by Foreign institutions or organizations. Additional information regarding Foreign grants is available in the NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part12.htm#_Toc54600260.

Section IV. Application and Submission Information

1. Address to Request Application Information

The fellowship application instructions are available at [PHS 416-1](#) in an interactive format. For further assistance, contact GrantsInfo -- Telephone: (301) 435-0714; Email: GrantsInfo@nih.gov. Note that the PHS 416-1 has been restructured (Rev. 10/05) and the instructions have been significantly modified. See the NIH Notice [NOT-OD-07-002](#), which was released on October 5, 2006.

Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the Ruth L. Kirschstein National Research Service Award (NRSA) Individual Fellowship Application Form PHS 416-1. Applications must have a Dun and

Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at <http://www.dnb.com/us/>. The D&B number should be entered on line 13b of the face page of the PHS 416-1 form (Rev, 10/05).

The title and number of this funding opportunity must be typed on line 3 of the face page of the application form. If the fellowship application is submitted in response to a Program Announcement (PA) or Request for Application (RFA) from a particular NIH IC, the applicant should identify the number of the PA or RFA in Item 3.

Applications must include at least three sealed letters of reference using the PHS 416-1 reference page. Applications without at least three letters of reference may be delayed in review or returned to the applicant without review. Information applicable to the required references is located in the application instructions, Part 1 Preparing Your Application, E. Application [Section III](#).

If the applicant has been lawfully admitted to the United States for permanent residence, the Permanent Resident of U.S. block should be checked on the Face Page of the PHS 416-1 application. Applicants who have applied for and have not yet been granted admission as a permanent resident should also insert the word "pending." A notarized statement documenting legal admission for permanent residence must be submitted prior to the issuance of an award.

3. Submission Dates and Times

Applications must be received on or before the receipt date described below ([Section IV.3.A](#)).
Submission times N/A.

3.A. Receipt, Review, and Anticipated Start Dates

Application Receipt Date: December 20 2007

Peer Review Date(s): February-March, 2008

Council Review Date: May 2008

Earliest Anticipated Start Date: July 2008

3.A.1. Letter of Intent

A letter of intent is not required for this funding opportunity.

3.B. Sending an Application to the NIH

Applications must be prepared using the [PHS 416](#) (Rev. 10/05) research fellowship grant application instructions and forms as described above.

Applicants must follow the instructions stated in the PHS 416-1 for submitting the original and one copy of the application in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (for U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for non-USPS express/courier delivery)

Personal deliveries of applications are no longer permitted (see
<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-040.html>).

At the time of submission, one additional paper copy of the application and one copy of the appendix materials in paper or pdf format (**pdf format is strongly encouraged**) must be sent to:

Referral Officer
National Cancer Institute
Division of Extramural Activities
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329 (for U.S. Postal Service express or regular mail)
Rockville, MD 20852 (for express/courier delivery; non-USPS service)
Telephone: (301) 496-3428
Fax: (301) 402-0275
Email: ncidearef@nih.gov

Using the RFA Label: The RFA label available in the PHS 416 application instructions must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at <http://grants.nih.gov/grants/funding/phs398/labels.pdf>.

Certification Procedure

No application will be accepted without the applicant's signing the certification block on the face page of the application. Individuals admitted to the U.S. as Permanent Residents must submit notarized evidence of legal admission prior to the award.

3.C. Application Processing

Applications must be **received on or before the application receipt date(s)** described above ([Section IV.3.A.](#)). If an application is received after that date, it will be returned to the applicant without review. Upon receipt, applications will be evaluated for completeness by the CSR. Incomplete and non-responsive applications will not be reviewed. At least three sealed letters of reference must be submitted with the application.

The NIH will not accept any application in response to this funding opportunity that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to a funding opportunity, it is to be prepared as a NEW application. That is, the application for the funding opportunity must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

Information on the status of an application should be checked by the Principal Investigator (PI) in the eRA Commons at <https://commons.era.nih.gov/commons/>.

4. Intergovernmental Review

This initiative is not subject to [intergovernmental review](#).

5. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>.

These awards are also subject to the NRSA Policies. For more information, go to http://grants1.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part10.htm.

Concurrent Awards

A Ruth L. Kirschstein-NRSA fellowship may not be held concurrently with another Federally sponsored fellowship or similar Federal award that provides a stipend or otherwise duplicates provisions of this award.

Tax Liability

Internal Revenue Code Section 117 applies to the tax treatment of all scholarships and fellowships. The Tax Reform Act of 1986, Public Law 99-514, impacts on the tax liability of all individuals supported under the NRSA program. Under that section, non-degree candidates are required to report as gross income all stipends and any monies paid on their behalf for course tuition and fees required for attendance. Degree candidates may exclude from gross income (for tax purposes) any amount used for tuition and related expenses, such as fees, books, supplies, and equipment required for courses of instruction at a qualified educational organization.

The U.S. Internal Revenue Service (IRS) and Treasury Department released regulations in January 2005 (Revenue Procedure 2005-11) clarifying the student exception to the FICA (Social Security and Medicare) taxes for students employed by a school, college, or university where the student is pursuing a course of study. Our understanding is that these final regulations do not apply to or impact Ruth L. Kirschstein-NRSA programs or awards. An NRSA stipend is provided by the NIH as a subsistence allowance for Ruth L. Kirschstein-NRSA fellows and trainees to help defray living expenses during the research training experience. NRSA recipients are not considered employees of the Federal government or the grantee institution for purposes of the award. We must note that the NIH takes no position on the status of a particular taxpayer and it does not have the authority to dispense tax advice. The interpretation and implementation of the tax laws are the domain of the IRS. Individuals should consult their local IRS office about the applicability of the tax laws to their situation and for information on their tax obligations.

Service Payback

As required by the NIH Revitalization Act of 1993, postdoctoral fellows incur a service obligation of 1 month for each month of support during the first 12 months of the Ruth L. Kirschstein-NRSA postdoctoral support. The 13th and subsequent months of Ruth L. Kirschstein-NRSA support are acceptable postdoctoral payback service. Thus, individuals who continue under the award for 2 years will have paid off their first year obligation by the end of the second year.

Applicants accepting an award for the first 12 months of a Ruth L. Kirschstein-NRSA postdoctoral support must sign a payback agreement (PHS Form 6031) in which they agree to engage in health-related research training, research, and/or teaching for 12 months.

Those who do not pay back their obligation through continued Ruth L. Kirschstein-NRSA supported training may satisfy their obligation by serving in a position in which health-related research, research training, or teaching are the primary activities. Such individuals must engage in research, research training, or teaching at a rate of 20 or more hours per week averaged over a full work-year. Payback service may be conducted in an academic, governmental, commercial, or nonacademic environment, in the United States or in a Foreign country. Examples of acceptable

payback service include research associateships/assistantships, postdoctoral research fellowships, and college or high school science teaching positions. Examples of unacceptable payback service include clinical practice and administrative responsibilities not directly related to scientific research.

Payback service positions are arranged by the individual, not by the NIH. The NIH will review and approve the activity at the end of the year in which it occurs. Service to satisfy any outstanding obligation must be initiated within 2 years after termination of Ruth L. Kirschstein-NRSA support, and must be performed on a continuous basis. For individuals who fail to fulfill their service obligation, the United States is entitled to recover the total amount of Ruth L. Kirschstein-NRSA funds paid to the individual for the obligated period plus interest at a rate determined by the Secretary of the U.S. Department of Treasury. Financial payback must be completed within 3 years, beginning on the date the United States becomes entitled to recover such amount.

Under certain conditions, the Secretary, DHHS, may extend the period for starting service, permit breaks in service, extend the period of repayment, or otherwise waive the payback obligation when compliance would constitute a substantial hardship against equity and good conscience.

Policies regarding the Ruth L. Kirschstein-NRSA payback obligation are explained in the Ruth L. Kirschstein-NRSA Section of the NIH Grants Policy Statement available at <http://grants.nih.gov/grants/policy/policy.htm>.

Specific questions may appear in a list of Frequently Asked Questions that appears on the Web at http://grants.nih.gov/training/faq_fellowships.htm. Other questions on payback should be directed to the appropriate NIH institute contact (go to http://grants.nih.gov/grants/guide/contacts/pa-07-107_contacts.htm or see http://grants1.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part10.htm).

Future Year Support: Funds for continuation beyond the initial year are determined by the progress described in the continuation application (PHS 416-9, rev. 10/05), the timely submission of all required forms, and the availability of funds.

6. Other Submission Requirements

Applicants are advised to pay special attention to the instructions in the [PHS 416-1](#). Please note several important changes and reminders on pages 1 and 2, and the new biographical sketch format page. Applicants should follow the most up-to-date [PHS 416-1](#) application form and instructions at the time of application.

Sponsor

The applicant's sponsor/mentor, who will directly supervise the applicant's research, should be an active investigator in the area of the proposed research and meet the eligibility requirements in [Section III](#). The sponsor must describe in detail his/her commitment to and proposed role in guiding the individual applicant during the research training experience. If appropriate for multidisciplinary training, an applicant may have more than one sponsor.

Training Plan

The applicant should provide a tailored research plan that is developed with the sponsor. The sponsor should indicate clearly his/her commitment and approval that the plan is realistic and appropriate. The plan must list experiences that are specifically planned for the fellow including classes, seminars, and opportunities for interaction with other groups and scientists, and how these will assist the applicant in achieving his/her research goals. Describe the research environment and available research facilities and equipment. Indicate the relationship of the proposed research training to the candidate's career goals. Describe the skills and techniques that the candidate will learn as they relate to the multidisciplinary nanotechnology research and the candidate's career goals in that direction.

Additionally, the quality of the facilities and related resources (e.g., equipment, laboratory space, computer time, available research support, etc.) must be described.

If the sponsoring institution is a Foreign institution, information must be provided describing how the institution and sponsor offer unique opportunities for research training not currently available in the United States.

Research Proposal

A description of the broad, long-term objectives and specific aims, making reference to the health relatedness of the research proposal must be included. The applicant must describe concisely the research design and methods for achieving these goals, as well as the rationale and techniques planned to pursue these goals.

Training Potential

The application should address the value of the training towards meeting the applicant's career goals. This should include: expansion of the scientific background, expansion of the laboratory skills, ability to prepare grant applications – all leading to the applicant becoming an independent and competitive researcher.

Instruction in the Responsible Conduct of Research

Applications must include the sponsoring institution's plan to provide and the candidate's plans for obtaining instruction in the responsible conduct of research, including the rationale, subject matter, appropriateness, format, frequency, and duration of instruction. The amount and nature of faculty participation must be described. Although the NIH has not established specific curriculum or format requirements for this training, it is suggested that the following topics be covered: conflict of interest; data sharing; responsible authorship; policies for handling misconduct; policies regarding the use of human and animal subjects; and data management. Applications without plans for training in responsible conduct of research will be considered incomplete and may be returned without review; no award will be made if an application lacks this component.

Human Subjects Research

If the proposed research involves human subjects, the applicant must be responsive to the instructions in the current version of the PHS 416-1. The adequacy of plans to include appropriate human subjects is included in the fellowship evaluation (see Additional Review Criteria below).

Note that NIH defines children as individuals under 21 years of age. Consult the decision tree for the exemptions that apply (go to http://grants.nih.gov/grants/peer/tree_children_hs.pdf).

Care and Use of Vertebrate Animals in Research

If vertebrate animals are to be used in the project, the applicant must be responsive to the instructions in the current version of the PHS 416-1. The adequacy of plans for the care and use of vertebrate animals is assessed as part of the fellowship evaluation.

Biohazards

The investigator and the sponsoring institution are responsible for protecting the environment and research personnel from hazardous conditions. If materials or procedures are proposed that are potentially hazardous to research personnel and/or the environment, please describe the procedures to be taken in order to ensure adequate protection.

Plan for Sharing Research Data

Not applicable.

Sharing Research Resources

Sharing Model Organisms: If the development of model organisms is anticipated, include a description of a specific plan for sharing and distributing unique model organism research resources or state appropriate reasons why such sharing is restricted or not possible. For many individual fellowships, it is anticipated that plans of this nature would have already been reported to the NIH by your sponsor in his/her research application. When this has occurred, indicate so in this section and include the appropriate grant number. For additional information on this policy, see Sharing Model Organisms Policy ([PHS 416-1](#)). If model organisms are not part of the planned research training plan, omit this section. *This description is not included in the Research Training Plan page limits.*

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process.

The following items will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review;
- Availability of funds; and
- Relevance of program priorities.

2. Review and Selection Process

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the Division of Extramural Activities at the NCI in accordance with the review criteria stated below. Incomplete and/or non-responsive applications will not be reviewed.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific merit will be discussed and assigned a priority score;
- Receive a written critique; and
- Receive a second level of review by the National Cancer Advisory Board.

The goal of the Multidisciplinary Fellowships in Cancer Nanotechnology Research program is to provide postdoctoral fellowships in the field of cancer nanotechnology (F32 awards) as well as support for independent scientists who wish to expand their expertise and acquire new research capabilities in this field. Thus, **F32 awards** function to support promising applicants with the potential to become productive and successful independent researcher investigators, whereas **F33 awards** enable individuals with at least seven years of research experience beyond the doctorate, and who have progressed to the stage of independent investigator, to take time from regular professional responsibilities for the purpose of receiving training to increase their scientific capabilities within the scope of biomedical, behavioral, or clinical research in scientific health-related fields relevant to the missions of NCI.

In their written critiques, reviewers will be asked to comment on each of the following criteria in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward. In addition to general evaluation criteria for F32/F33 applications, as indicated below, some aspects to be evaluated are unique to this FOA.

Review criteria:

1. Candidate

- An assessment of the candidate's previous and current academic and research performance.
- An assessment of the candidate's potential to, and commitment to, becoming an important contributor to biomedical, behavioral, or clinical science.

Specific to this RFA:

- Appropriateness of the candidate's prior experiences in cancer nanotechnology research for multidisciplinary training.

2. Sponsor/Mentor and Training Environment

- An assessment of the quality of the training environment including the institutional commitment to research training, the quality and availability of the facilities and related resources (e.g., equipment, laboratory space, computer time, subject populations), and the availability of research support.

- The qualifications of the sponsor as a mentor for the proposed research training experience, as well as a researcher including successful competition for research support.
- If applicable, the quality and appropriateness of unique research training opportunities proposed at a Foreign site that are not available in the United States.

Specific to this RFA:

- Adequacy of the sponsor/training environment in terms of multidisciplinary nanotechnology research.

3. Research Training Proposal

- The merit of the scientific proposal and its relationship to the applicant's career plans.
- The quality of the research training plan.
- Potential of the proposed research training to serve as a sound foundation that will lead the candidate to a productive research career.

Specific to this RFA:

- Relevance to cancer nanotechnology.

4. Training Potential

- An assessment of the value of the proposed fellowship experience as it relates to the candidate's needs in preparation for a career as an independent researcher.

Specific to this RFA:

- Advantage of multidisciplinary training for advancement of the candidate's cancer nanotechnology research.

2.A. Additional Review Criteria

In addition to the above criteria, the following items will continue to be considered in the determination of scientific merit and the priority score:

Protection of Human Subjects from Research Risk: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Inclusion of Women, Minorities and Children in Research: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Care and Use of Vertebrate Animals in Research: If vertebrate animals are to be used in the project, the five items described under Section F of the PHS Form 398 research grant application instructions will be assessed.

Biohazards: If materials or procedures are proposed that are potentially hazardous to research personnel and/or the environment, determine if the proposed protection is adequate.

2.B. Additional Review Considerations

Responsible Conduct of Research: Every NRSA fellow must receive instruction in the responsible conduct of research (<http://grants.nih.gov/grants/guide/notice-files/not92-236.html>). Applications must include the sponsoring institution's plans to provide and the candidate's plans for obtaining instruction in the responsible conduct of research, including the rationale, subject matter, appropriateness, format, frequency and duration of instruction. The amount and nature of faculty participation must be described. The plan will be discussed after the overall determination of merit, so that the review panel's evaluation of the plan will not be a factor in the determination of the priority score. The plan will be judged as acceptable or unacceptable. The acceptability of the plan will be described in an administrative note of the summary statement. Regardless of the priority score, an application with an unacceptable plan will not be funded until the applicant provides a revised acceptable plan. Staff in the NIH awarding component will judge the acceptability of the revised plan.

2.C. Sharing Research Data

Not Applicable.

2.D. Sharing Research Resources

Sharing Model Organisms: For many individual fellowships it is anticipated that plans for sharing model organisms would have already been reported to the NIH by the sponsor in his/her research application. When this has occurred, applicants will indicate so and include the appropriate grant number. However, if the development of a new model organism is anticipated, applicants will include a description of a specific plan for sharing and distributing unique model organism research resources or state appropriate reasons why such sharing is restricted or not possible.

The reviewers will assess the adequacy of plans for sharing model organisms, and will describe their assessment of the sharing plan in an administrative note, but will not include their assessment in the overall priority score. The adequacy of the resources sharing plan will be considered by Program staff of the funding IC when making recommendations about funding applications.

3. Anticipated Announcement and Award Dates

Not Applicable.

Section VI. Award Administration Information

1. Award Notices

After the peer review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) via the [eRA Commons](#).

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. A request for just-in-time information should not be interpreted as indicating that an award will be issued.

A formal notification in the form of a Notice of Research Fellowship Award (NRFA) will be provided electronically to the designated sponsoring institution business official listed on the face page of the application. The NRFA may also be retrieved by the institution through its eRA Commons account. The NRFA signed by the grants management officer is the authorizing document indicating that an award has been made.

Selection of an application for award is not an authorization to begin performance. An awardee has up to 6 months from the issue date on the NRFA to activate the award.

Activation: No funds may be disbursed until the fellow has started training under the award and an Activation Notice (PHS 416-5, Rev. 10/05) and a Payback Agreement (PHS 6031, Rev. 10/05) has been submitted to the NIH. A fellow has up to 6 months from the issue date on the award notice to activate the award. Under unusual circumstances, an NIH Institute may grant an extension of the activation period upon receipt of a specific request from the fellow.

2. Administrative and National Policy Requirements

Ruth L. Kirschstein NRSA Postdoctoral Fellowships require payback agreements. For more information, see [Section IV.5. Funding Restrictions and](#) http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part10.htm.

All NIH grants and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm) and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm).

Fellowships must be administered in accordance with the current NRSA section of the Grants Policy Statement at <http://grants.nih.gov/grants/policy/policy.htm>, and any terms and conditions specified on the Notice of Research Fellowship Award.

Leave Policies

In general, fellows may receive stipends during the normal periods of vacation and holidays observed by individuals in comparable training positions at the sponsoring institution. For the purpose of these awards, however, the period between the spring and fall semesters is considered to be an active time of research and research training and is not considered to be a vacation or holiday. Fellows may receive stipends for up to 15 calendar days of sick leave per year. Sick leave may be used for the medical conditions related to pregnancy and childbirth. Fellows may also receive stipends for up to 30 calendar days of parental leave per year for the adoption or the birth of a child when those in comparable training positions at the grantee institution have access to paid leave for this purpose and the use of parental leave is approved by the program director.

A period of terminal leave is not permitted and payment may not be made from fellowship funds for leave not taken. Fellows requiring periods of time away from their research training experience longer than specified here must seek approval from the NIH awarding component for an unpaid leave of absence.

Part-time training

While Ruth L. Kirschstein-NRSA awardees are required to pursue research training full time, normally defined as 40 hours per week, or as specified by the sponsoring institution in accordance with its own policies, under unusual and pressing personal circumstances, a fellow may submit a written request to the awarding component to permit less than full-time training. Such requests will be considered on a case-by-case basis. They must be approved by the awarding NIH Institute

or Center in advance for each budget period. The nature of the circumstances requiring the part-time training might include medical conditions, disability, or pressing personal or family situations such as child or elder care. Permission for part-time training will not be approved to accommodate other sources of funding, job opportunities, clinical practice, clinical training, or for other responsibilities associated with the fellow's position at the institution. In each case, the fellow must submit a written request countersigned by the sponsor and an appropriate institutional business official that includes documentation supporting the need for part-time training. The written request also must include an estimate of the expected duration of the period of part-time training, an assurance that the fellow intends to return to full-time training when that becomes possible, and an assurance that the trainee intends to complete the proposed research training program. In no case will it be permissible for the fellow to be engaged in Ruth L. Kirschstein-NRSA supported research training for less than 50 percent effort. Individuals who must reduce their commitment to less than 50 percent effort must take a leave-of-absence from Ruth L. Kirschstein-NRSA fellowship support. The fellowship notice of award will be reissued and the stipend will be pro-rated during the period of any approved part-time training. Part-time training may affect the rate of accrual or repayment of the service obligation for postdoctoral fellows.

Certification Requirements

Individuals admitted to the United States as Permanent Residents must submit notarized evidence of legal admission prior to the award. A Payback Agreement Form (PHS 6031, Rev. 10/05) must accompany the Activation Notice for any award that occurs during the individual's initial 12 months of Ruth L. Kirschstein-NRSA postdoctoral support. When support ends, the fellow must submit a Termination Notice (PHS 416-7, Rev. 10/05) to the NIH. If the fellow has a payback obligation, he or she must notify the NIH of any change in address and submit Annual Payback Activities Certification Forms (PHS 6031-1, Rev. 10/05) until the payback service obligation is satisfied. Forms will be provided to awardees by the NIH awarding component. Forms may also be found on the NIH Website at <http://grants.nih.gov/grants/forms.htm>.

Inventions

Fellowships made primarily for educational purposes are exempted from the U.S. Public Health Service (PHS) invention requirements. F32/F33 awards will not contain any provision giving PHS rights to inventions made by the awardee.

Publication and Sharing of Research Results

NIH supports the practical application and sharing of outcomes of funded research. Therefore, fellows should make the results and accomplishments of their Ruth L. Kirschstein-NRSA fellowship activities available to the research community and to the public at large. The grantee organization

should assist fellows in these activities, including the further development of discoveries and inventions for furthering research and benefiting the public.

Fellows are encouraged to submit reports of their findings for publication to the journals of their choice. Responsibility for direction of the project should not be ascribed to the NIH. However, NIH support must be acknowledged by a footnote in language similar to the following: "This investigation was supported by National Institutes of Health under Ruth L. Kirschstein National Research Service Award (number)." In addition, Federal funding must be acknowledged as provided in "[Public Policy Requirements and Objectives-Availability of Information-Acknowledgment of Federal Funding](#)".

Copyrights

Except as otherwise provided in the terms and conditions of the award, the recipient is free to arrange for copyright without approval when publications, data, or other copyrightable works are developed in the course of work under a PHS grant-supported project or activity. Any such copyrighted or copyrightable works shall be subject to a royalty-free, nonexclusive, and irrevocable license to the Government to reproduce, publish, or otherwise use them, and to authorize others to do so for Federal government purposes.

3. Reporting

All forms were revised in October 2005 for immediate use, see NIH Notices: [NOT-OD-06-017](#) and [NOT-OD-06-018](#) which were released on December 9, 2005, for additional details. As indicated in NIH Notice [NOT-OD-07-002](#), which was released on October 5, 2006, revised instructions and Form pages have been posted on the NIH Forms Page at
<http://grants.nih.gov/grants/funding/416/phs416.htm>.

Activation Notice

An awardee has up to 6 months from the issue date on the Notice of Research Fellowship Award to activate the award using the Ruth L. Kirschstein National Research Service Award Individual Fellowship Activation Notice (PHS 416-5, Rev. 10/05) available at <http://grants.nih.gov/grants/forms.htm>. Under unusual circumstances, an NIH Institute may grant an extension of the activation period upon receipt of a specific request from the fellow. Such a request must be countersigned by the Sponsor and an authorized institutional official.

Payback Agreement

A Payback Agreement Form (PHS 6031, Rev. 10/05) must accompany the Activation Notice for any award that occurs during the individual's initial 12 months of Kirschstein-NRSA postdoctoral support.

Application for Continued Support

An awardee will be required to submit the form PHS 416-9, Rev. 10/05, Continuation of an Individual National Research Service Award, annually (<http://grants.nih.gov/grants/funding/416-9/phs416-9.htm>) as required in the NIH Grants Policy Statement. The report is due 2 months before the beginning date of the next budget period and must include information related to the current year's progress as well as the plans for the coming year. Note that the instructions request that a listing of all courses and publications completed during the past year be included in the application for continued support.

Termination Notice

When support ends, the fellow must submit a Termination Notice (PHS 416-7, Rev. 10/05) to the NIH within 30 days following termination. If the fellow has a payback obligation, he or she must notify the NIH of any change in address and submit Annual Payback Activities Certification Forms (PHS 6031-1, Rev. 10/05) until the payback service obligation is satisfied. Forms may be found at <http://grants.nih.gov/grants/forms.htm>.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific/Research Contacts:

Jerry S.H. Lee, Ph.D.
Nanotechnology Project Manager, NCI Alliance for Nanotechnology in Cancer
Email: leejerry@mail.nih.gov

or

Piotr Grodzinski, Ph.D.
Program Director, NCI Alliance for Nanotechnology in Cancer
Email: grodzinp@mail.nih.gov

Office of Technology and Industrial Relations
Office of the Director
National Cancer Institute
Building 31, Room 10A-52, MSC 2580
31 Center Drive
Bethesda, MD 20892-2580 (for U.S. Postal Service express or regular mail)
Telephone: (301) 496-1550
FAX: (301) 496-7807

2. Peer Review Contacts:

Referral Officer
Division of Extramural Activities
National Cancer Institute
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329 (for U.S. Postal Service express or regular mail)
Rockville, MD 20852 (for non-USPS delivery)
Telephone: (301) 496-3428
FAX: (301) 402-0275
E-mail: nciref@dea.nci.nih.gov

3. Financial or Grants Management Contacts:

Dena Solomon
Grants Management Specialist
Office of Grants Administration
National Cancer Institute
6120 Executive Boulevard, EPS Room 243, MSC 7150
Bethesda, MD 20892-7150 (for U.S. Postal Service express or regular mail)
Rockville, MD 20852 (for non-USPS delivery)
Telephone: (301) 496-7208
FAX: (301) 496-8601
E-mail: solomond@gab.nci.nih.gov

Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:

Recipients of PHS support for activities involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals

(<http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf>) as mandated by the Health Research Extension Act of 1985 (<http://grants.nih.gov/grants/olaw/references/hrea1985.htm>), and the USDA Animal Welfare Regulations (<http://www.nal.usda.gov/awic/legislat/usdaleg1.htm>) as applicable.

Human Subjects Protection:

Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained

(<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>).

Data and Safety Monitoring Plan:

Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity and dose-finding studies (phase I); efficacy studies (Phase II); and efficacy, effectiveness, and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>).

Sharing Research Data:

Investigators submitting an NIH application seeking \$500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible

(http://grants.nih.gov/grants/policy/data_sharing).

Investigators should seek guidance from their institutions, on issues related to institutional policies and local institutional review board (IRB) rules, as well as local, State, and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Access to Research Data through the Freedom of Information Act:

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are: (1) first produced in a project that is supported in whole or in part with Federal funds; and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this funding opportunity in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Sharing of Model Organisms:

NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time, the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh-Dole Act (see the NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal, beginning with the October 1, 2004, receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Inclusion of Women And Minorities in Clinical Research:

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research" (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The

amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:

The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects (<http://grants.nih.gov/grants/funding/children/children.htm>).

Required Education on the Protection of Human Subject Participants:

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

Human Embryonic Stem Cells (hESC):

Criteria for federal funding of research on hESCs can be found at <http://stemcells.nih.gov/index.asp> and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (<http://escr.nih.gov>). It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

NIH Public Access Policy:

NIH-funded investigators are requested to submit to the NIH manuscript submission (NIHMS) system (<http://www.nihms.nih.gov>) at PubMed Central (PMC) an electronic version of the author's final manuscript upon acceptance for publication, resulting from research supported in whole or in part with direct costs from NIH. The author's final manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process.

NIH is requesting that authors submit manuscripts resulting from: 1) currently funded NIH research projects; or 2) previously supported NIH research projects if they are accepted for publication on or after May 2, 2005. The NIH Public Access Policy applies to all research grant and career development award mechanisms, cooperative agreements, contracts, Institutional and Individual Ruth L. Kirschstein National Research Service Awards, as well as NIH intramural research studies. The Policy applies to peer-reviewed, original research publications that have been supported in whole or in part with direct costs from NIH, but it does not apply to book chapters, editorials, reviews, or conference proceedings. Publications resulting from non-NIH-supported research projects should not be submitted.

For more information about the Policy or the submission process, please visit the NIH Public Access Policy Web site at <http://publicaccess.nih.gov> and view the Policy or other Resources and Tools including the Authors' Manual (http://publicaccess.nih.gov/publicaccess_Manual.htm).

Standards for Privacy of Individually Identifiable Health Information:

The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information," the "Privacy Rule," on August 14, 2002. The Privacy Rule is a Federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (<http://www.hhs.gov/ocr/>) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>.

URLs in NIH Grant Applications or Appendices:

All applications and proposals for NIH funding must be self-contained within specified page limitations. For publications listed in the appendix and/or Progress report, internet addresses (URLs) **must** be used for **publicly** accessible on-line journal articles. Unless otherwise specified in

this solicitation, Internet addresses (URLs) should **not** be used to provide any **other** information necessary for the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople>.

Authority and Regulations:

This program is described in the Catalog of Federal Domestic Assistance at <http://www.cfda.gov/> and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 487 of the Public Health Service Act as amended (42 USC 288) and under Federal Regulations 42 CFR 66. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Loan Repayment Programs:

NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The LRP is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50% of their time (at least 20 hours per week based on a 40 hour week) for 2 years to the research. For further information, please see <http://www.lrp.nih.gov>.

[Weekly TOC for this Announcement](#)

[NIH Funding Opportunities and Notices](#)



Office of
Extramural
Research
(OER)



National
Institutes of
Health (NIH)
9000 Rockville
Pike
Bethesda,
Maryland
20892



Department of
Health
and Human
Services (HHS)



Note: For help accessing PDF, RTF, MS Word, Excel, PowerPoint, RealPlayer, Video or Flash files, see
[Help Downloading Files.](#)