

At the Intersection of Nanotechnology and Bio- Pharma Convergence: What is a "Drug"- New Definitions, New Modalities?



U.S. Food and Drug Administration



Department
of
Health and
Human Services

August 2004

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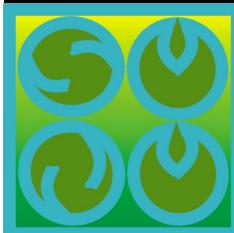
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<http://www.nanosig.org/nanoelectronics.htm>

<http://www.technofutures.com/charles1.htm>



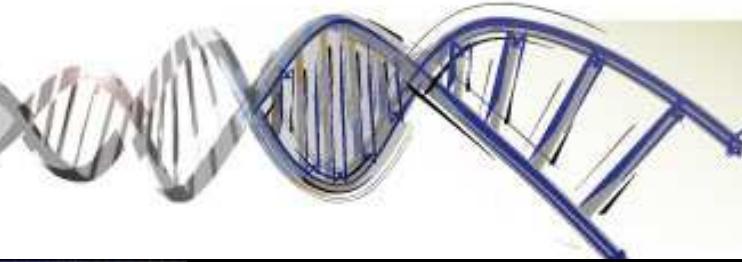
SILICON VALLEY
NANO VENTURES



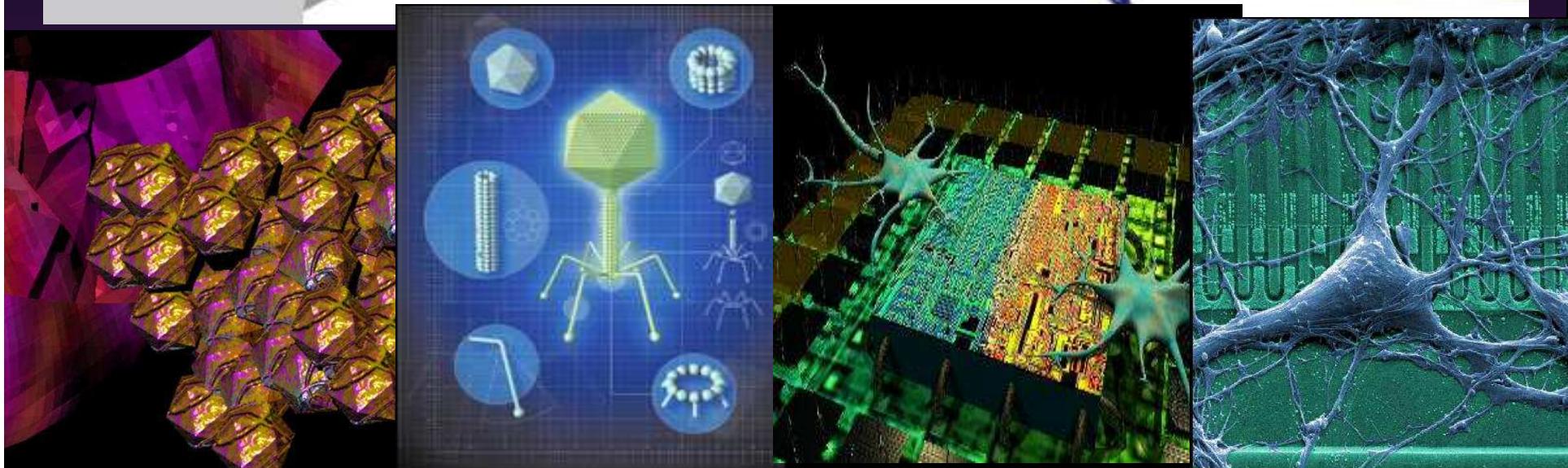
Nano Electronics
& Photonics Forum

INSTITUTE FOR
GLOBAL
FUTURES.

Synthetic Biology



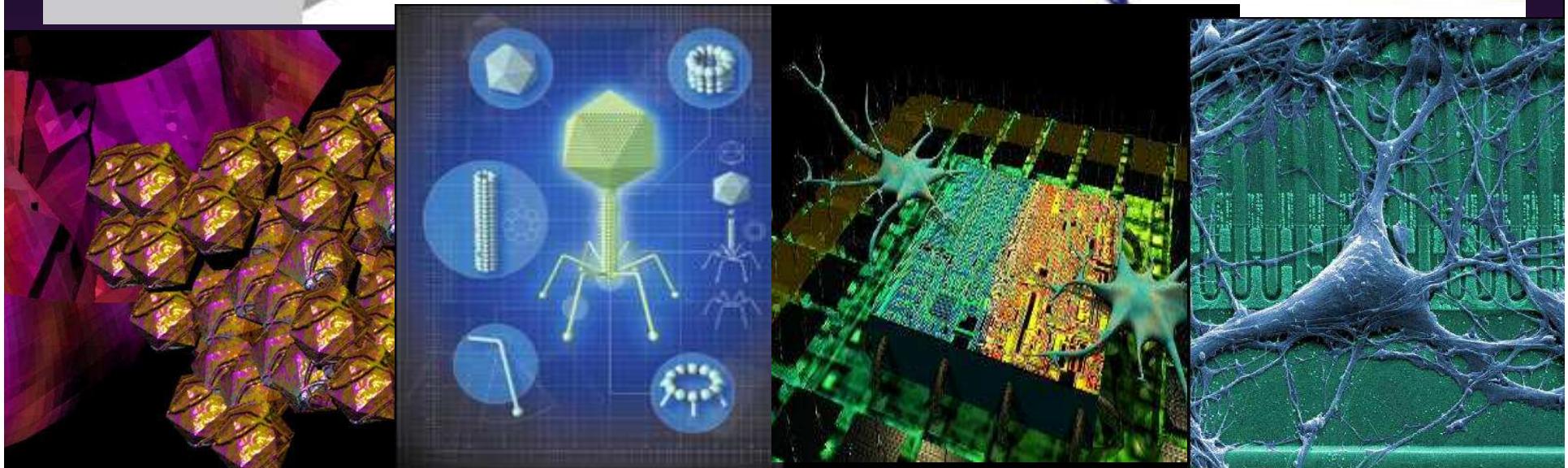
PHYSICAL
BIOSCIENCES
DIVISION



Define Nanotechnology - the precise patterning of matter at
the molecular scale of interaction

Synthetic Biology

PHYSICAL
BIOSCIENCES
DIVISION

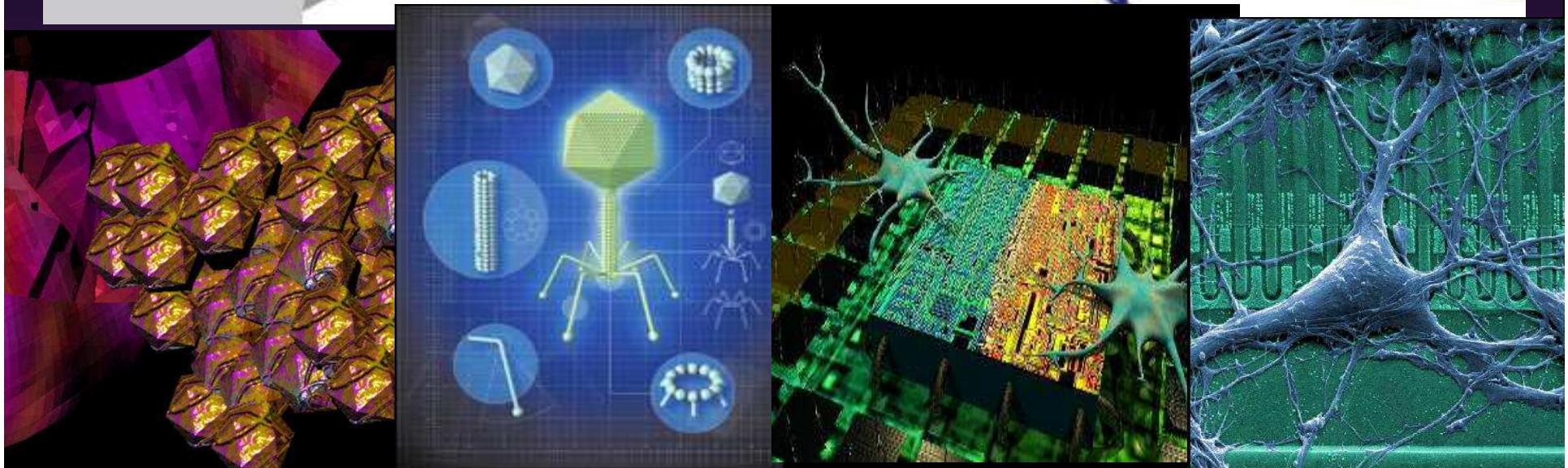


Define Nanotechnology - the precise patterning of matter at the molecular scale of interaction

Define Drug - substance used to cure, alleviate, diagnose, or prevent disease

Synthetic Biology

PHYSICAL
BIOSCIENCES
DIVISION



Define Nanotechnology - the precise patterning of matter at the molecular scale of interaction

Define Drug - Device used to cure, alleviate, diagnose, or prevent disease

Post-Genomic
Society

Nanotechnology

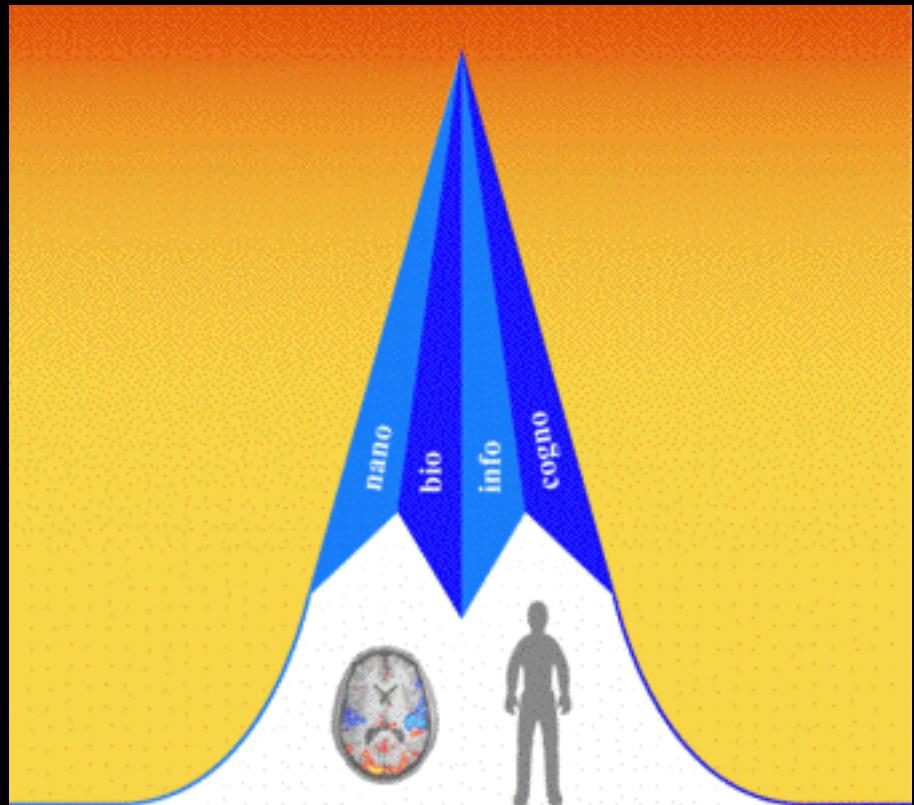
Health Care Future Map

Smart IT

Performance
Enhancement

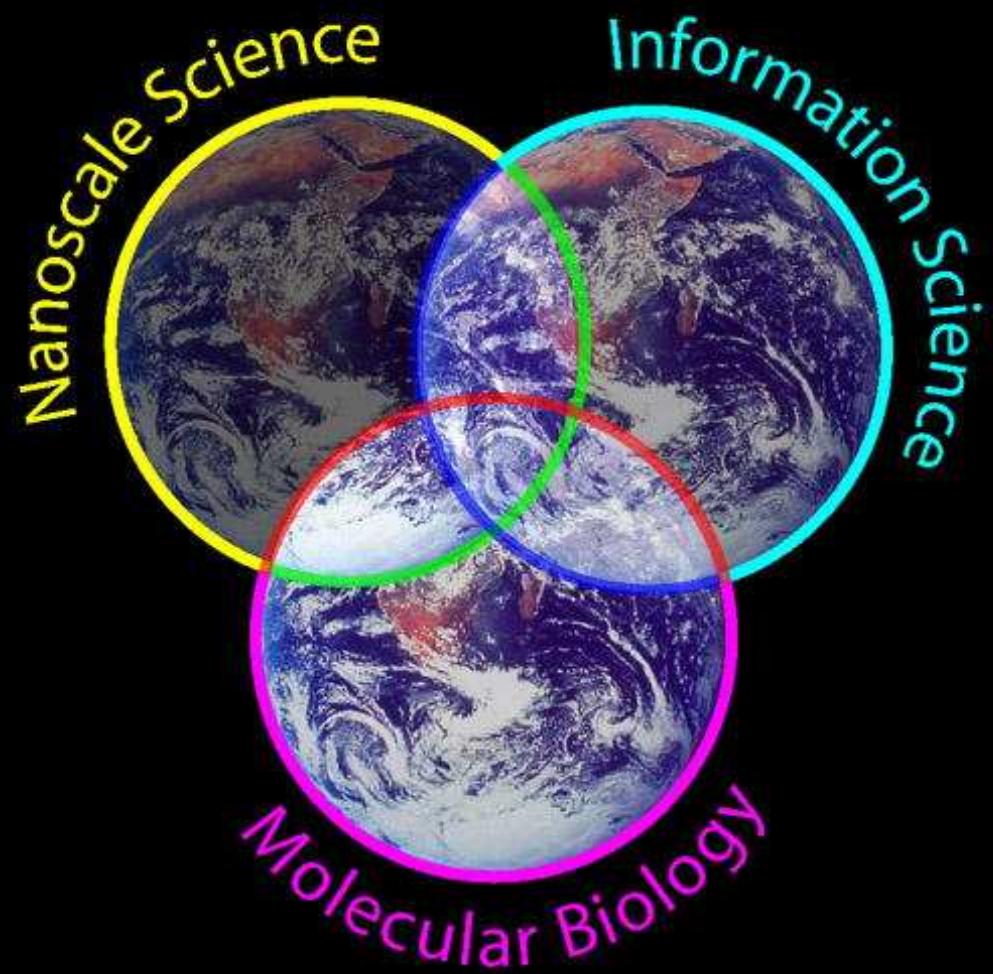
The Emergent Infotech / Biotech / Nanotech / Cognotech Operational Ecology

NBIC Conference
Converging Technologies
for Improving Human
Performance:
Nanotechnology,
Biotechnology, Information
Technology and Cognitive
Science
NSF/DOC-sponsored report
<http://www.wtec.org/ConvergingTechnologies>

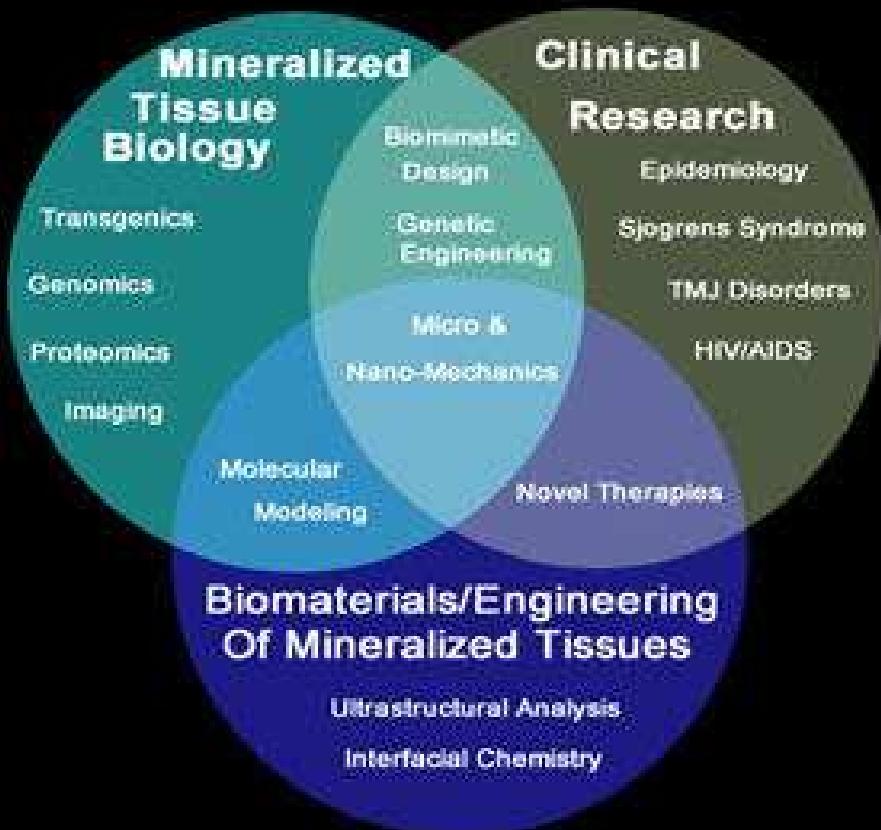


The Infotech / Biotech / Nanotech Convergence

NNI - National Nanotechnology Initiative

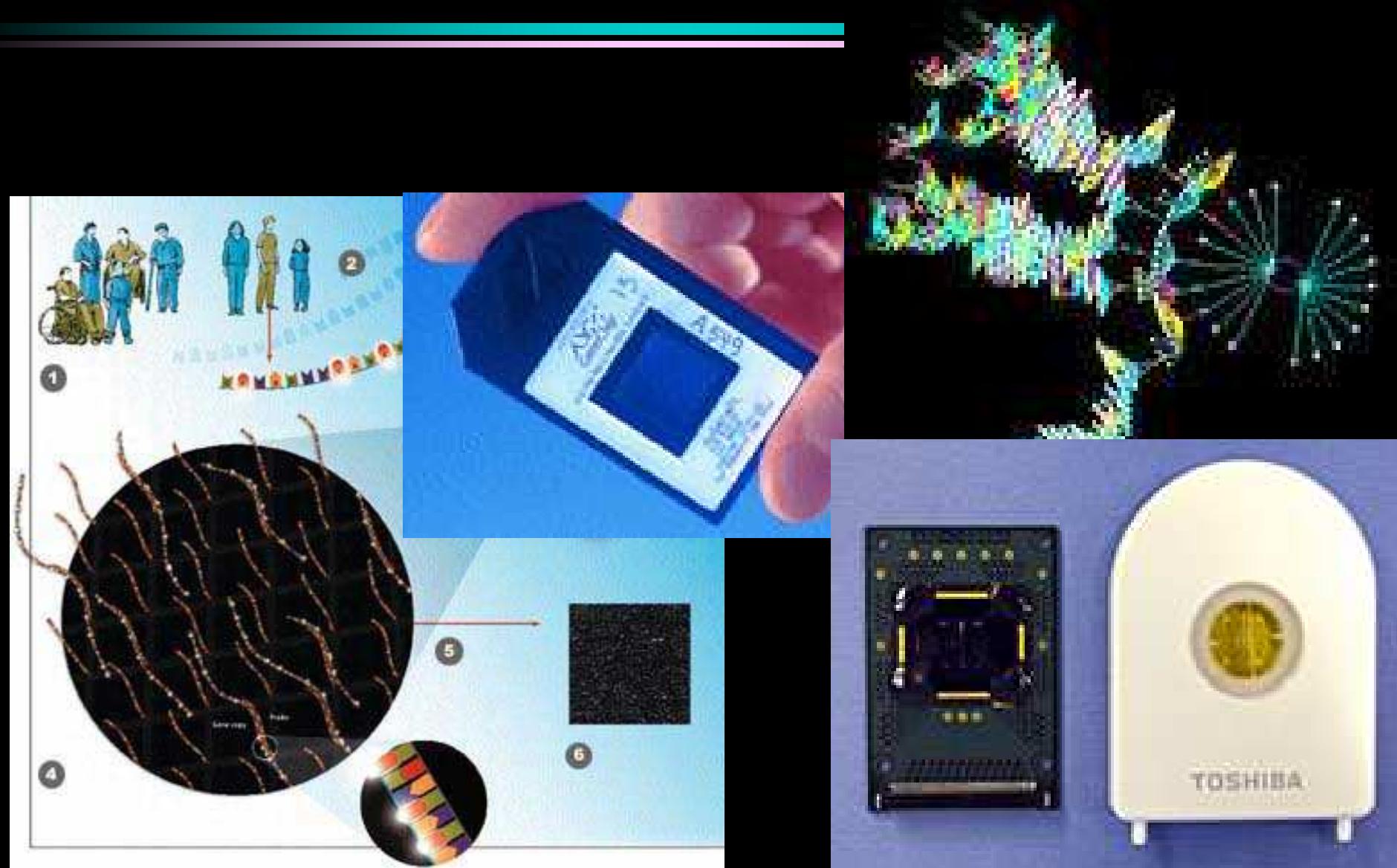


The Infotech / Biotech / Nanotech Convergence Synthetic Biology Manifestation



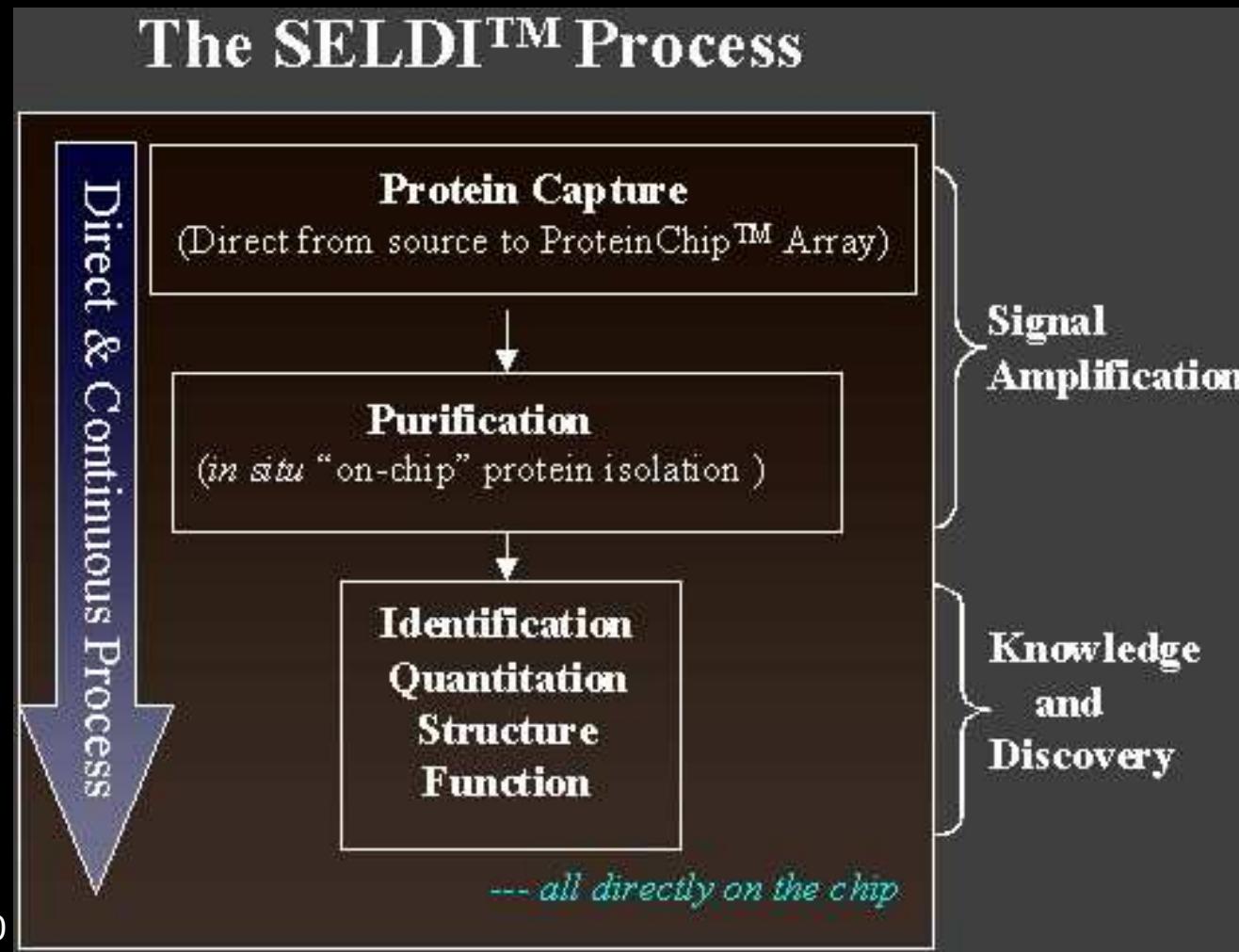
Nanotech / Biotech / Infotech Convergence

Diagnostic > Therapeutic Pipeline

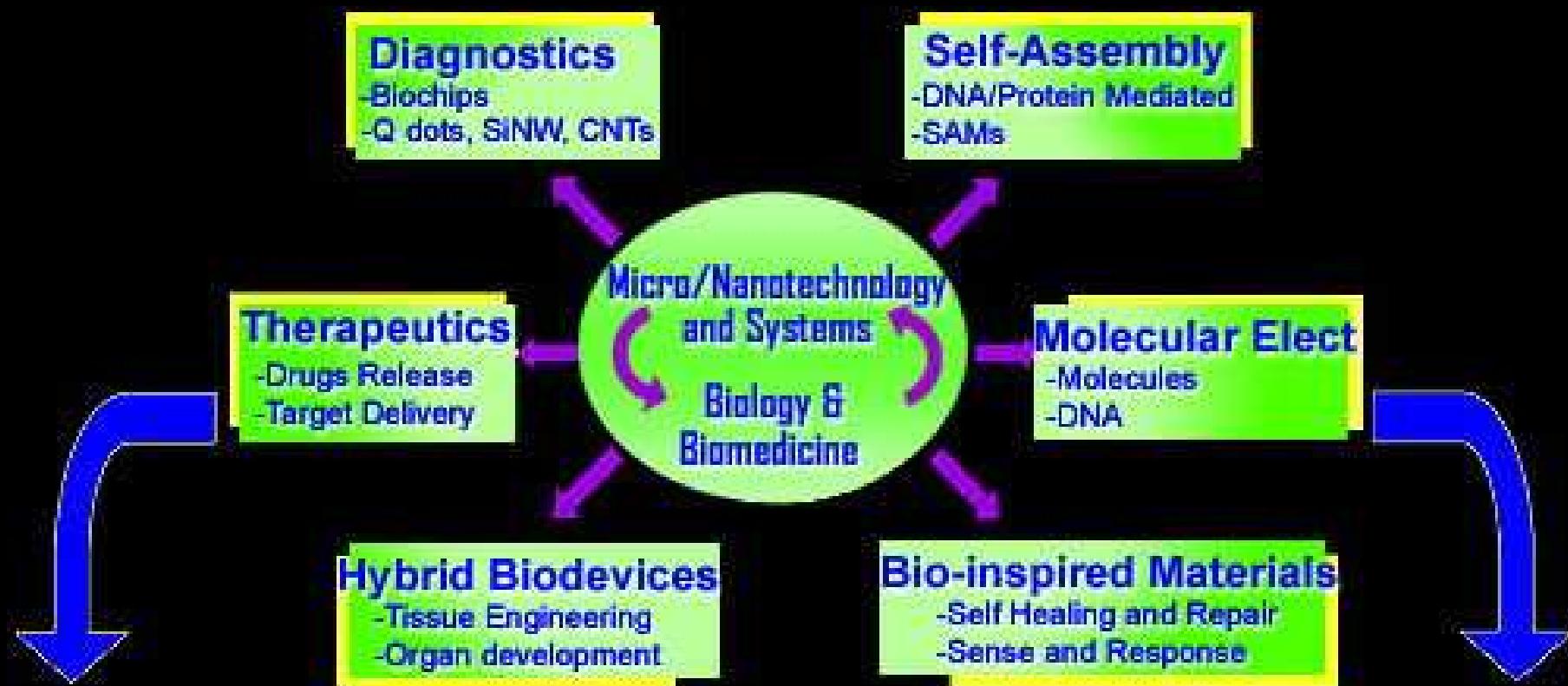


Nanotech / Biotech / Infotech Convergence

Diagnostic > Therapeutic Pipeline

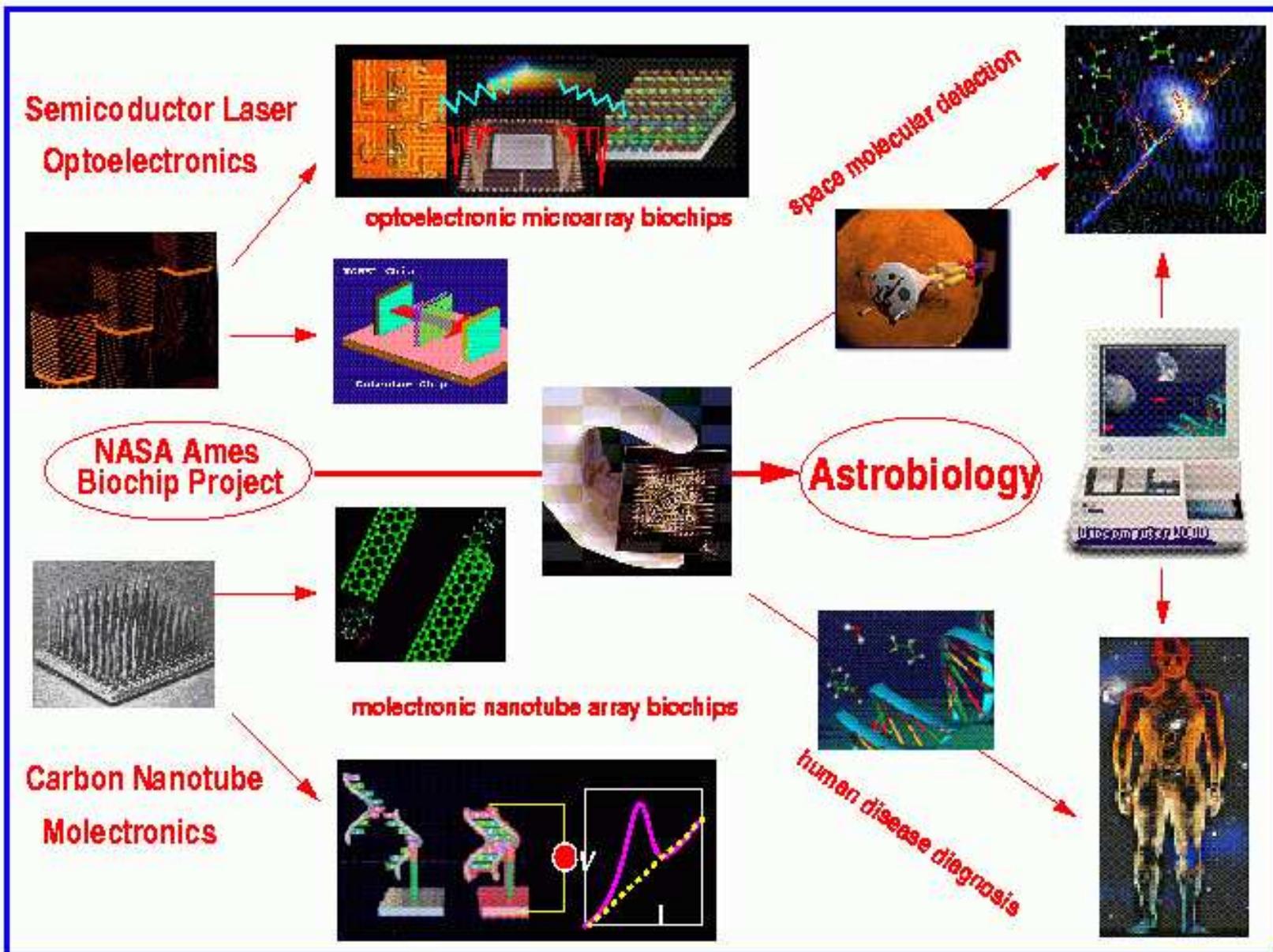


The Infotech / Biotech / Nanotech Convergence Nanopharmaceuticals



Novel Solutions for Frontiers in
Medicine and Biology

Novel Solutions for Frontiers in
Materials and Information
Processing



Han et al. NASA Ames Research Center, Oct. 1998

Nanomedicine - Intersection of Material Science and Medically Relevant Chemistry

- Precise targeting and penetration of intra-cellular subsystems, membranes, organelles
- Sustained dynamic physiological interaction
- Broad spectrum of potential design strategies for tightly coupled diagnostics, monitoring, and therapeutic deployment
- Nanostructured materials derived platforms > nanodevices > bio-functional deliverables

Nanotechnology Enabled Process Development Trajectories

- Enhance “Friendliness” to Novel Materials in “Traditional” Micro-litho Fab Facilities
- Integrated Biological and Non-Biological NanoStructures
- Supra-molecular Synthesis
- Integrated / Inter-related Techniques for Patterning Matter
- Chemical Handles for Attachment to Surfaces
- Utilizing Biology as a Foundry

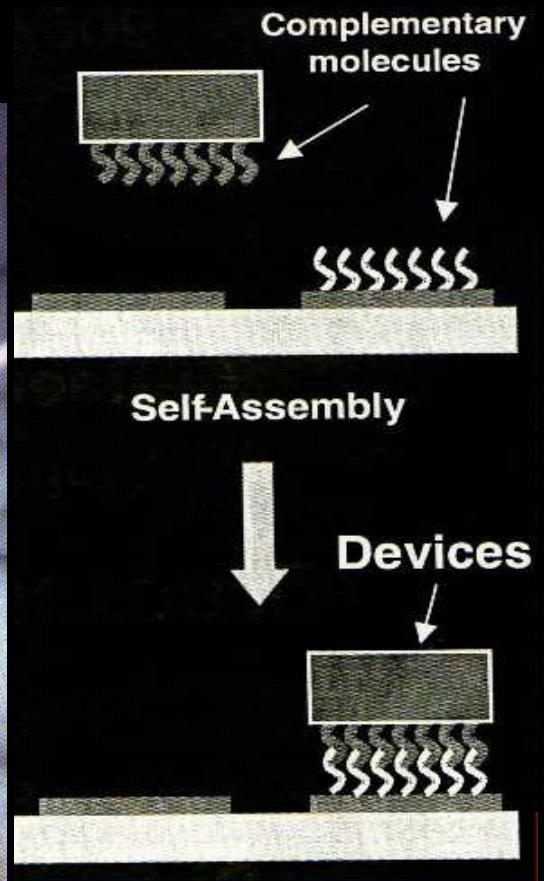
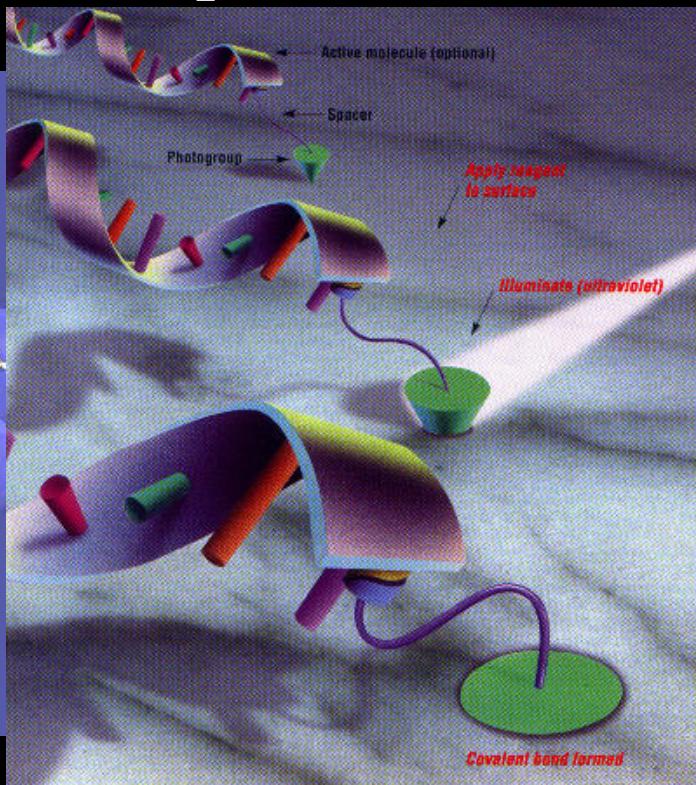
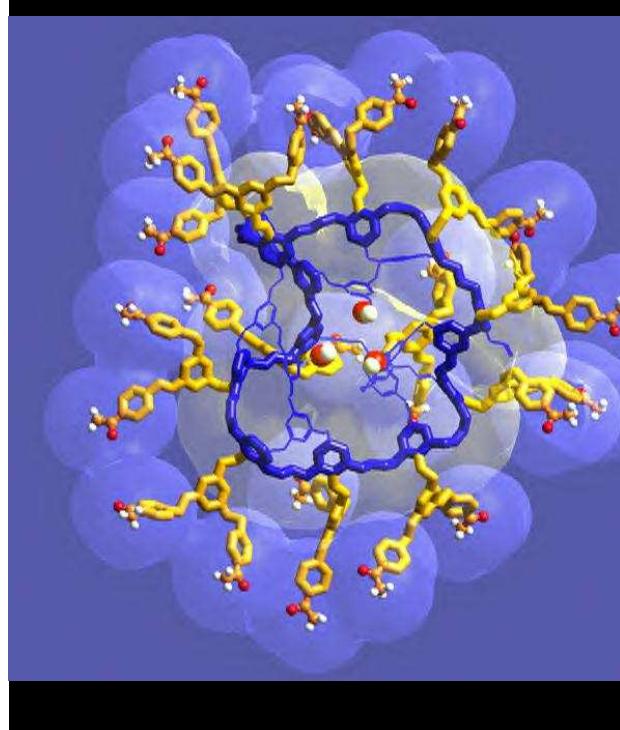


Key Nano-Industrial Infrastructure Development Indicators

- Diverse Methods for Patterning Matter
- Conjunction of Hard and Soft Matter
- Implementation of “Bioconjugates” as an Assembly System
- Whitney’s Interchangable Parts Paradigm Applied to Materials / Integrated Device Creation
- Merging of Materials, Devices, Circuits

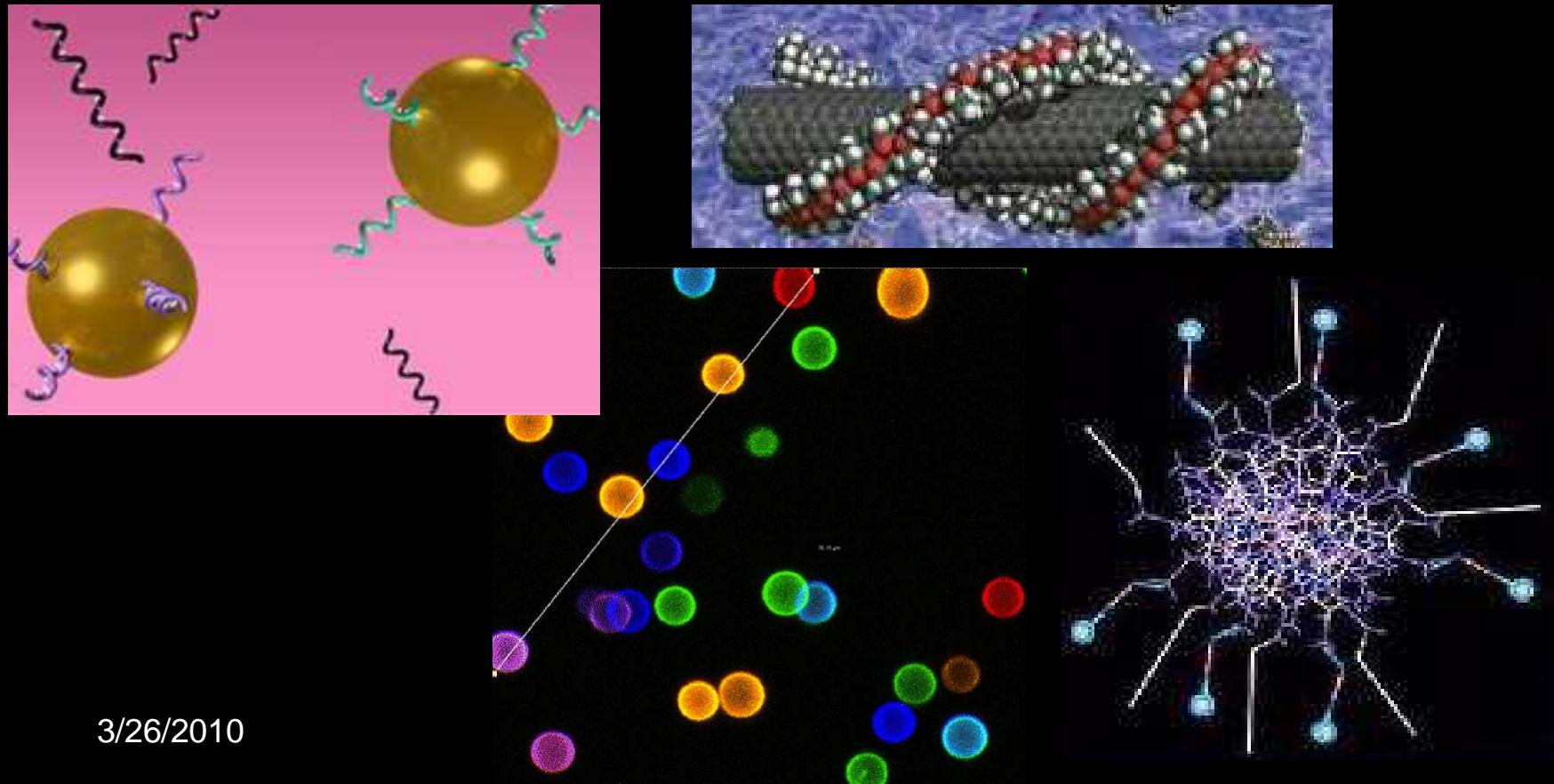
The goal is process integration

- Self Assembly / Self Organization
- Biolithography / “Soft” lithography
- Supra molecular manipulation



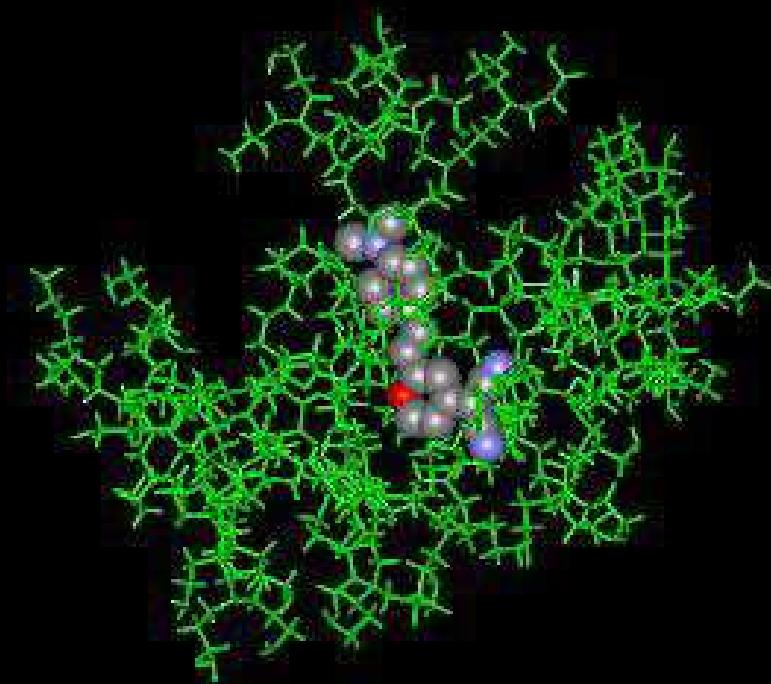
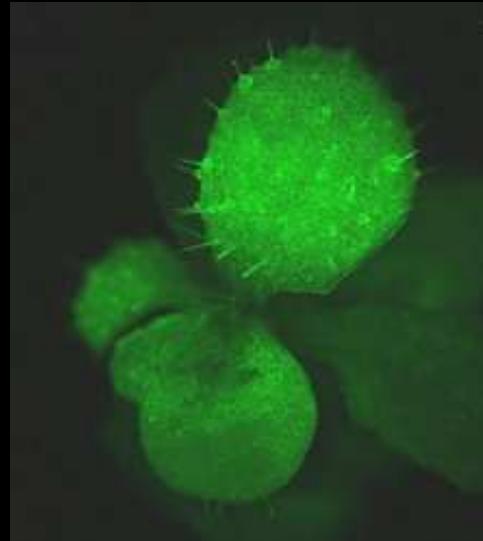
Complimentary Chemistries in Molecular Components

- Integration of organic and in-organic dopants with carbon nanotubes, dendrimers, various molecular structures



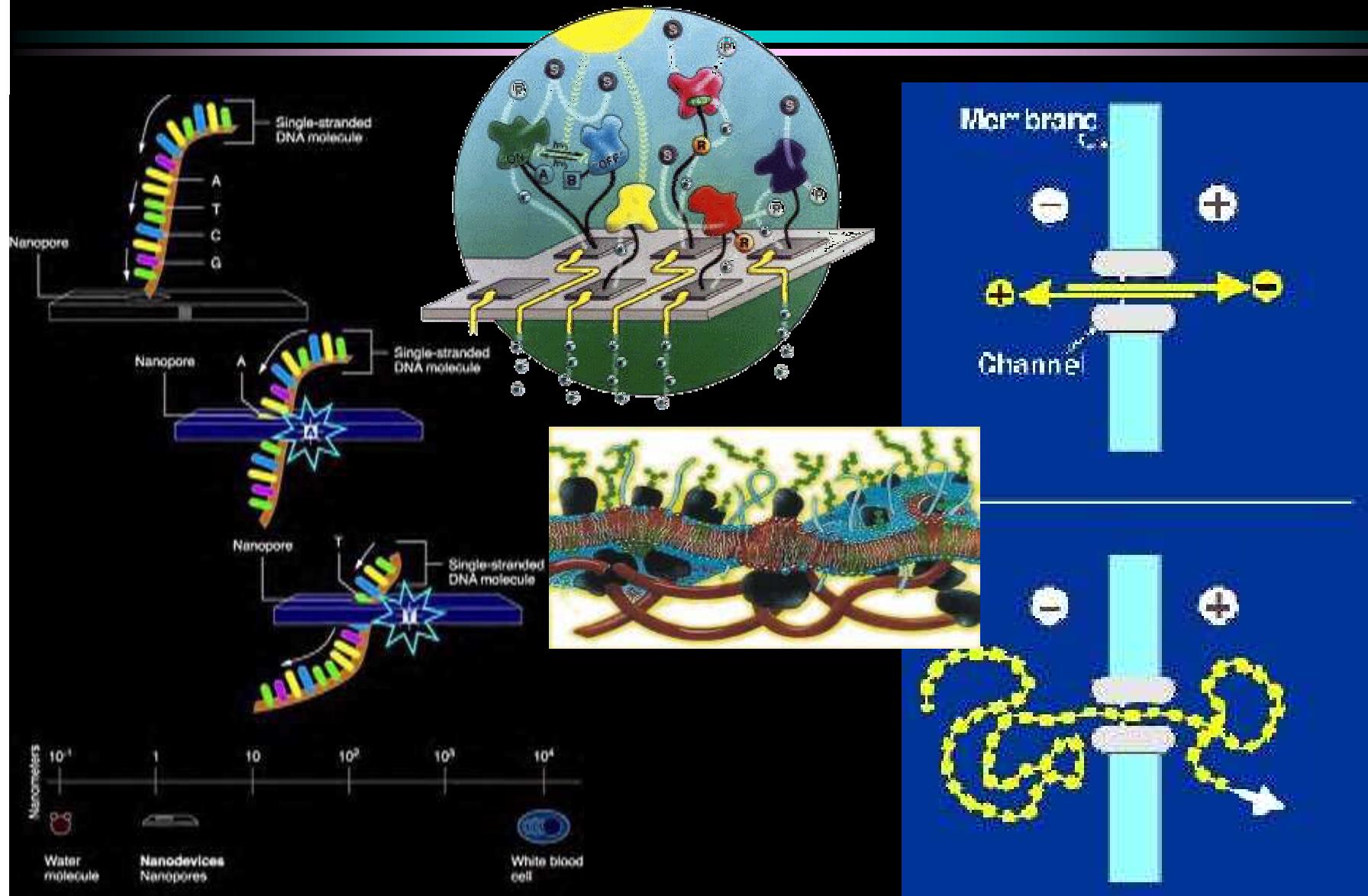
NanoDevice Platform Deliverables - Molecular Components

- Precision targeting > selective functionalities
- Prophylactic > Pathogen Inhibitor
- Synthetic systems / architectures > organelles, cells
- Enhancement
- Regulation
- Monitoring

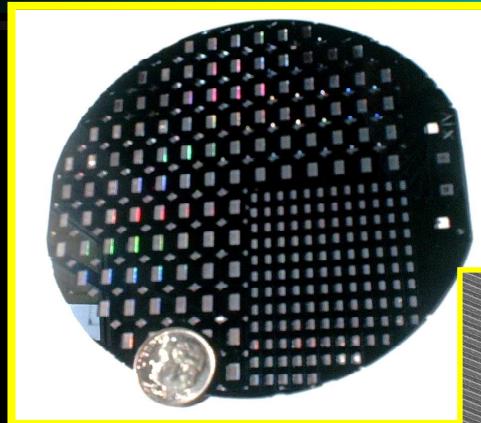


Programmable Nanoporous Materials

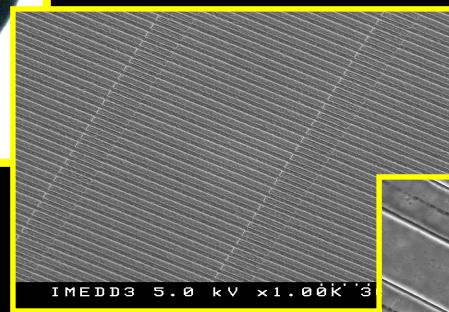
Selective / “Smart” Membranes



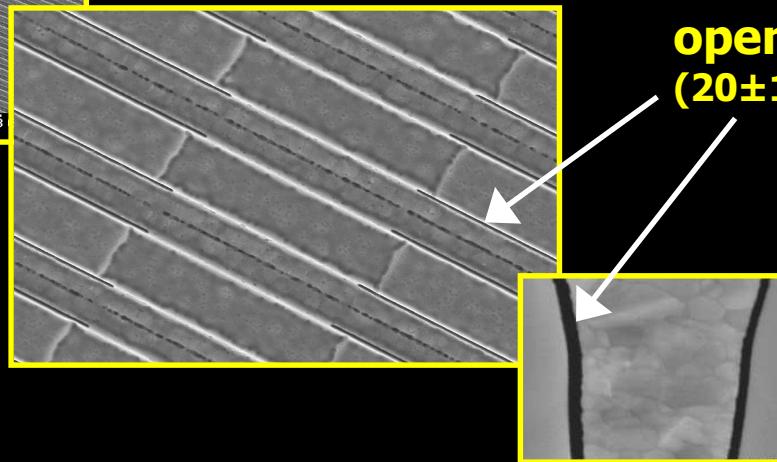
NanoGATE Membrane



4 inch wafer



Close-ups of
Membrane area

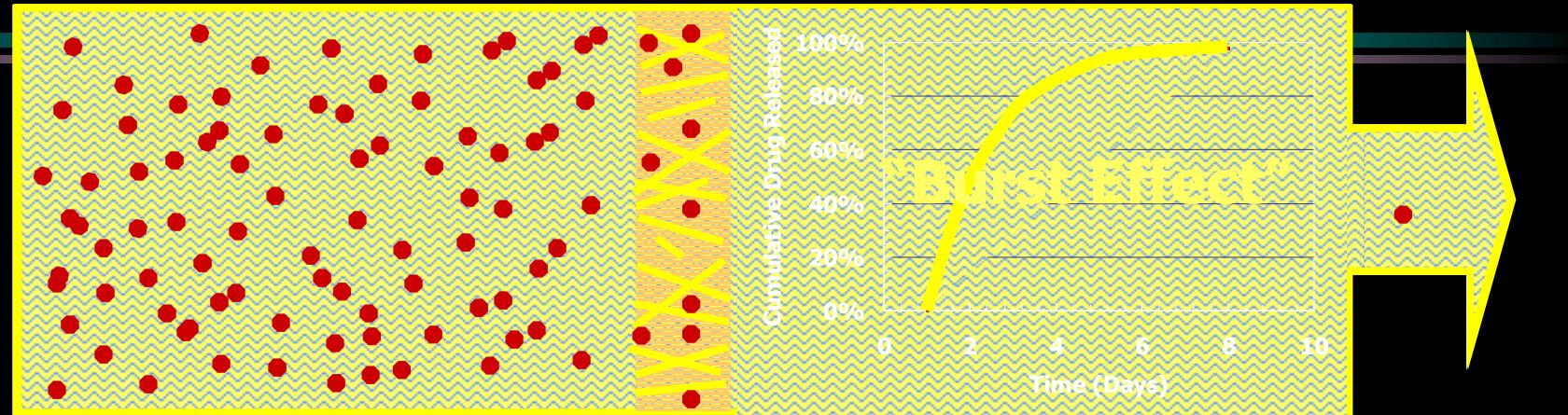


NanoGATE
openings
(20 ± 1 nm)

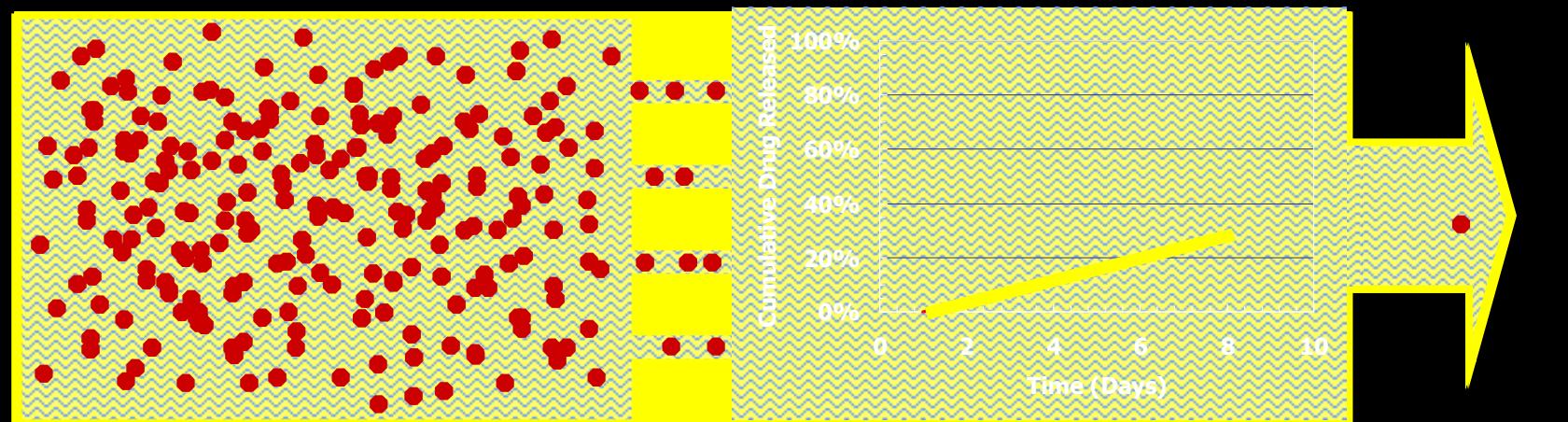
Cross-section of
Membrane

NanoGATE = Molecular Gating

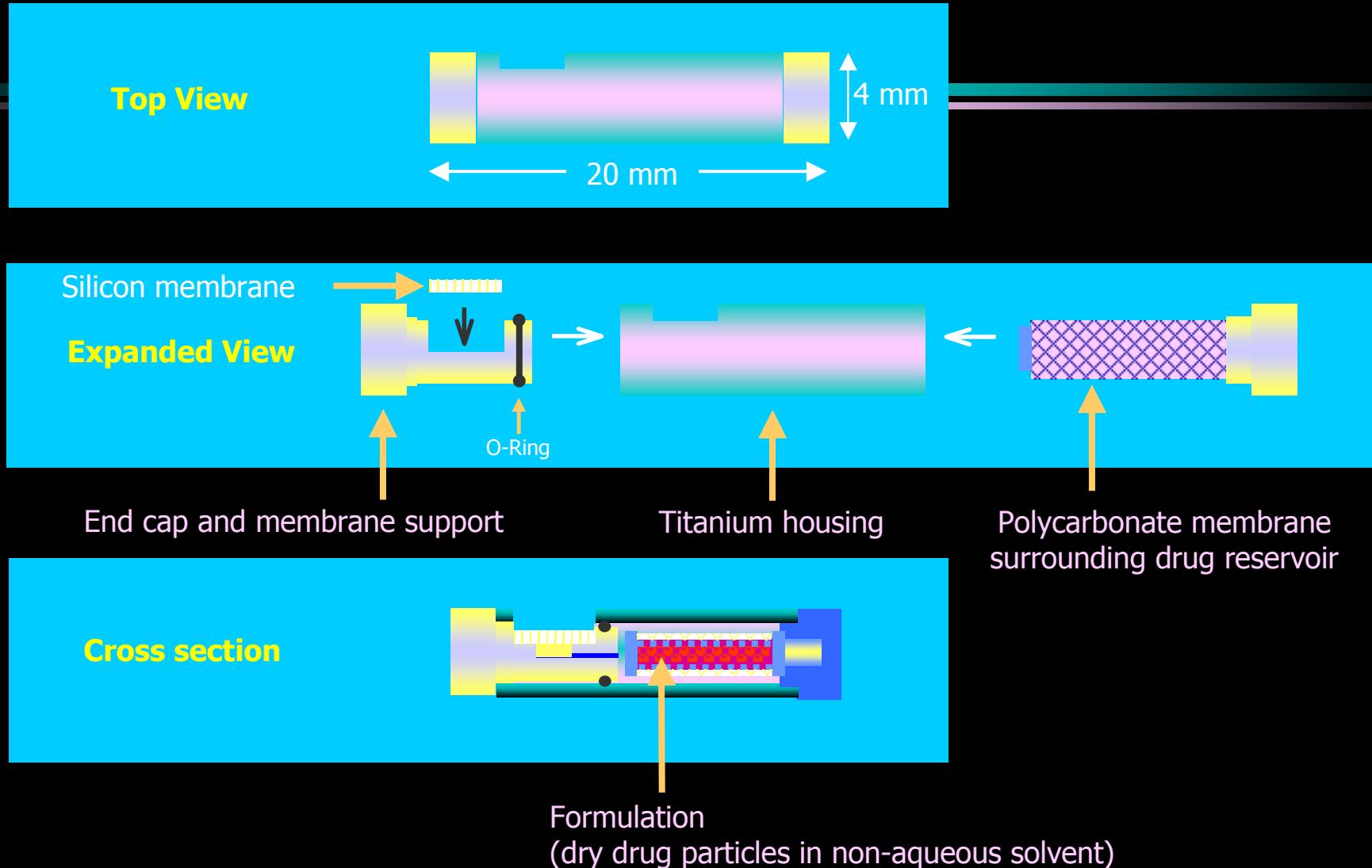
Diffusion of Drug through conventional membrane (Fickian release rate)



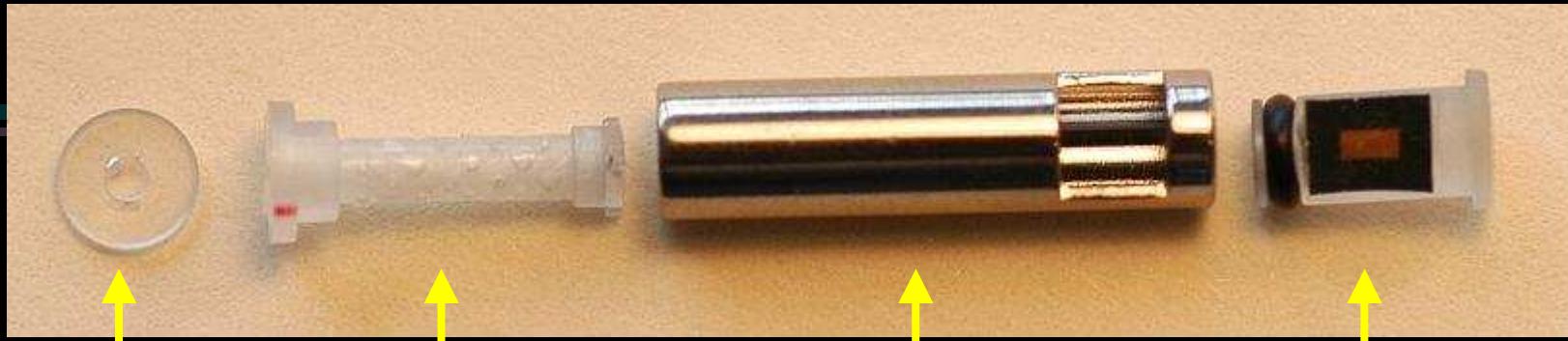
Diffusion of Drug through NanoPORE membrane (Zero-order release rate)



NanoGATE Prototype



NanoGATE Prototype



End
cap

Non-aqueous
reservoir

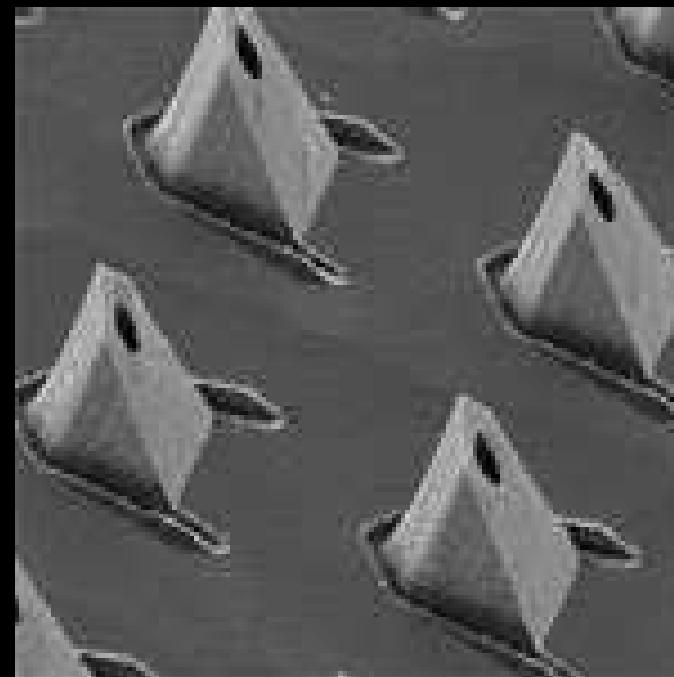
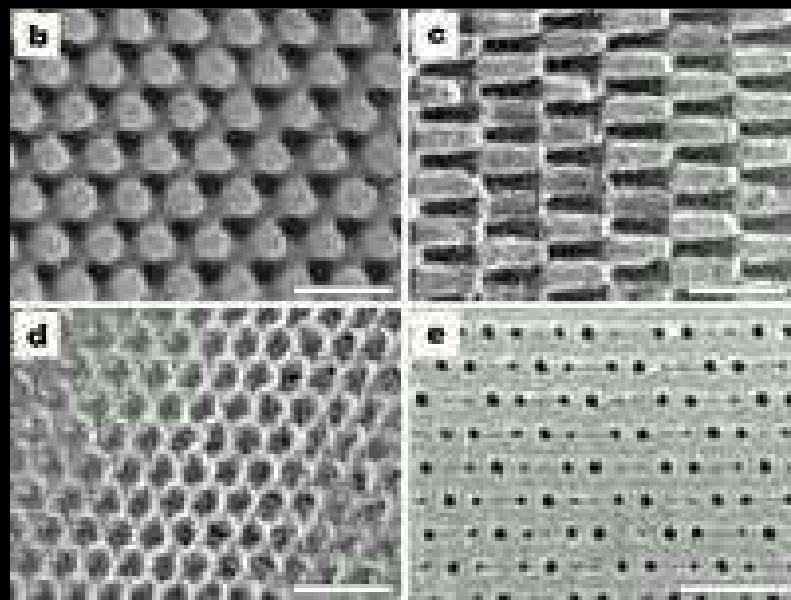
Titanium
housing

Silicon
membrane
with support



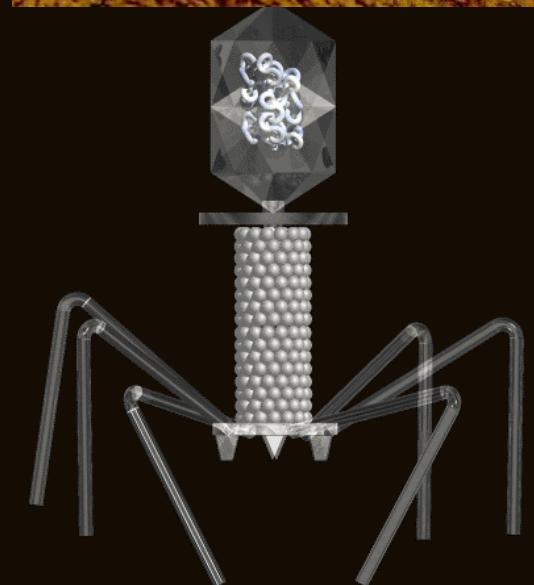
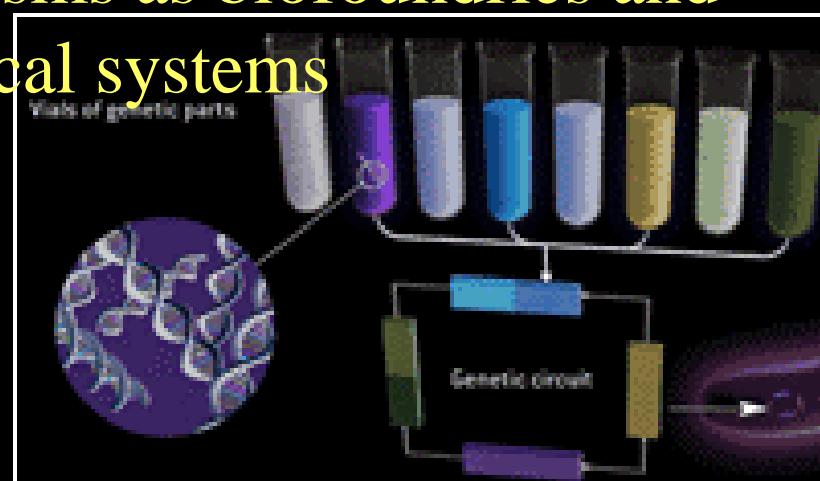
3/26/2010

Drug Delivery via micro / nano structured mechanisms

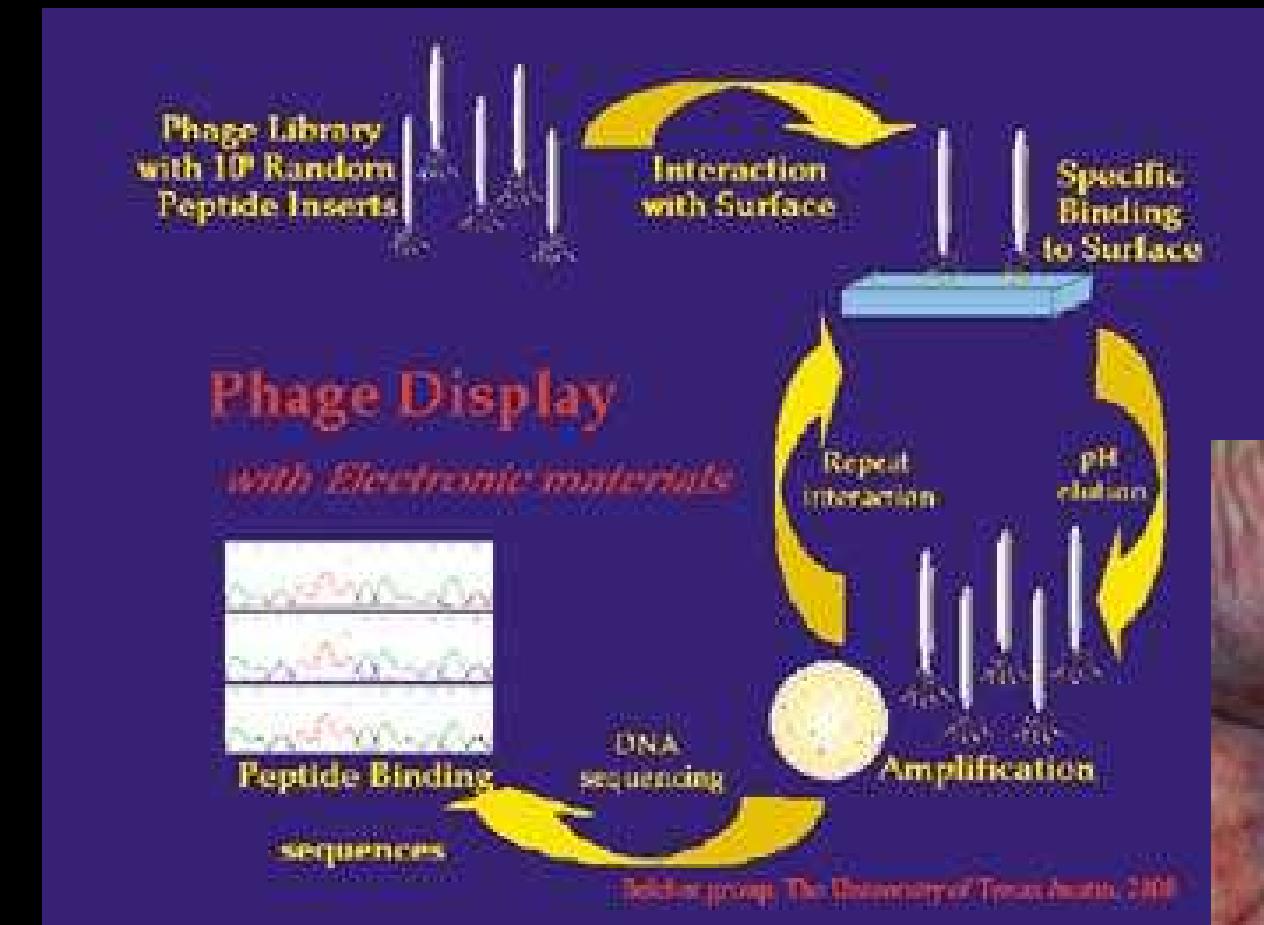


Examples of Nanofabrication Enabled by Self Assembly and Biologically Inspired Processes

- Self organizing / assembling nanostructures
- Integrated 2D and 3D structures
- Genetic “magnification” of desired attributes and affinities in biologically derived materials
- Living organisms as biofoundries and nanomechanical systems

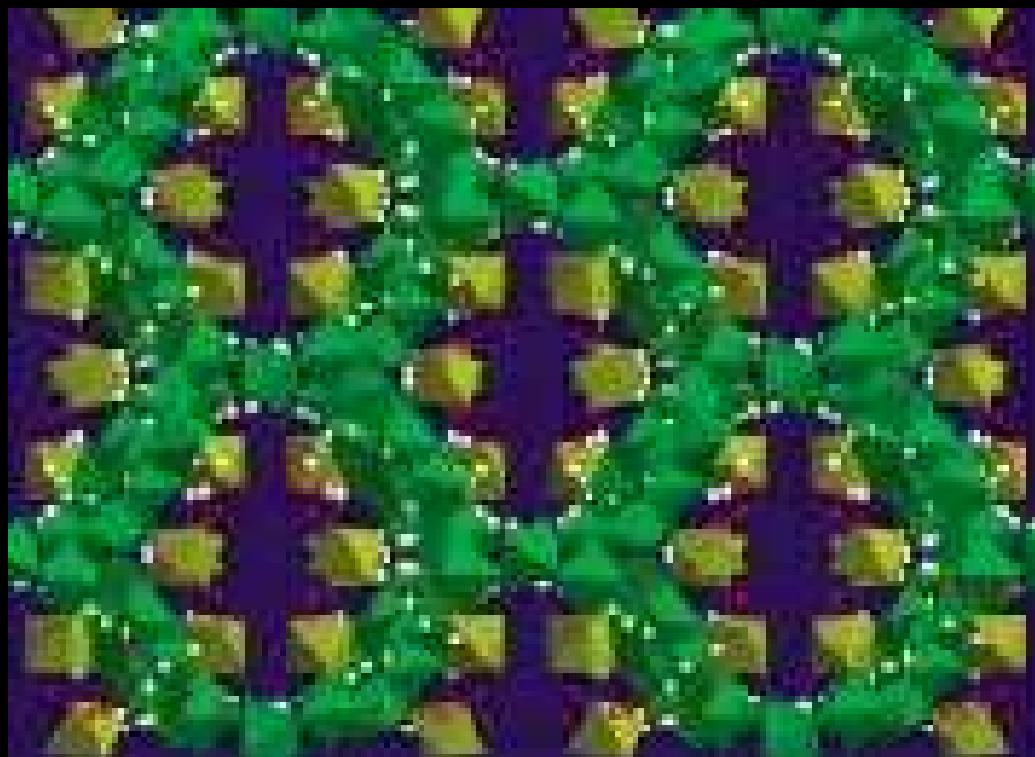


Define Foundry Living Systems as BioFoundries

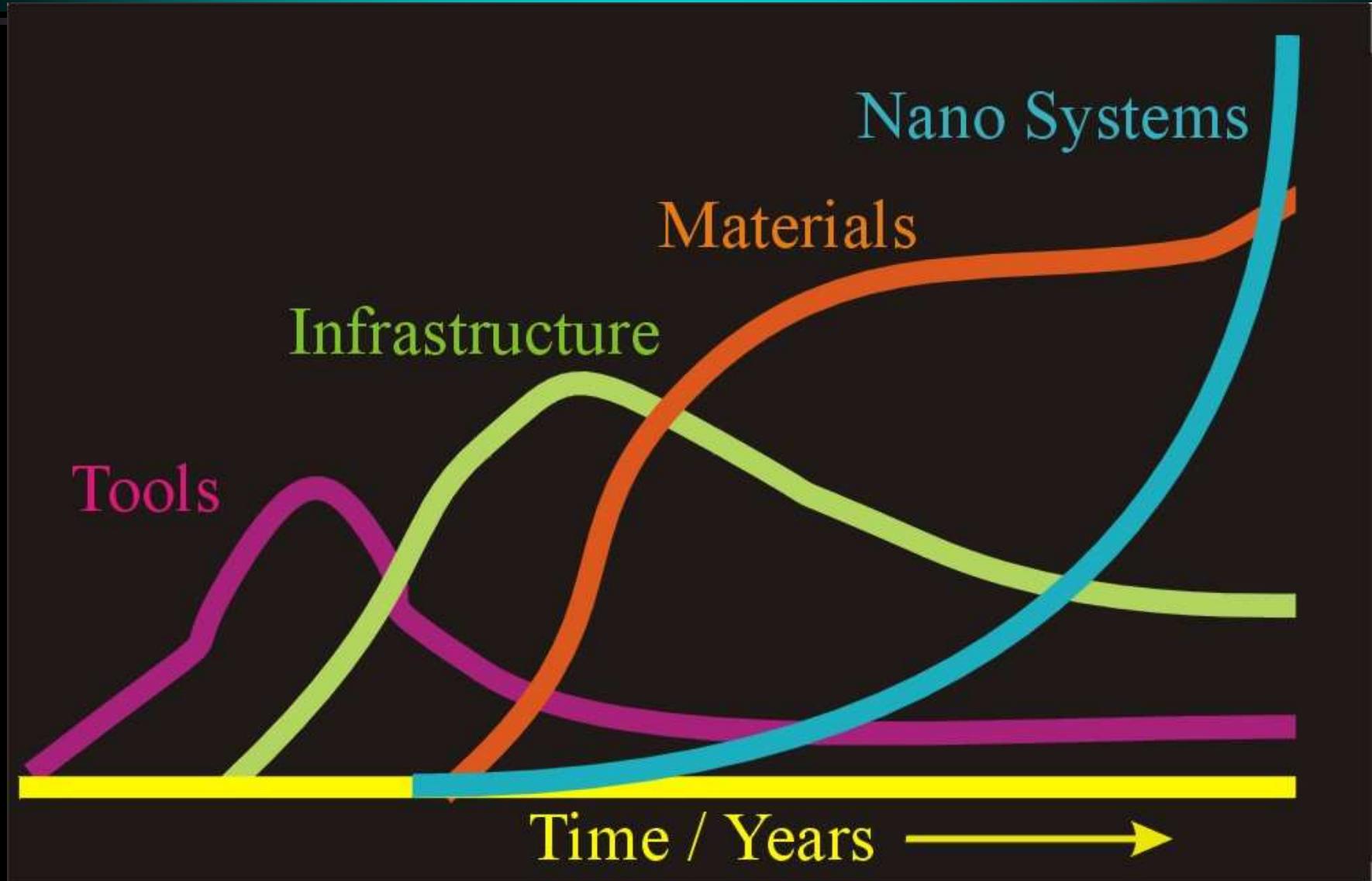


Define Foundry Living Systems as BioFoundries

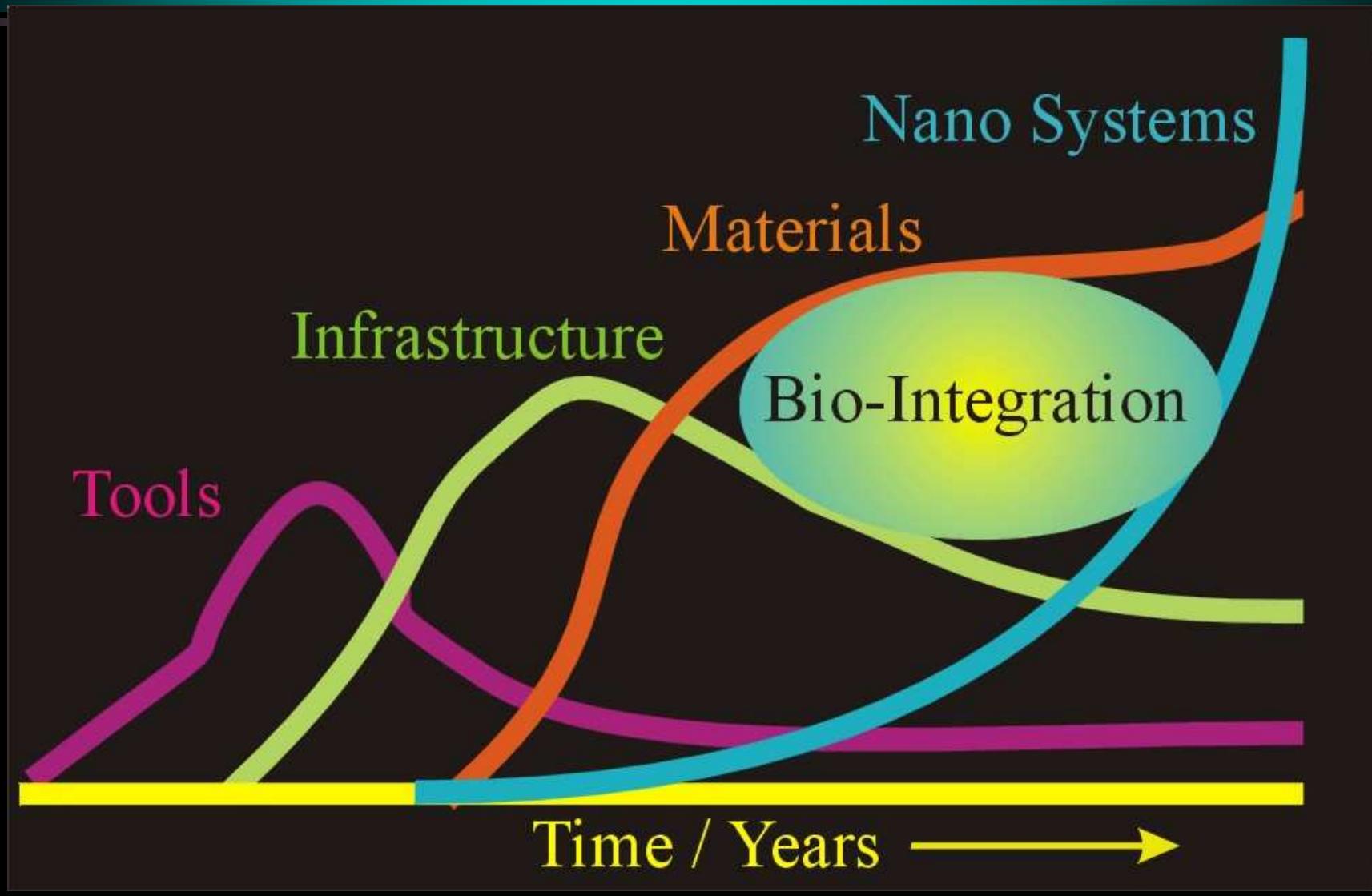
Exotic Materials
Constructs from
hybrid combinatory
bio-conjugates and
inorganic nano-
structures



The Nano-Industrial Development Stream

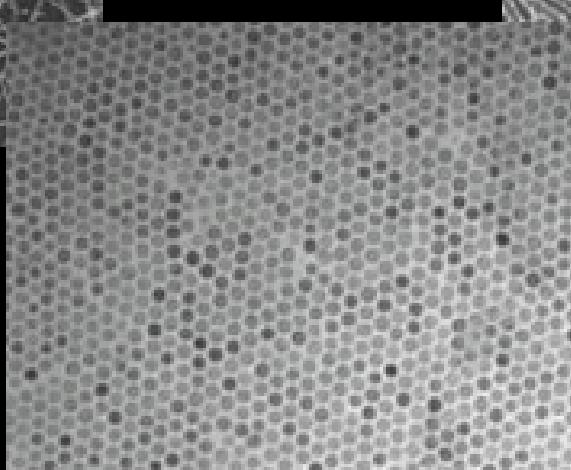
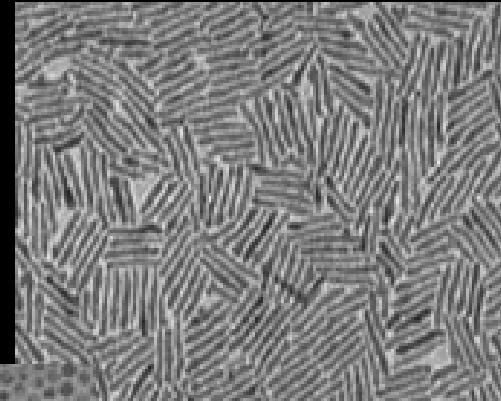
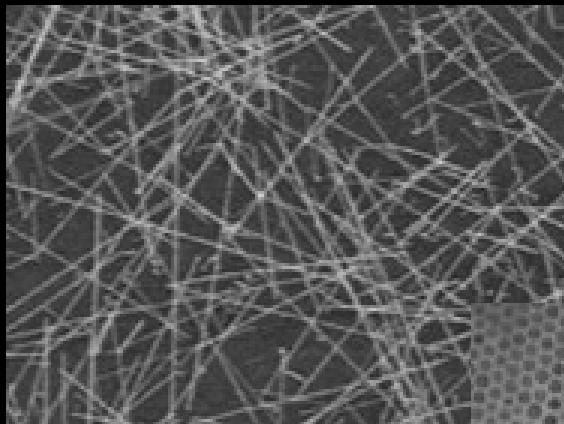


The Nano-Industrial Infrastructure Development Stream



Nanostructured Materials

- Foundry processes / fabrication techniques enabling mass production of nanostructural components
- Broad range of functionality

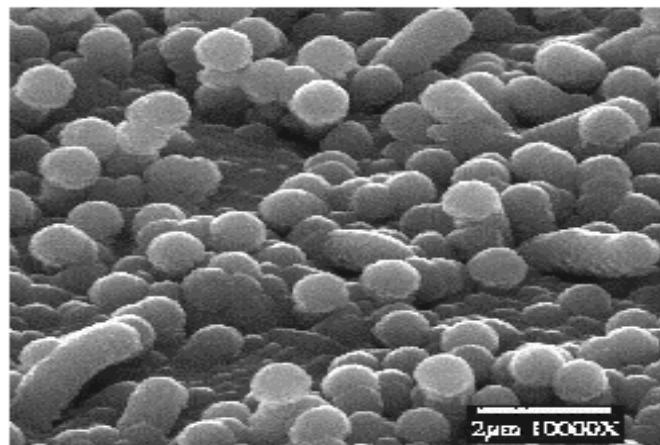


Self Assembly as a Foundry Process

Self-assembly is the most practical and realizable approach to fabricate arrays of nanodevices with the sub-100nm size features in short-term (the conventional lithographic methods of microsystem processing offer very limited control over the fabrication on the sub-100 nm scale)

Spontaneous self-assembly

This approach relies on structural disorder at the interface between the two materials with different physical properties (heteroepitaxy, fluctuations of the dopant concentration, etc.)

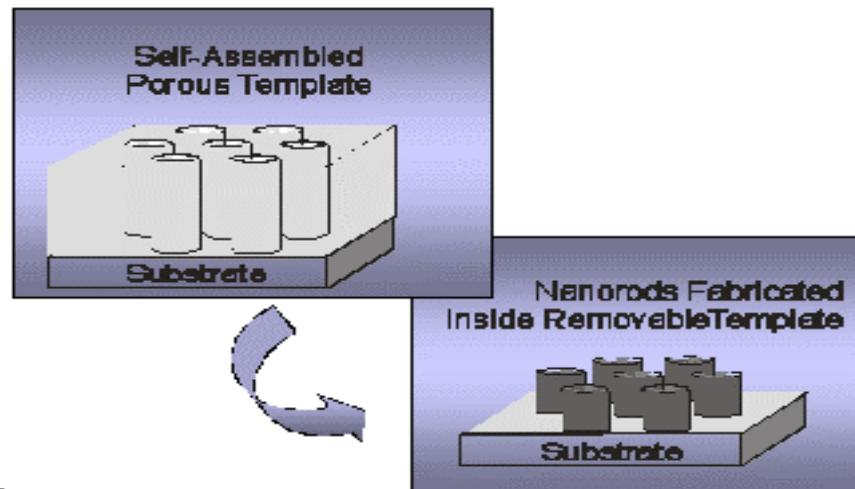


Self-assembled Si nanowires grown by magnetron sputtering

(E.A. Gulians and W.A. Anderson, "A Novel Method of Structure Control in Si Thin Film Technology 197th Meeting of The Electrochemical Society Toronto, ON, May 2000)

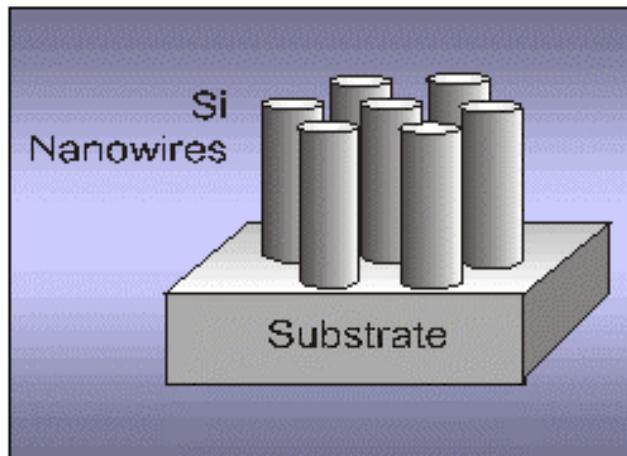
Controllable self-assembly

Involves self-assembly of the tools for fabrication of nanostructures and nanodevices such as masks or templates.

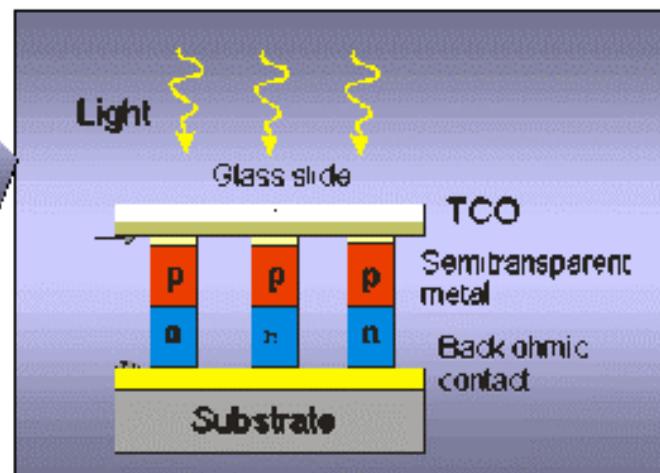
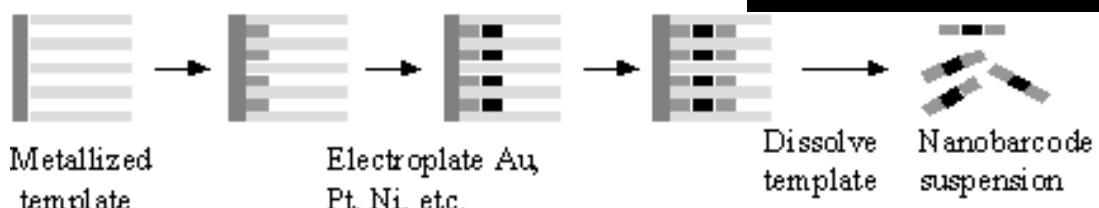
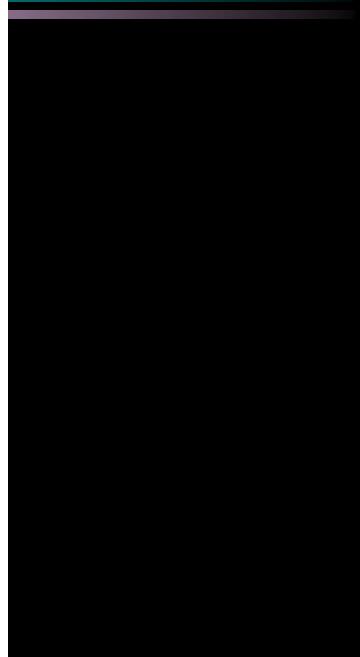


Periodic Nanostructures

Some of the potential applications of periodic nanostructures are:



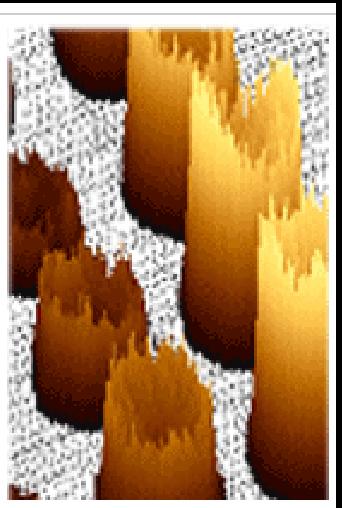
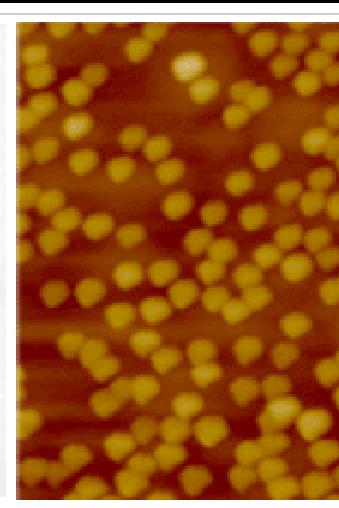
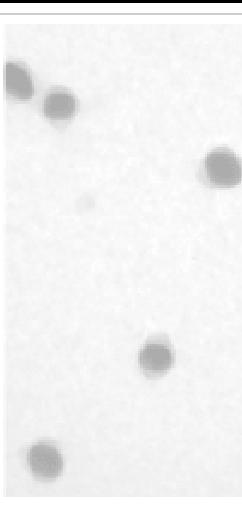
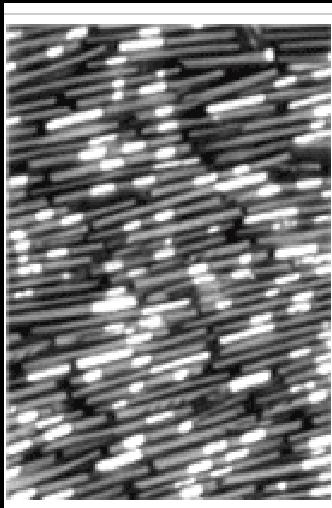
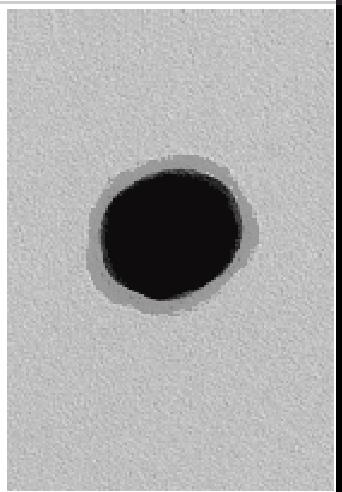
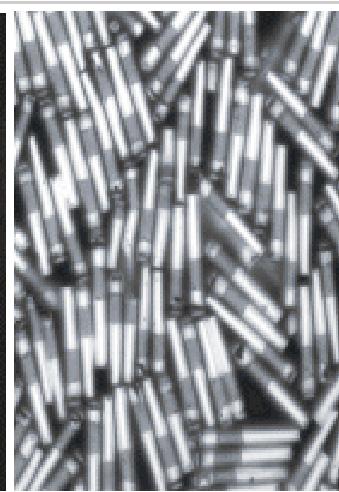
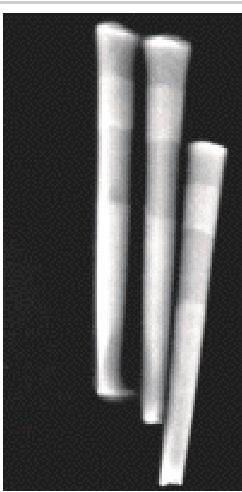
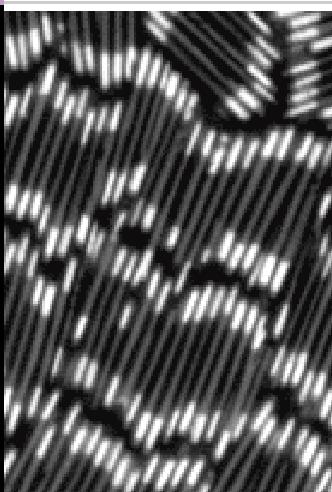
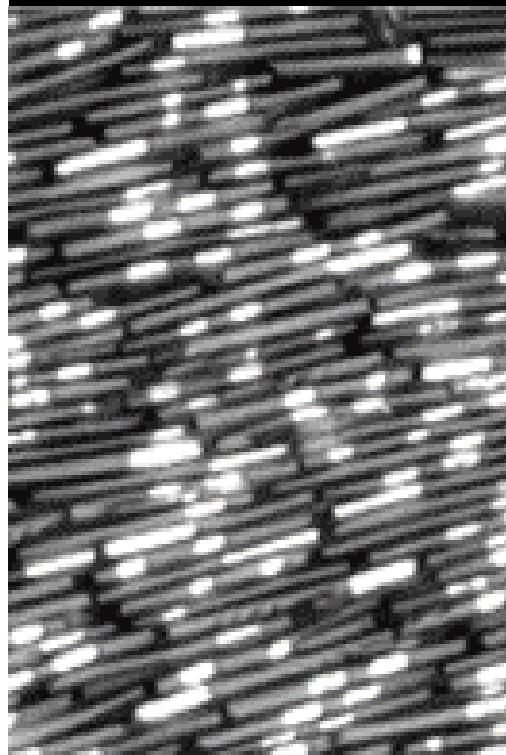
- Quantum effect dots
- Resonant tunneling diodes
- Single-domain/bit magnetic storage media
- Single electron transistors (SETs)
- Light-emitting diodes (LEDs)
- Photodetectors
- Quantum well optoelectronic devices
- Quantum cellular automata
- High-density memory



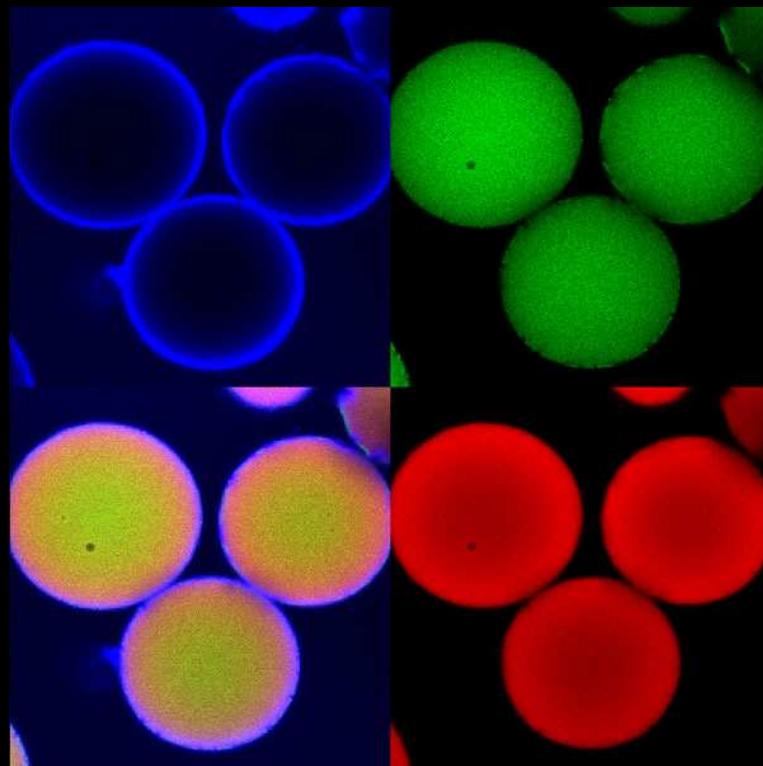
Schematic of a Si photodetector array fabricated on periodic Si nanowires

Periodic Nanostructures

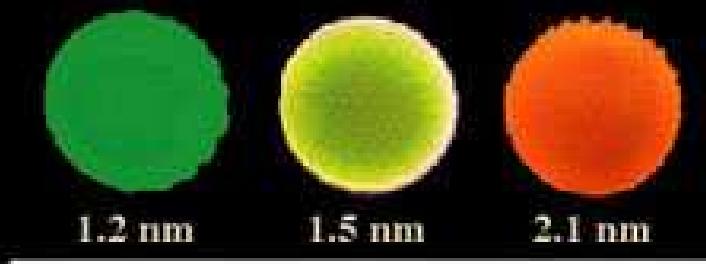
NanoPlex
Technologies



Spherical Periodic Nanostructures



The color of the light emitted by the dots is dictated by their size.



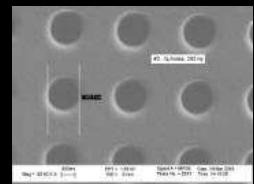
GE Nanotechnology Platforms

NanoTubes/NanoRods

SW/MWNT, Pt, Ni, MoC...

Application Areas

- Sensors...

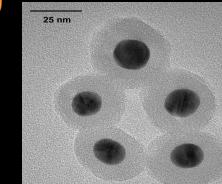
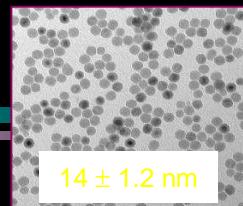


NanoParticles

Fe_2O_3 , Gd_2O_3 , Au...

Application Areas

- Molecular Imaging
- BioSensors...

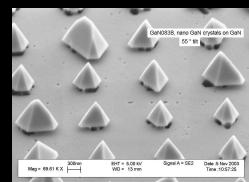
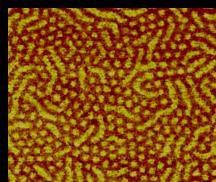


NanoHybrids

Block copolymers, GaN...

Application Areas

- Lighting – white LED...



NanoCeramics

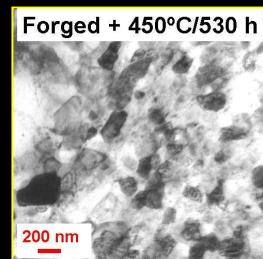
Application Areas

- Optical materials
- Structural ceramics...

NanoMetallics

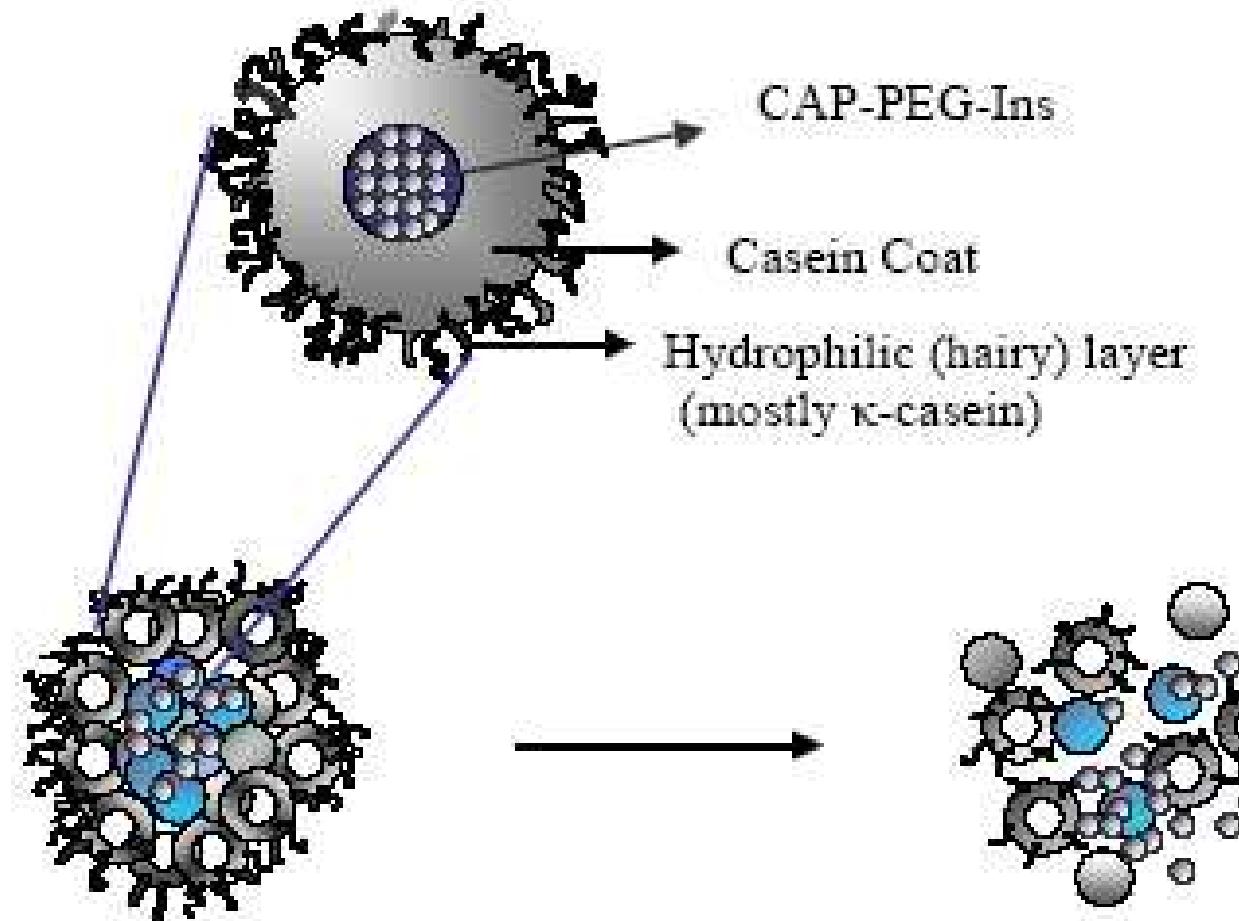
Application Areas

- High strength materials
- Thermal barriers...



broad range of nanomaterials

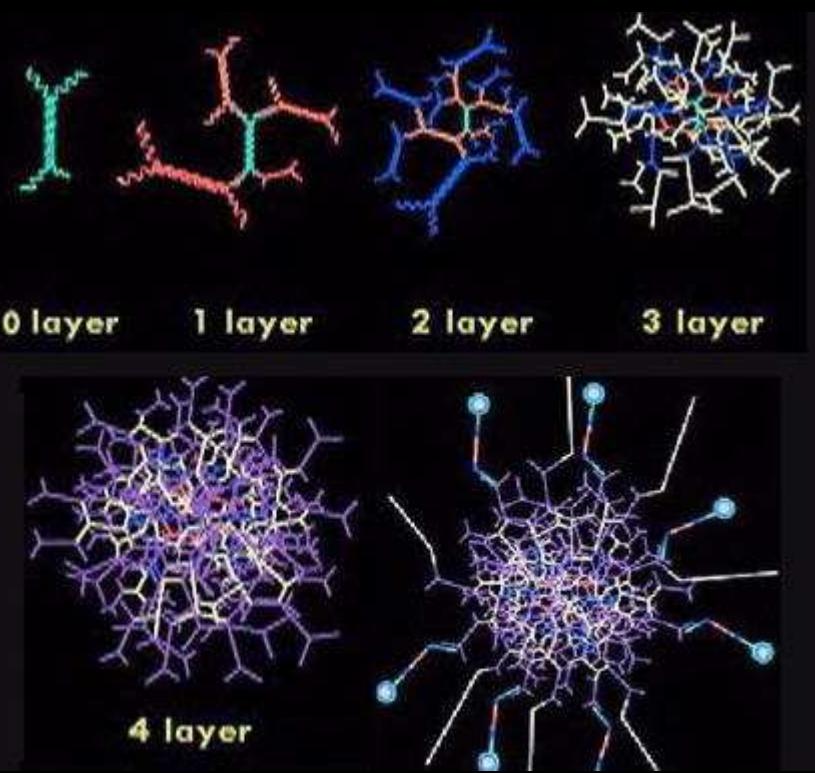
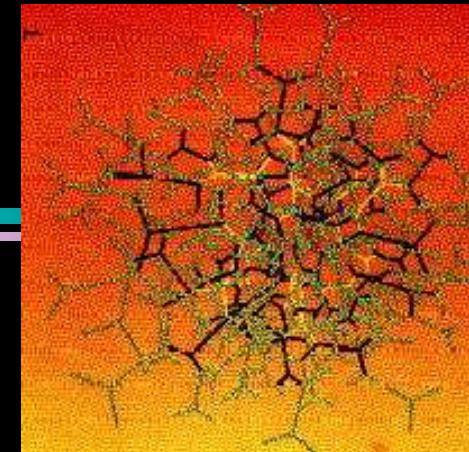
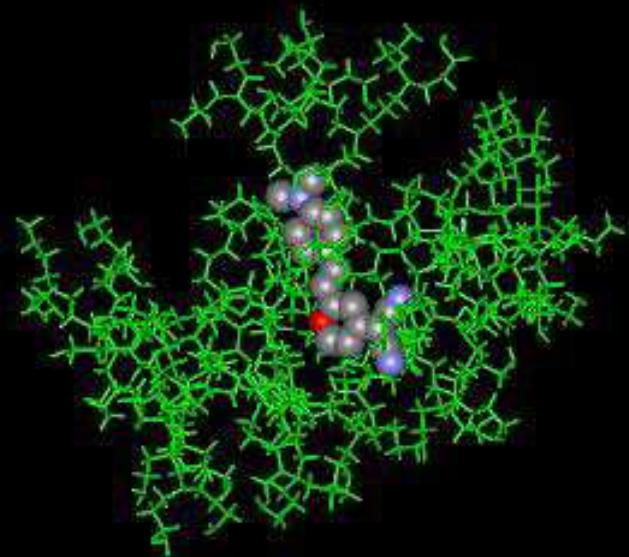
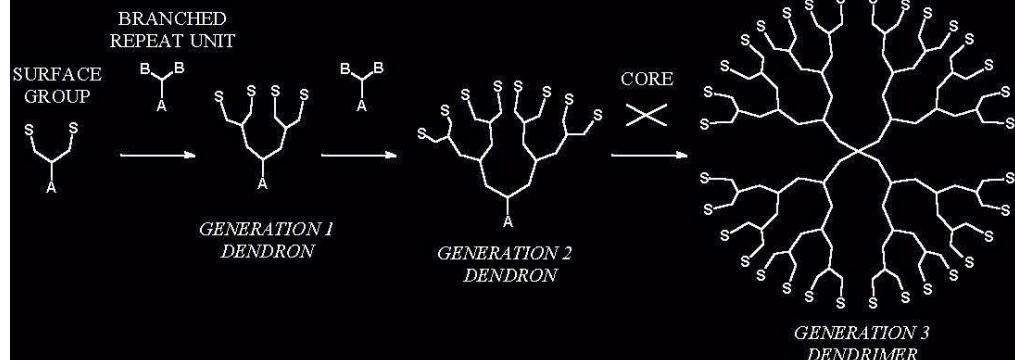
BioSante – Casein coated CAP-PEG-Ins (biodegradable calcium phosphate insulin) particles for potential oral delivery



CAPIC formulation in
acidic pH of the Stomach

CAPIC in > 5.5 pH of
the intestines

Dendrimers – molecular delivery vehicle

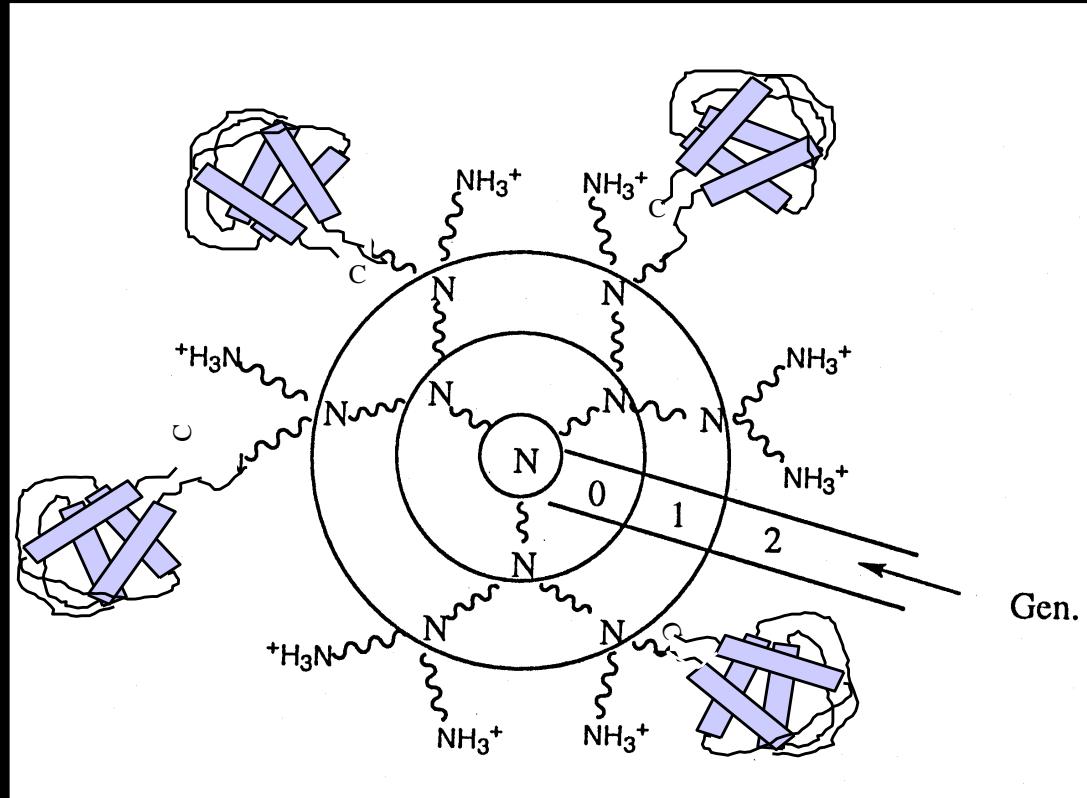


Immune responses to nanomaterials ...

One approach:
isofunctional
device variants
tailored to
individuals

one device
becomes many...
What if it contained
multiple proteins?

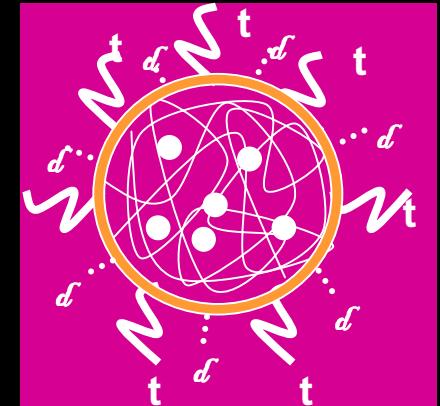
Lee *et al.* 2001. Biomedical Microdevices. 3: 51-57.
Lee *et al.* 2004. Biomedical Microdevices, *in press*



How many possible protein components of nanodevices are there?

- At least 25,000 genes in humans¹
- At least 100,000 proteins¹
- >3X 10⁹ living species described to date
- Exponential numbers of engineered variants of each protein are possible

1. Southan. 2004. Proteomics 4: , 1712-1726
2. Edwards et al. 2000. Science (2000 Sep 29), 289: 2312-4.



Is there a reason for fungible protein components of nanodevices?

Protein Size Mimicry

10 nanometers

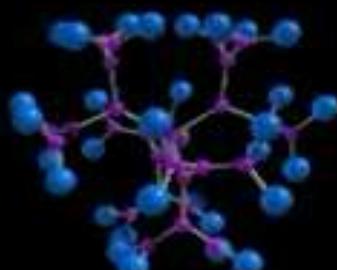


Insulin



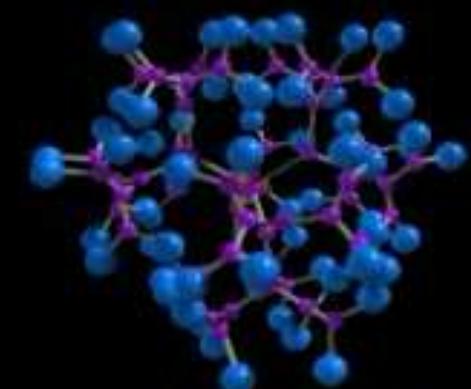
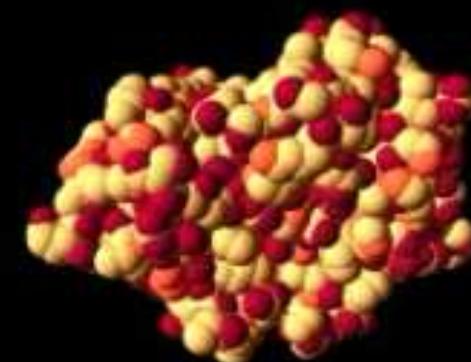
Generation 3
3 nanometers

Cytochrome



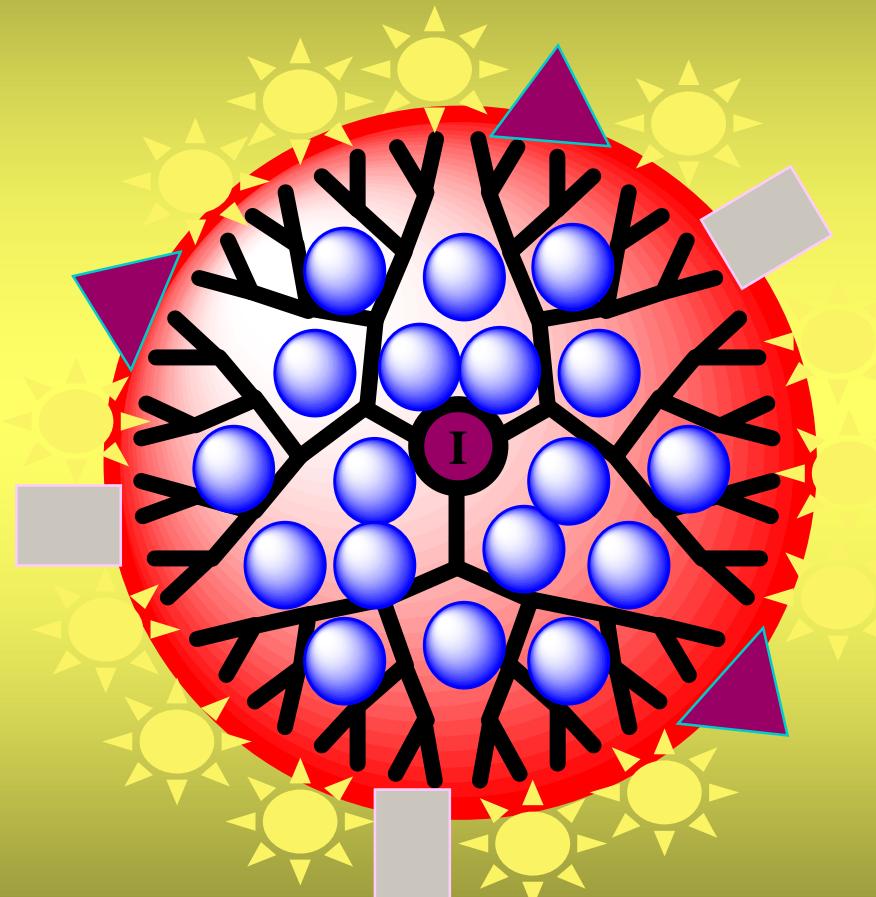
Generation 4
4 nanometers

Hemoglobin



Generation 5
5 nanometers

Dendrimers as Nano-Diagnostics



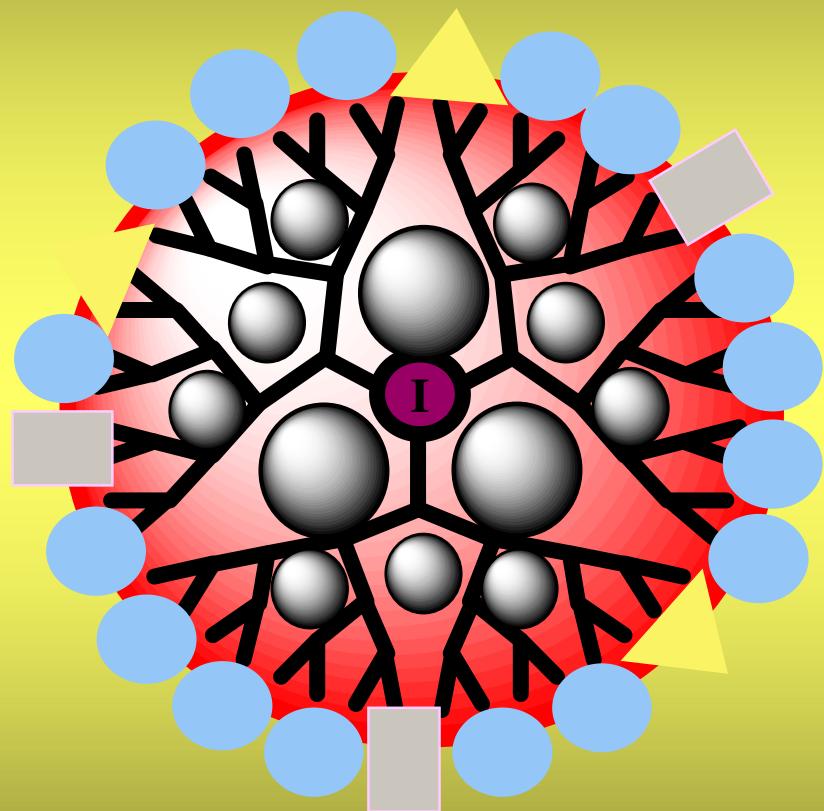
Signal Amplifier

Opacifiers

Targeting Groups

**Modifying Groups
(bio-distribution)**

Dendrimers as Nano-Delivery Containers



Active Pharma



**Delivery Control
Groups**

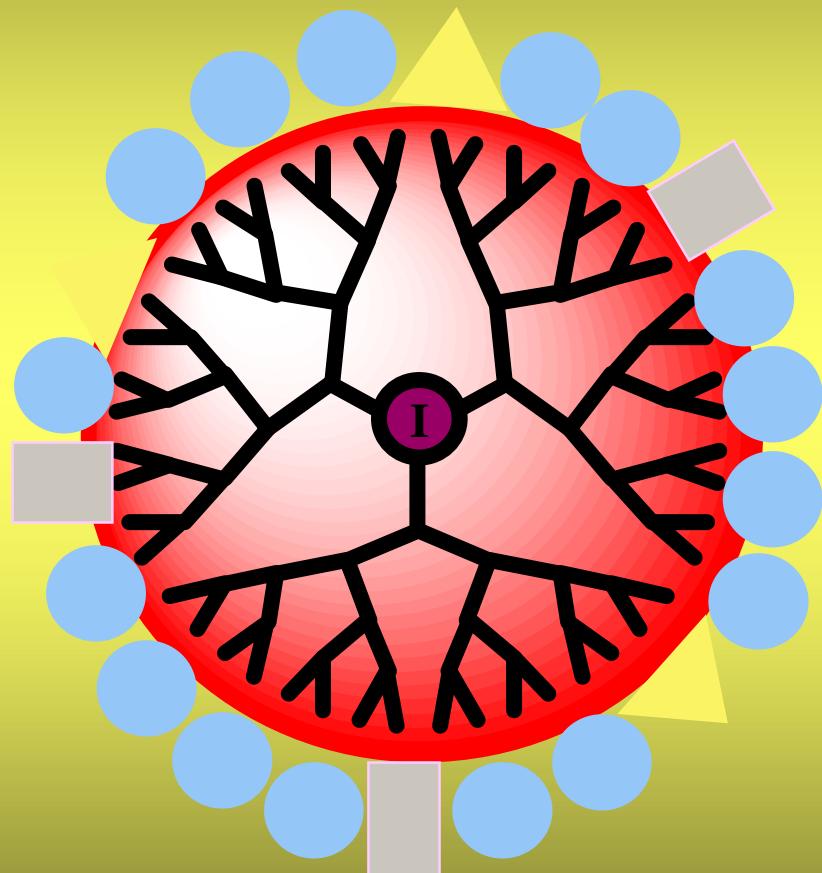


Targeting Groups



**Modifying Groups
(bio-distribution)**

Dendrimers as Nano-Drugs



Active Groups

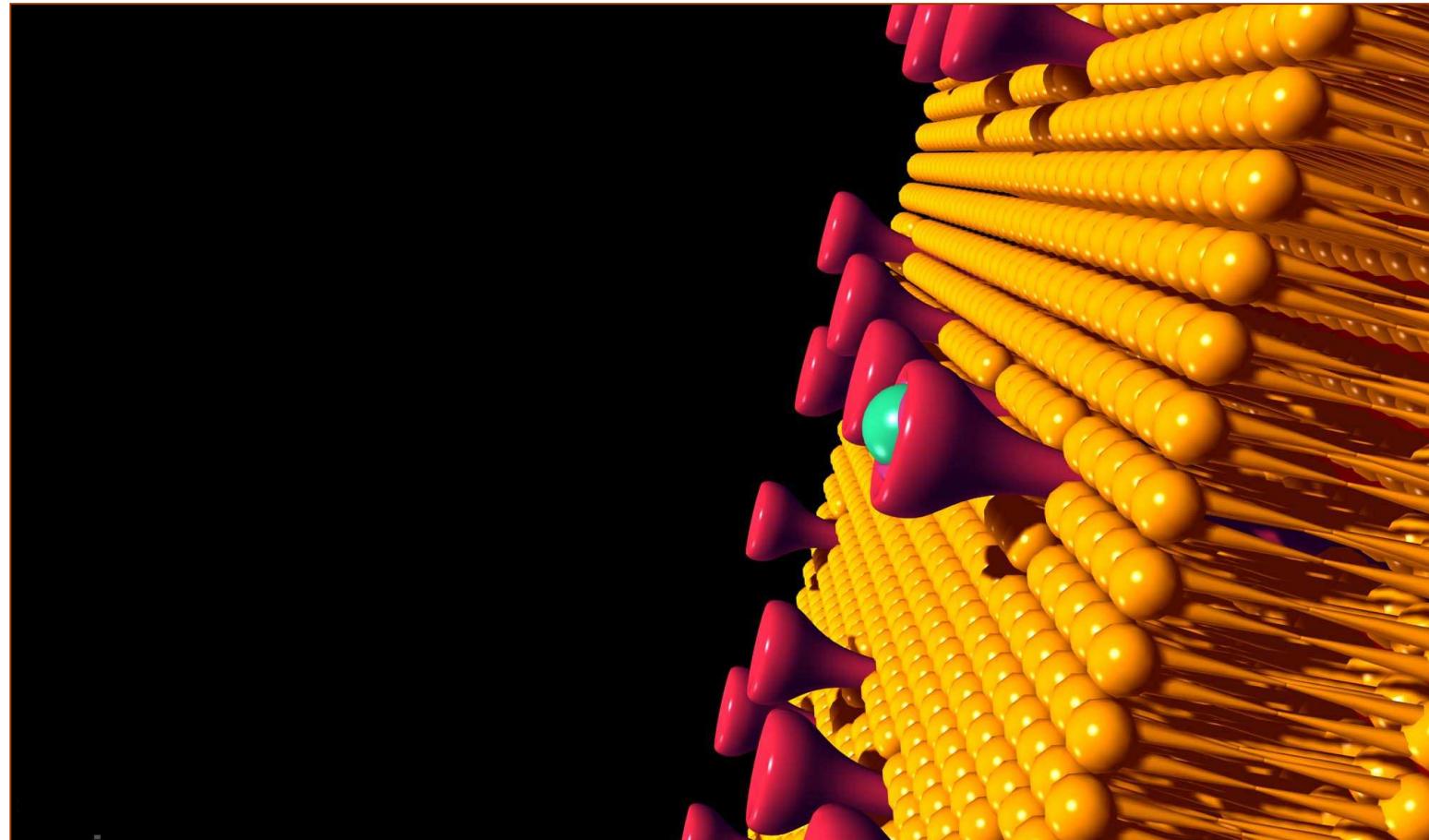


Targeting Groups



**Modifying Groups
(bio-distribution)**

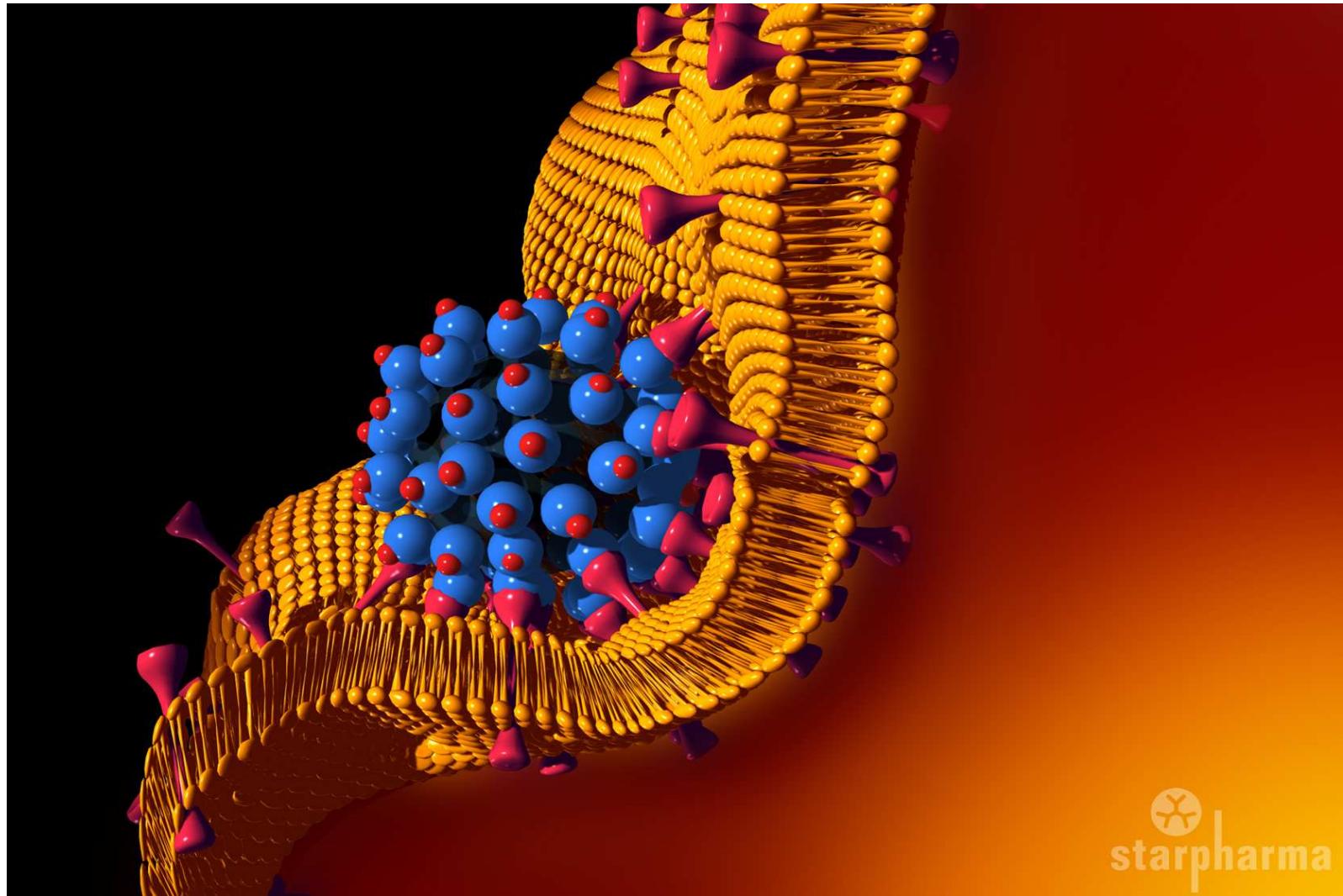
Traditional Monovalent Drugs



Most small molecule drugs are only capable of monovalent binding.



Dendrimer Based Polyvalent Drugs



Dendrimers are capable of polyvalent (multiple receptor-site) binding to cell or viral receptors.

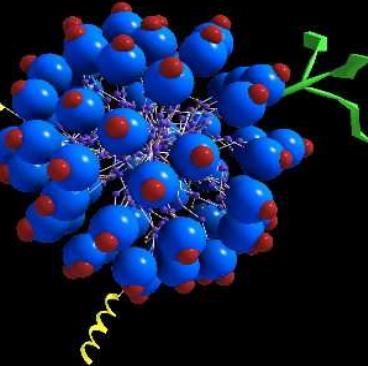
DNT's Opportunities

Nano - catalysts

Nano - optics

Nano - electronics

Nano - sensors



Thin Films

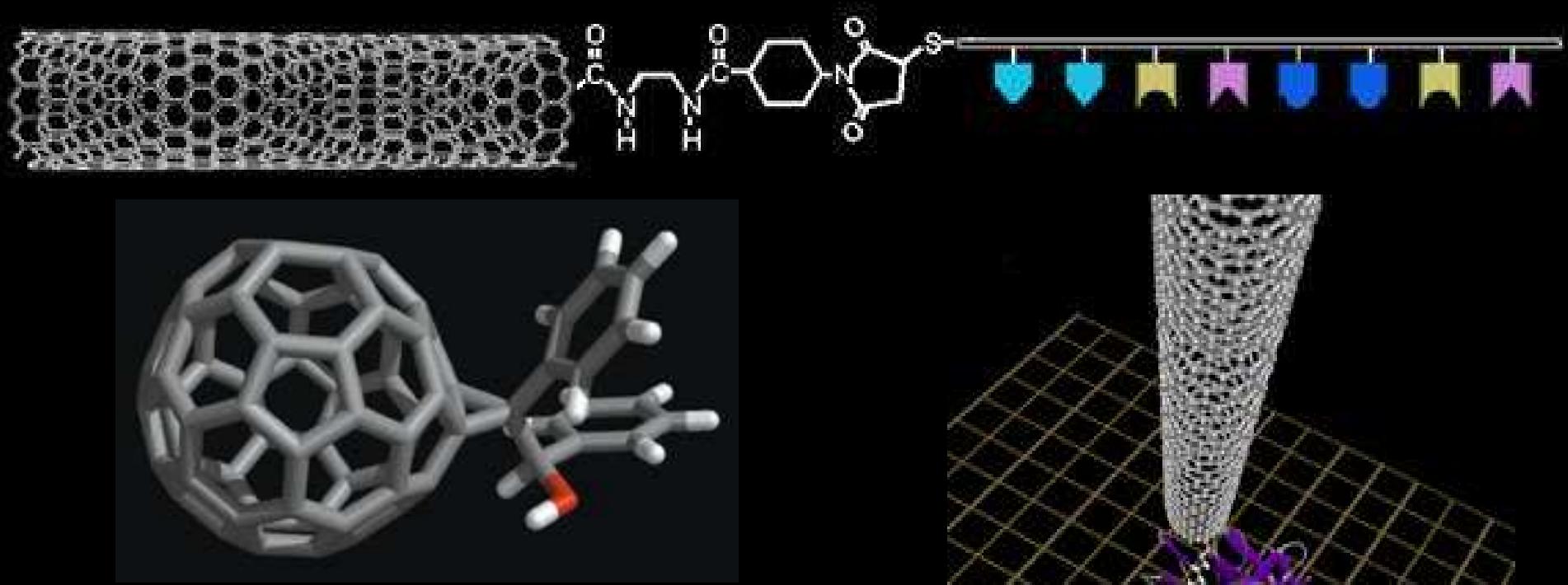
Nano - reagents

Military

Pharmaceutical



Value Proposition is in Synergistic Opportunity Carbon Fullerenes – from probes to delivery platforms

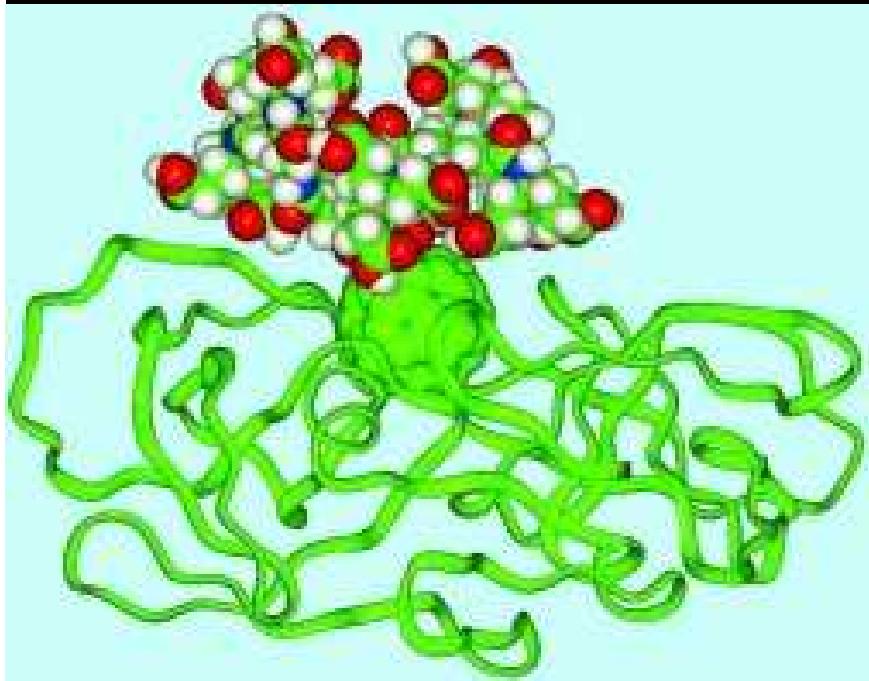


BUCKY DRUG. Model of a fullerene-based HIV protease inhibitor recently designed by Simon Friedman.

3/26/2010

Value Proposition is in Synergistic Opportunity

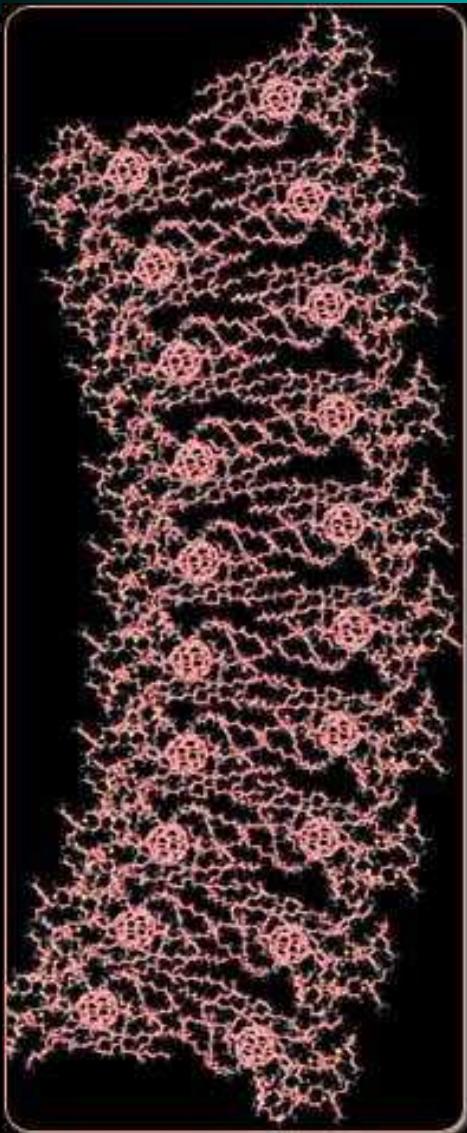
Carbon Fullerenes – from probes to delivery platforms



Fullerene-based protease inhibitor fights HIV by binding to the active site of the protease enzyme (green ribbon). The carbon-60 molecule (green ball) is decorated with various chemical appendages (green, red, white, and blue). C Sixty plans to test it in patients.
A. Kirschner/NYU

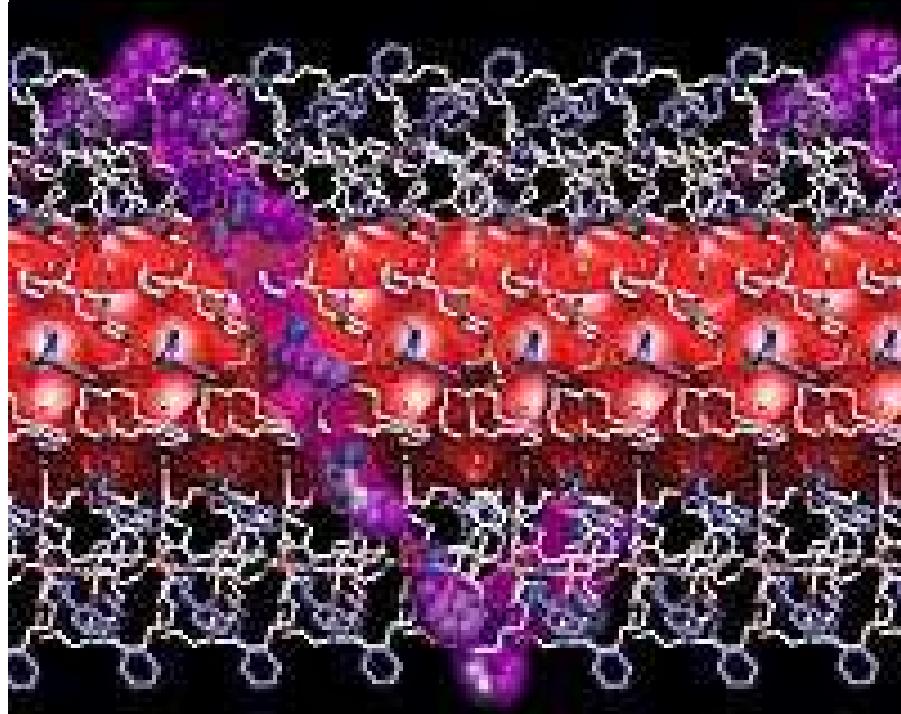
Value Proposition is in Synergistic Opportunity

Carbon Fullerenes – synthetic architectures



*Computer model image of a
fullerene-based artificial membrane
courtesy of Andreas Hirsch, Ph.D.,
University of Erlangen, Germany*

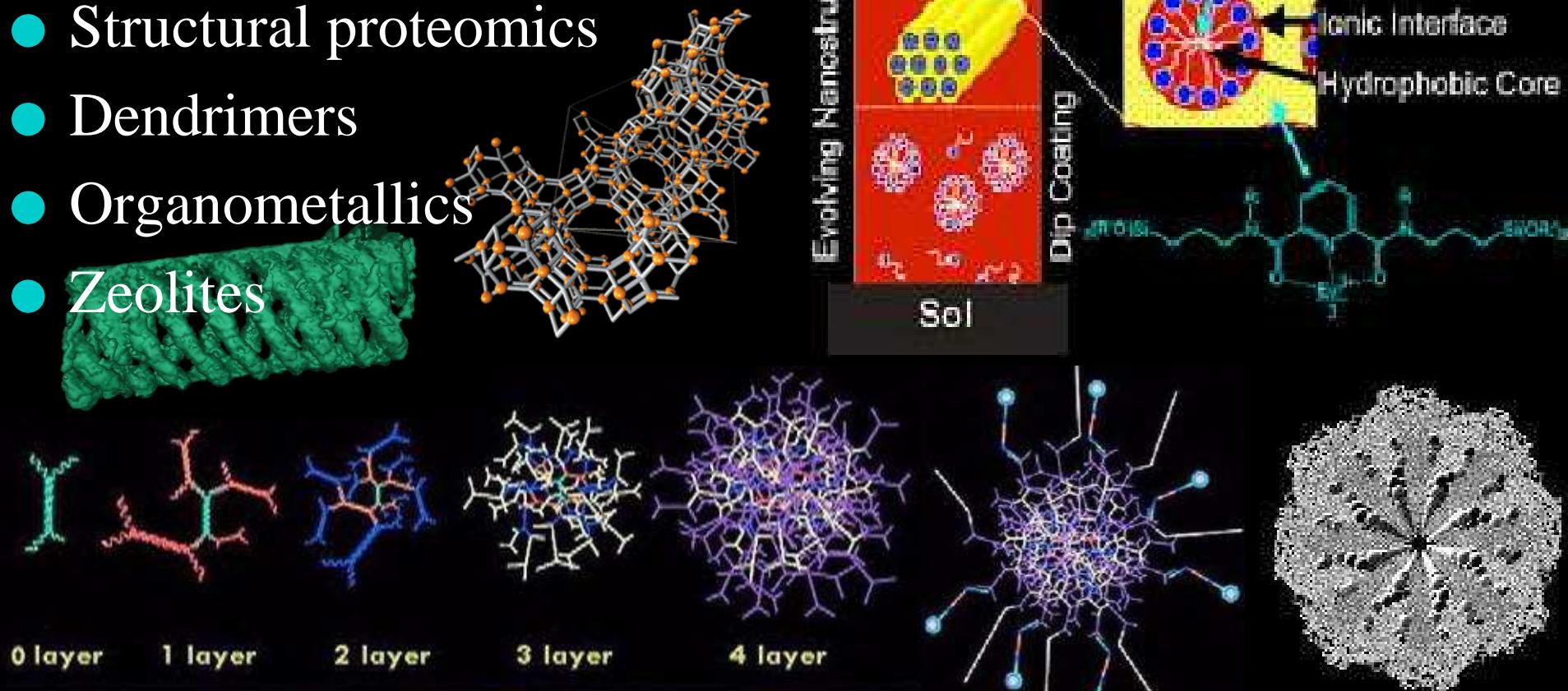
Nanotubes from other materials – polymers, proteins, synthetic organic molecules



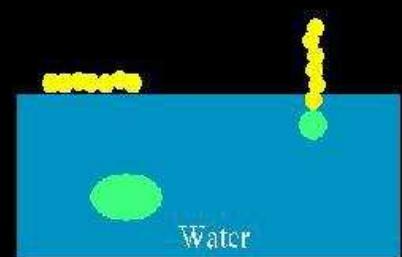
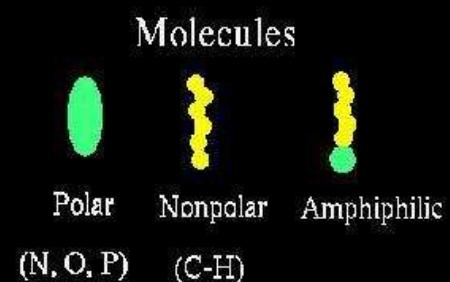
A self-assembled rosette nanotube and its mirror image prepared in the Fenniri laboratory. These materials are now made with predefined chiroptical, physical and chemical properties. The Fenniri group's nanotubes promote their own formation and offer numerous potential applications. (Purdue University Department of Chemistry)

Molecules as Tools – Not Just Endproducts

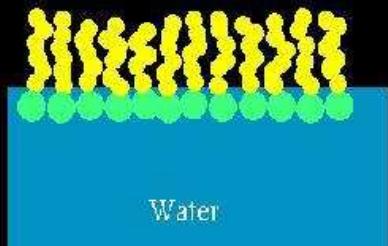
- Nanotubes - carbon, polymer, protein, etc.
- Structural proteomics
- Dendrimers
- Organometallics
- Zeolites



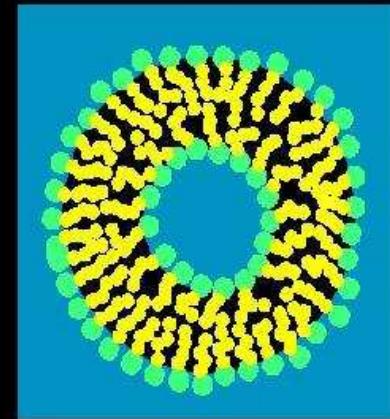
Molecules as Tools - Not Just Endproducts > Complex Nanostructures > Nanodevices



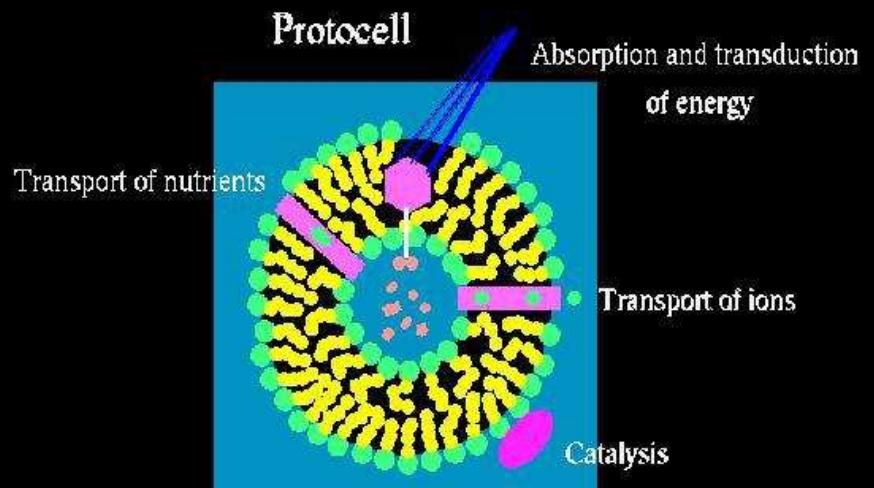
Monolayer of amphiphiles



Bilayer Vesicle



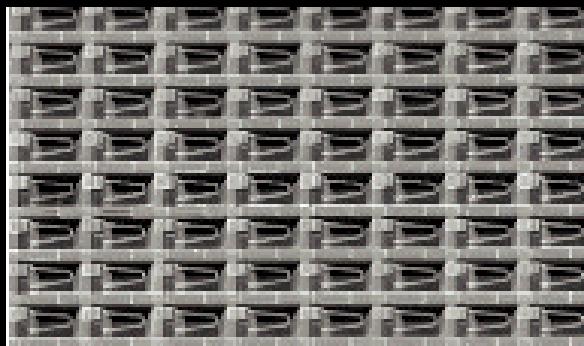
Protopcell



Define “Tools”

Goal of the tool is to manipulate molecules and pattern matter

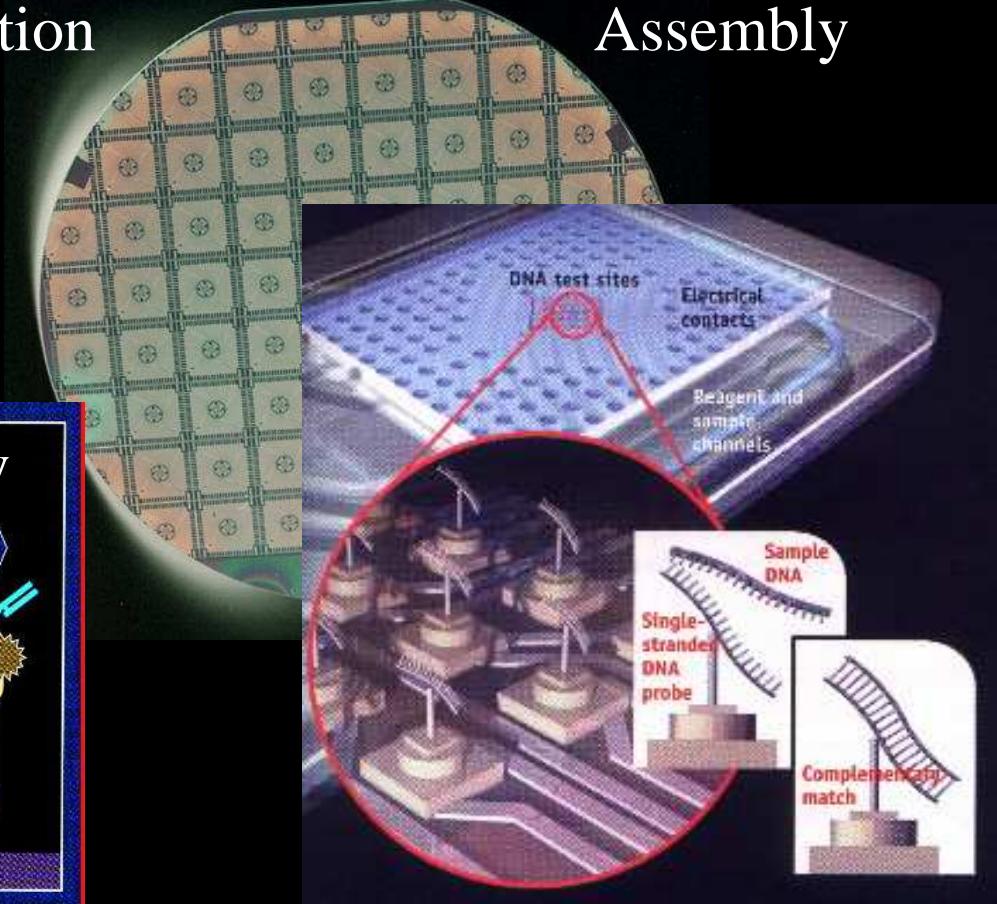
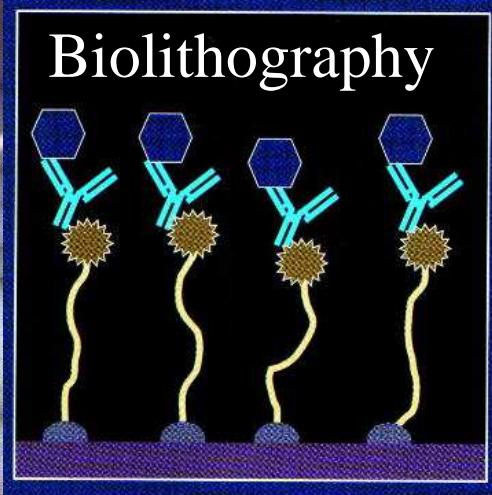
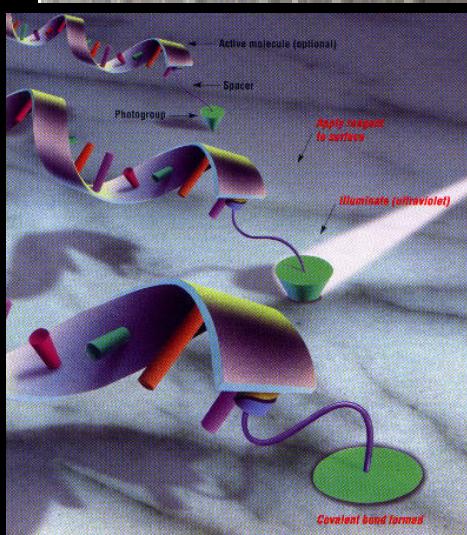
AFM devices / arrays



Electro-Molecular
Manipulation

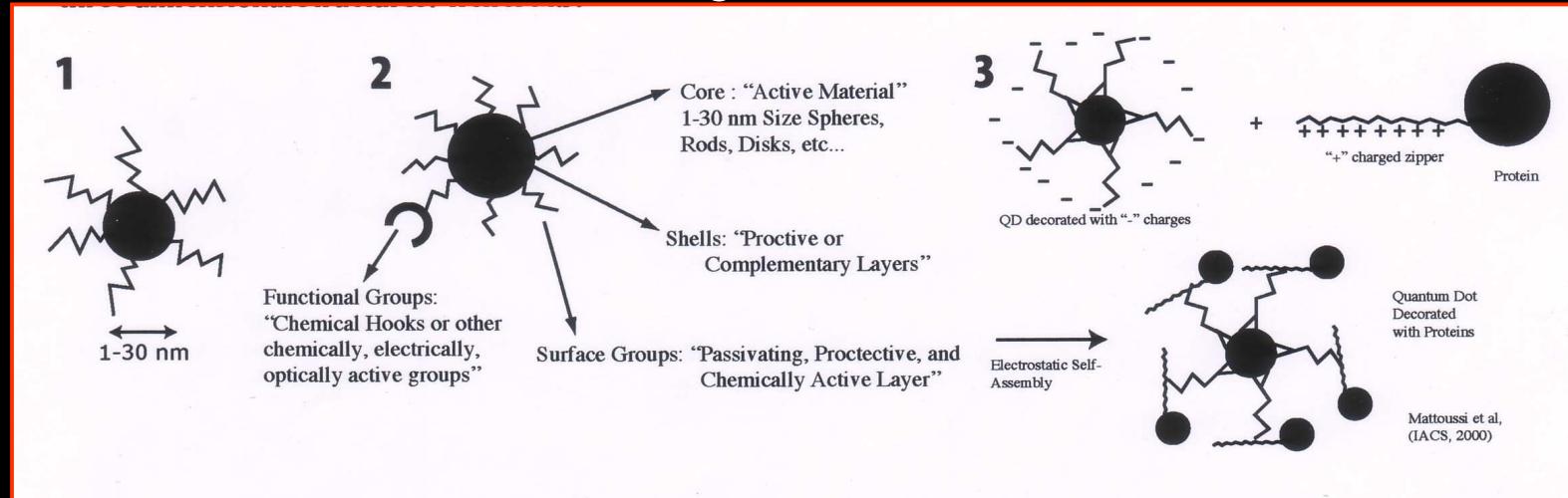


Heterogeneous
Assembly

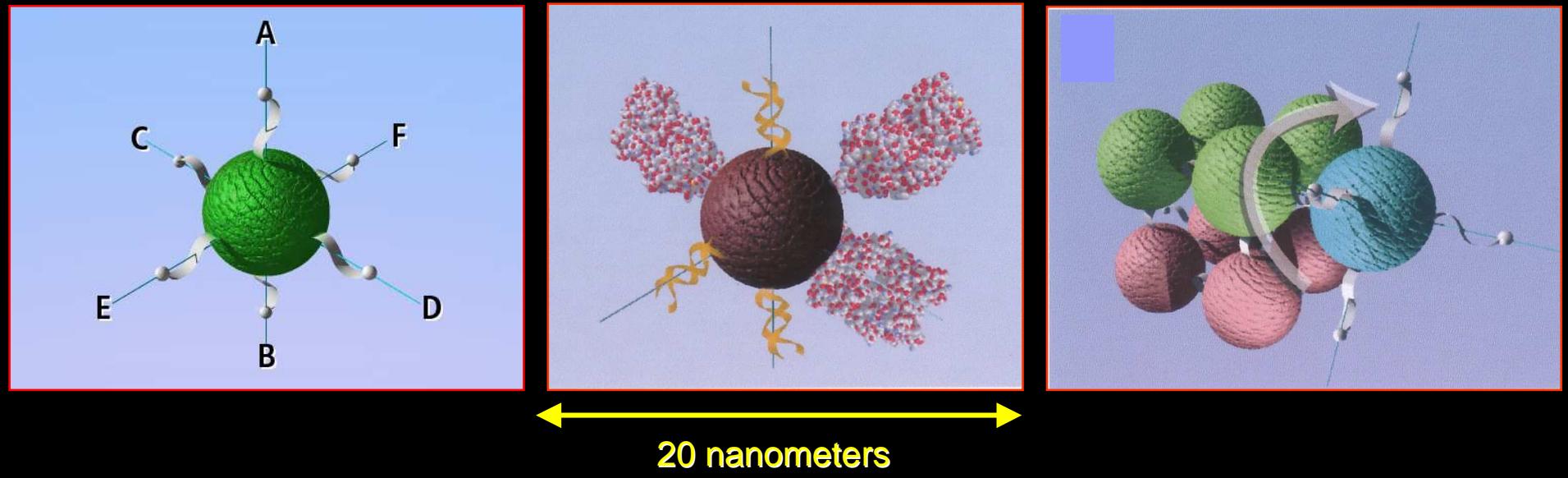


Objective: Improved Processes for Manufacturing High Precision Functionalized Nanostructures

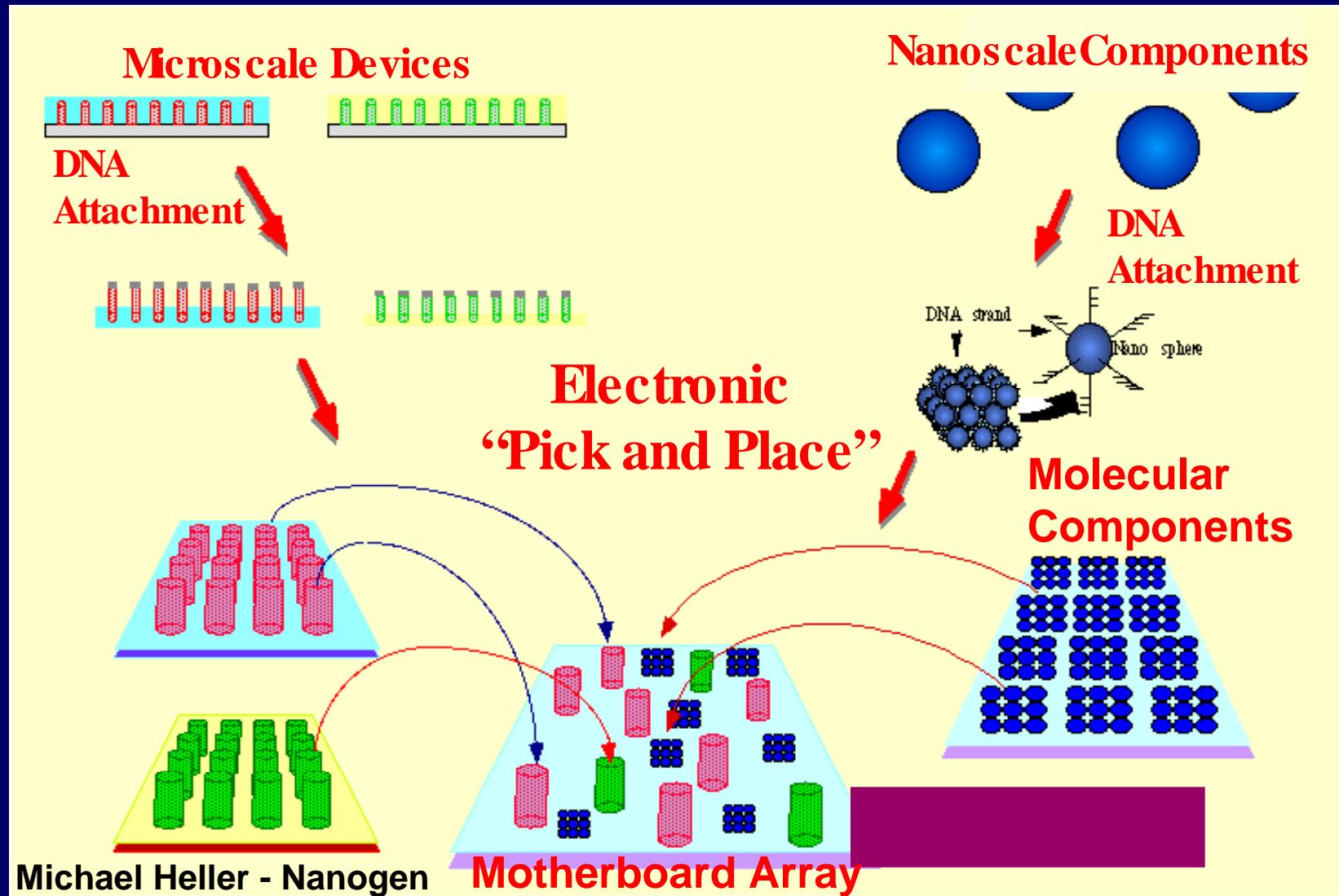
Present strategies for nanofabrication



Target future nanofabrication goals



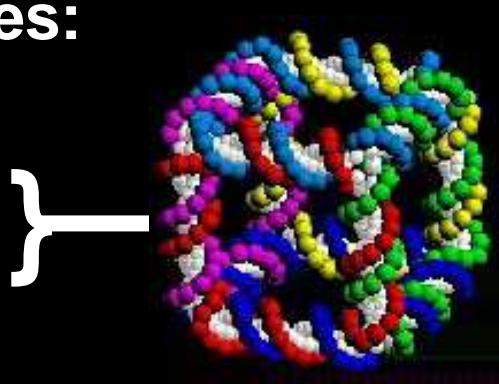
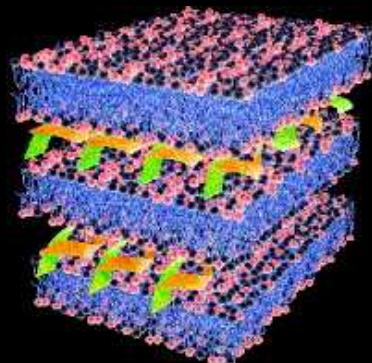
Heterogeneous Integration Process for Micro/Nanofabrication – Synergy of Top-Down with Bottom-Up Processes



Biology as a mechanism for material production, patterning, and fabrication

Key Properties:

Photonic
Electronic
Mechanical
Chemical



Living Systems as Biofoundry



Genetic Magnification

Dynamic Agent



Material Patterning / Structural Systems

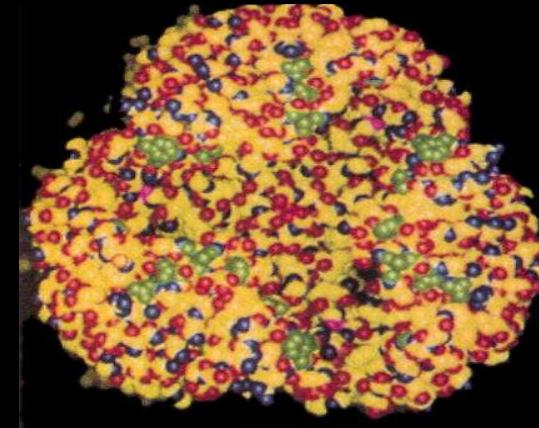
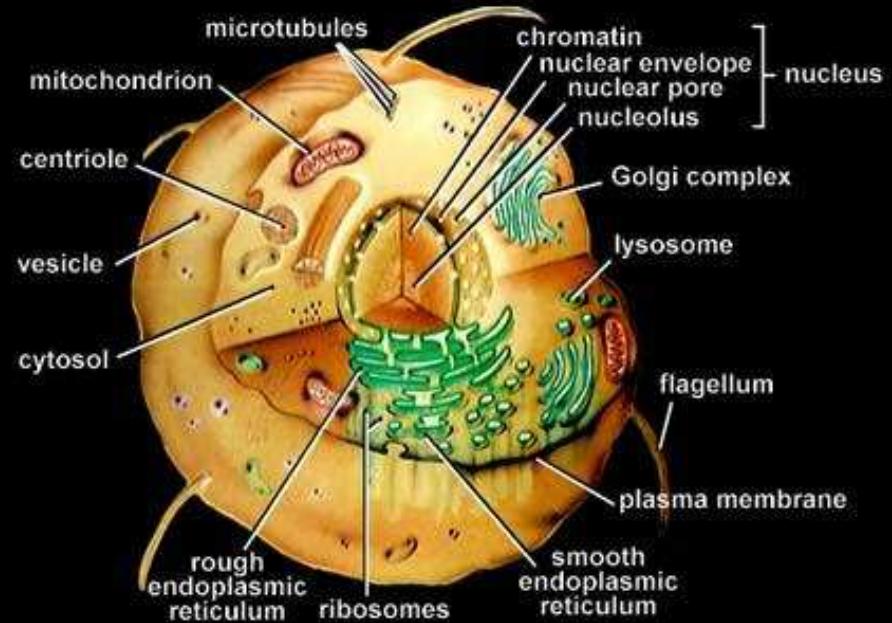
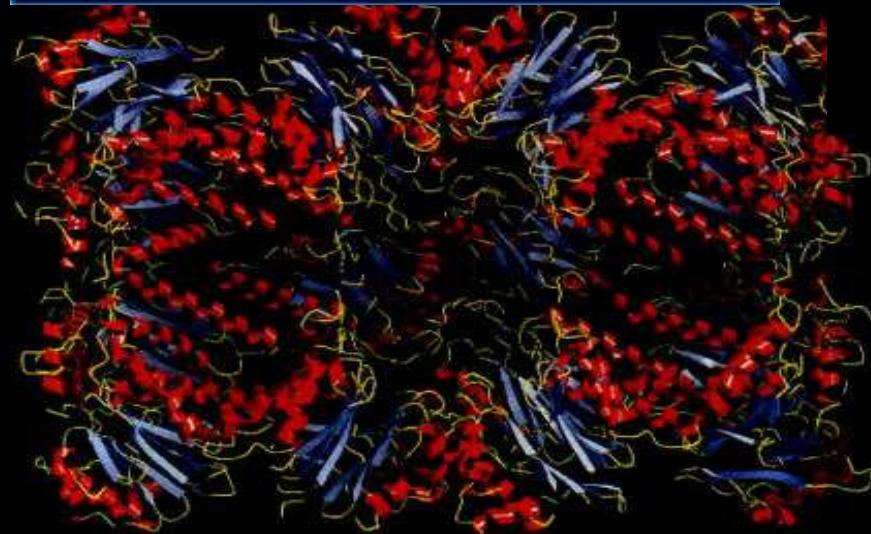
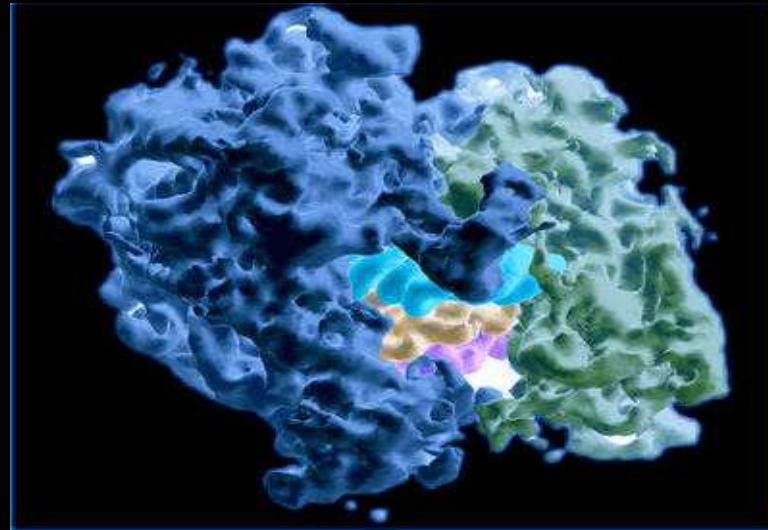


Controlled Replication

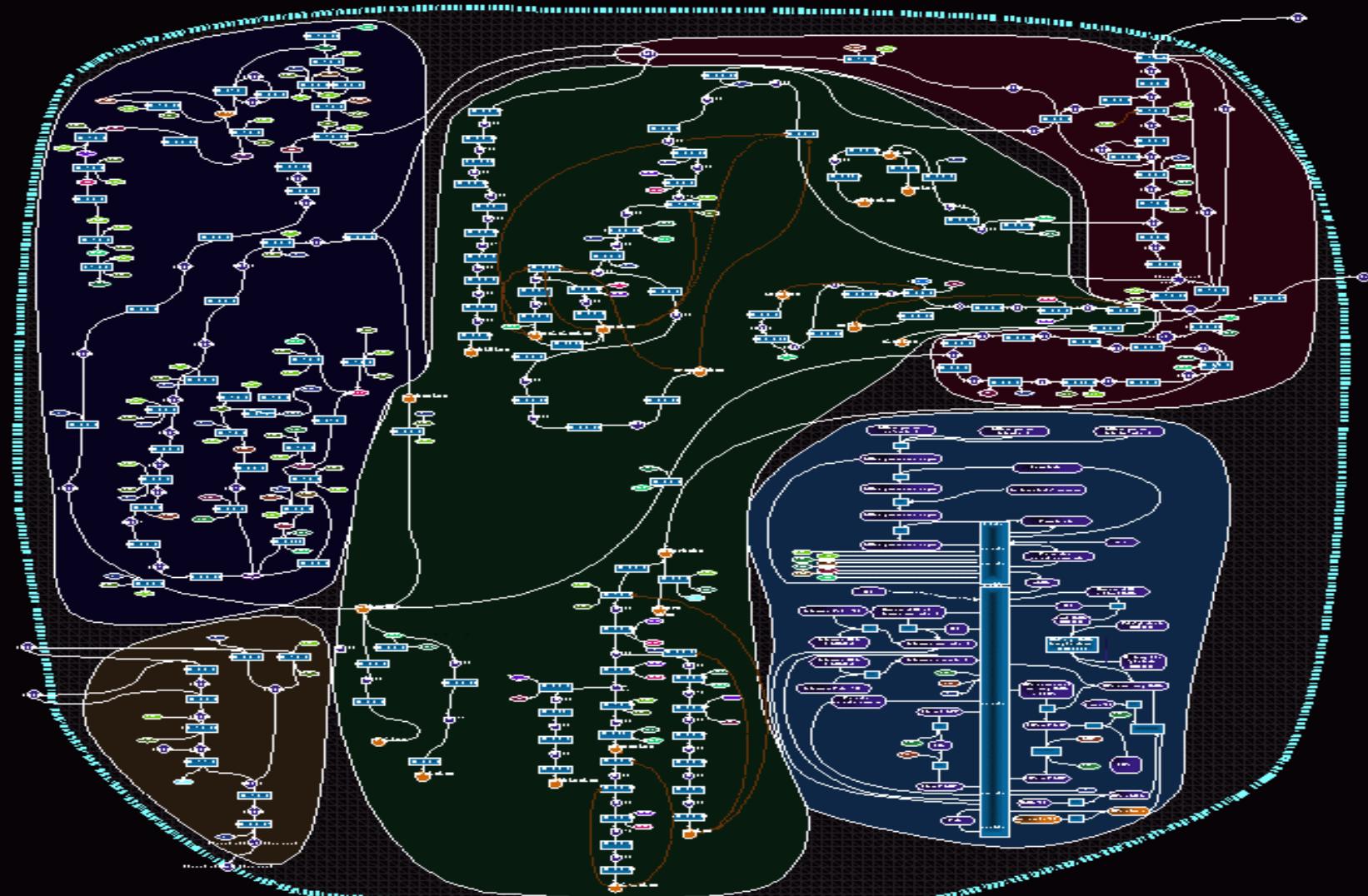


Materials Harvest / “Biocomponents”

Nature's Nanofoundries



In-Silico Biology – Schematic Engine of Biological Systems



HOW A GENETIC PART WORKS

Assemblies of genes and regulatory DNA can act as the biochemical equivalent of electronic components, performing Boolean logic.

A COMPONENT

A biochemical inverter performs the Boolean NOT operation in response to an input signal, in the form of a protein encoded by another gene.

ON

When no input protein is present (input = 0), the inverter gene is "on"—it gives rise to its encoded protein (output = 1).

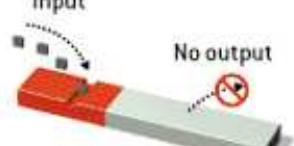
No input



OFF

When input protein is abundant (input = 1), the inverter gene turns off (output = 0).

Input



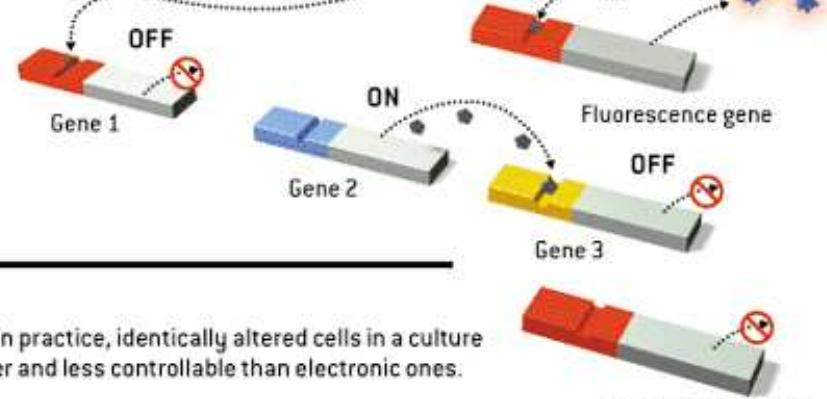
A CIRCUIT

One simple genetic circuit connects three inverters, each of which contains a different gene (gene 1, 2 or 3). The genes oscillate between on and off states as the signal propagates through the circuit. The behavior is monitored through a gene (*far right*) that intercepts some of the output protein generated by one of the inverter genes (gene 3) and gives rise to fluorescence in response.

AT 150 MINUTES

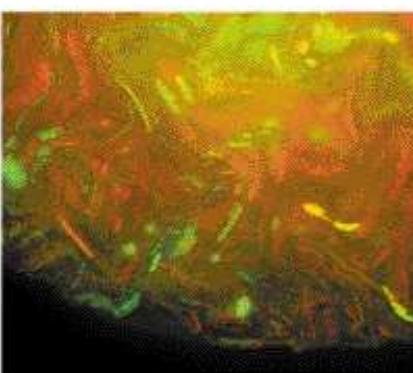
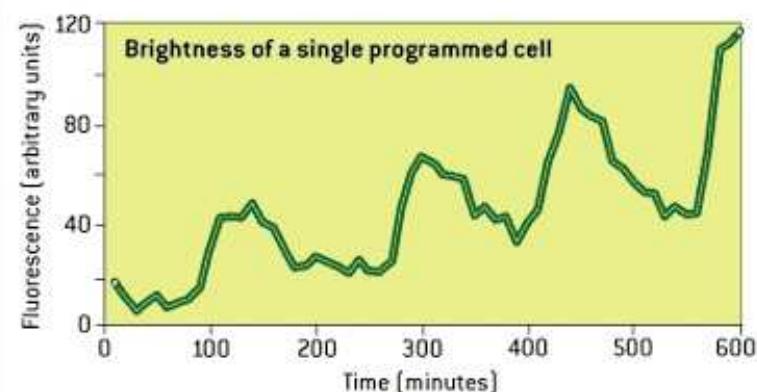


AT 200 MINUTES



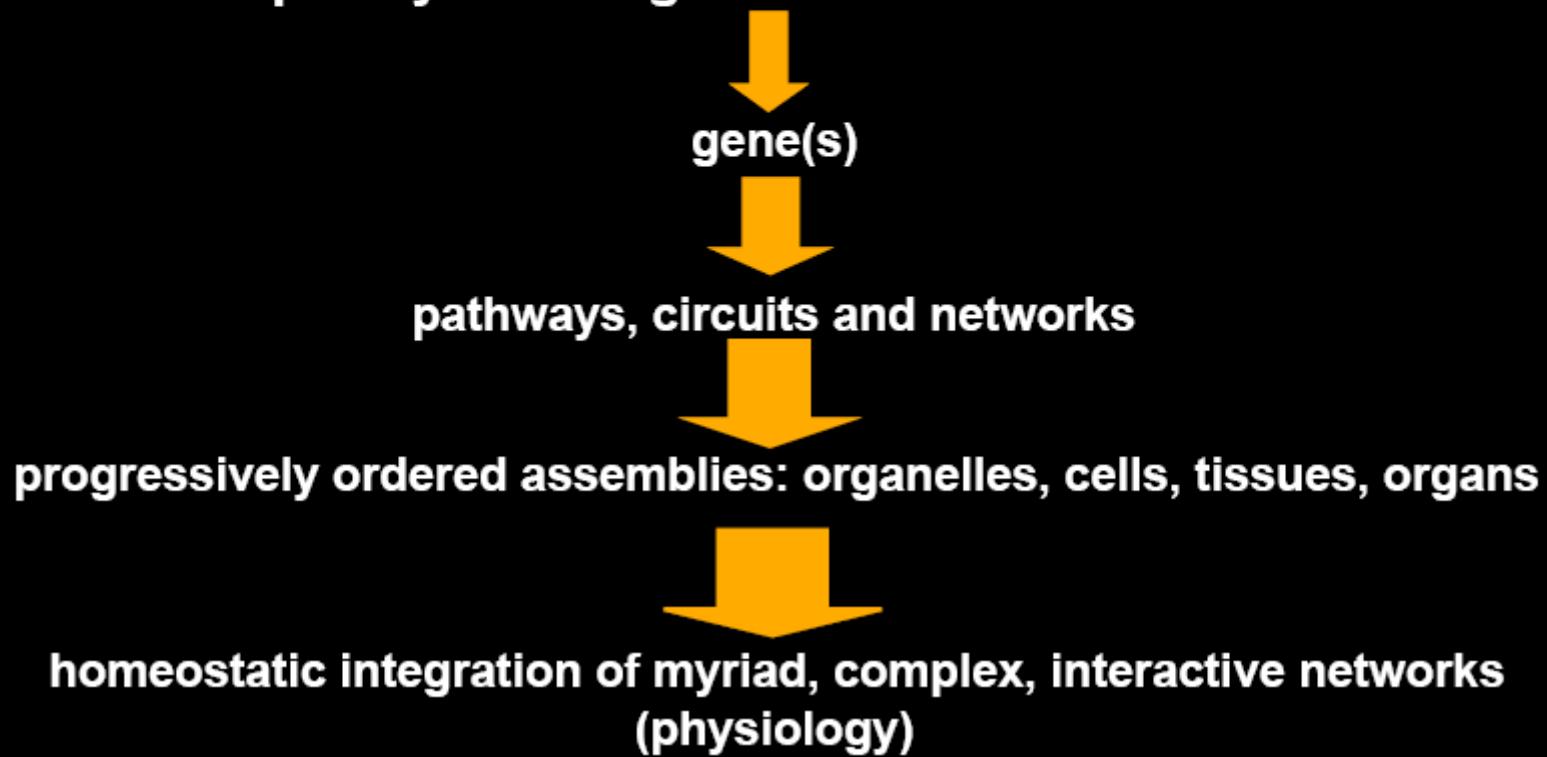
A CIRCUIT IN ACTION

Cells containing such a circuit blink on and off repeatedly [graph]. But in practice, identically altered cells in a culture [photograph] blink at varying rates, because genetic circuits are noisier and less controllable than electronic ones.



From Reductionism to Integrated Systems Biology

- **understanding the information content encoded in biological networks**
- **mapping the design rules for progressively greater complexity of biological order**



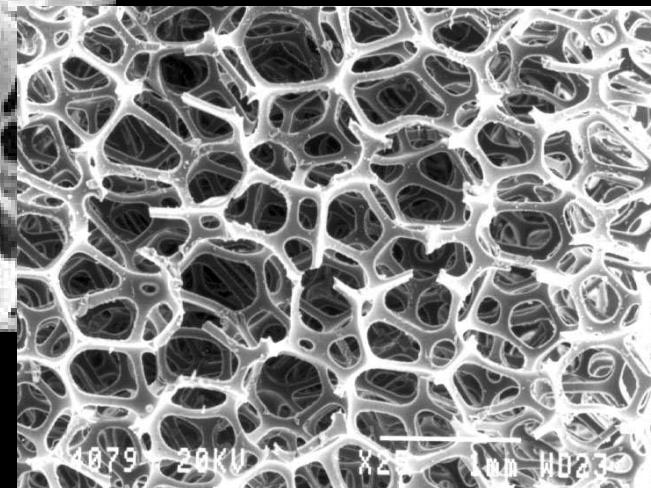
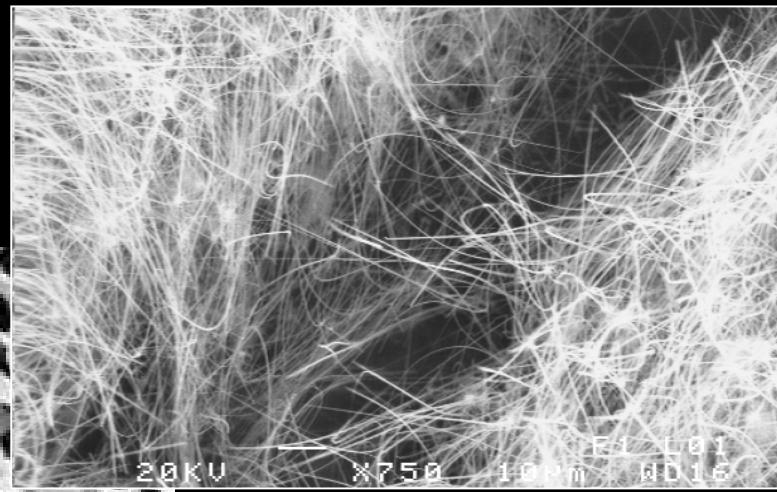
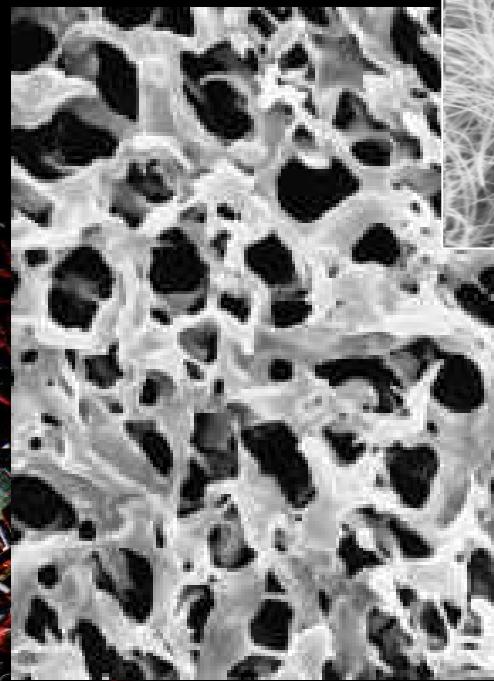
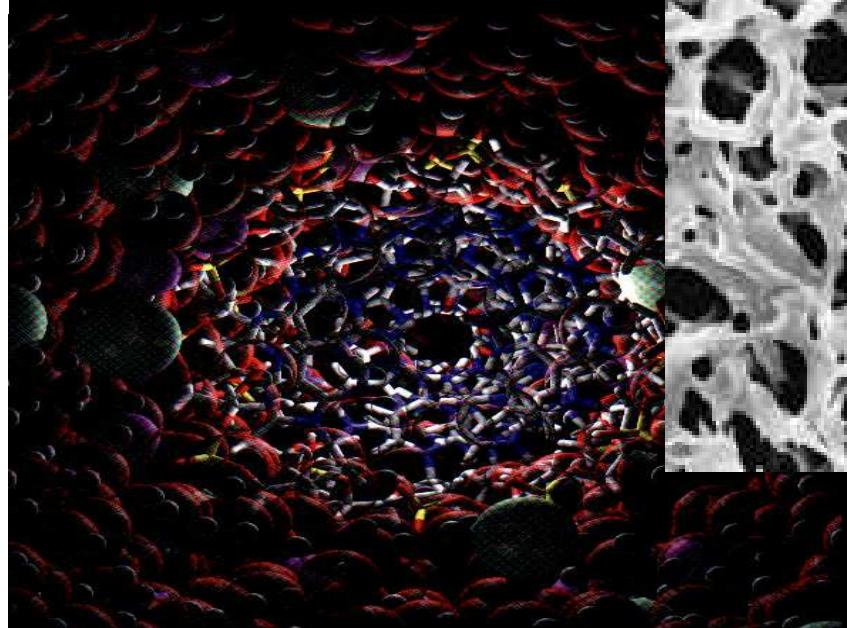
**Dr. George Poste
Director**

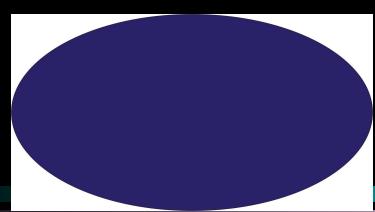
**Address: george.poste
Server: asu.edu**

Enhanced Biology . . .

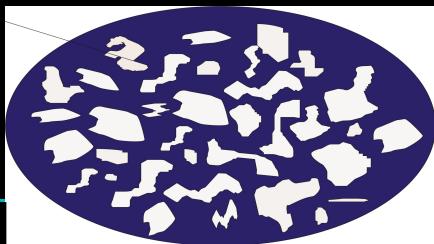
Nanostructured Cellular Environments

Scaffolds for tissue





HF
treatment



Silicon wafer after
porosification

Detachment



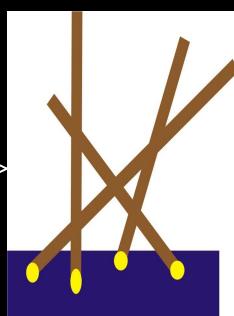
Mesoporous silicon

Silicon wafer

“top-down” porous silicon fabrication

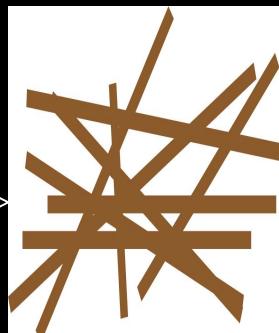


Silicon wafer substrate
with gold catalyst



Silicon whisker synthesis and growth
on substrate

Detachment



Free-standing Silicon
whisker carpet

Non-resorbable “bottom-up” porous mesh based on Si wires

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Jeff Coffer -TCU - j.cofer@tcu.edu

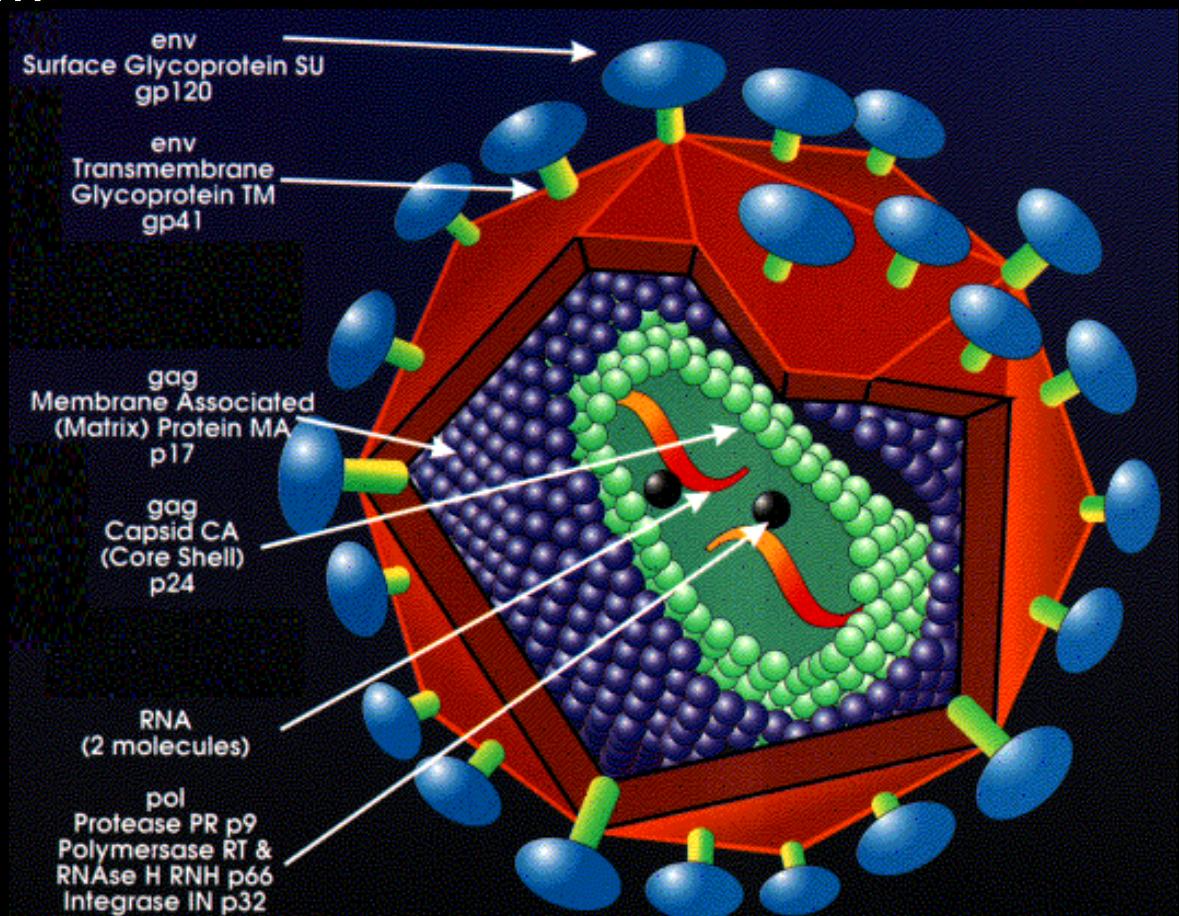
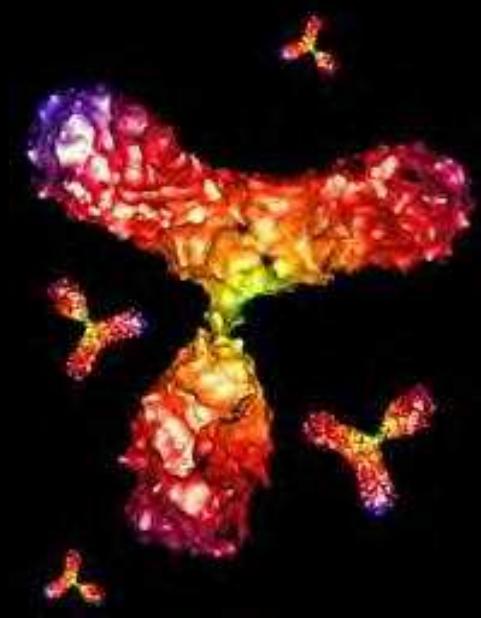
Synthetic Biology . . .

How far will this paradigm go?

Artificial Immune System

Synthetic Antibodies

Bionic Cells



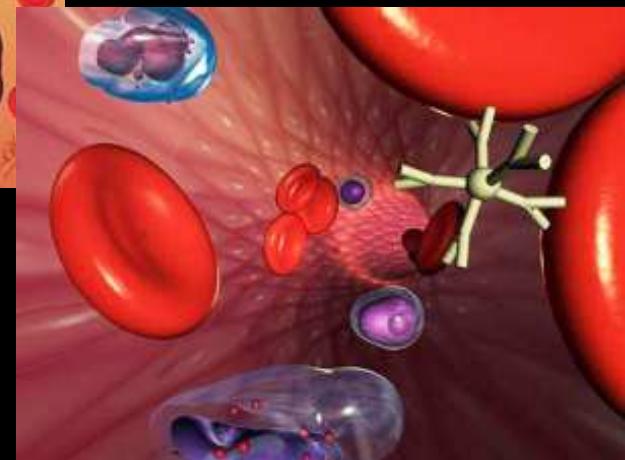
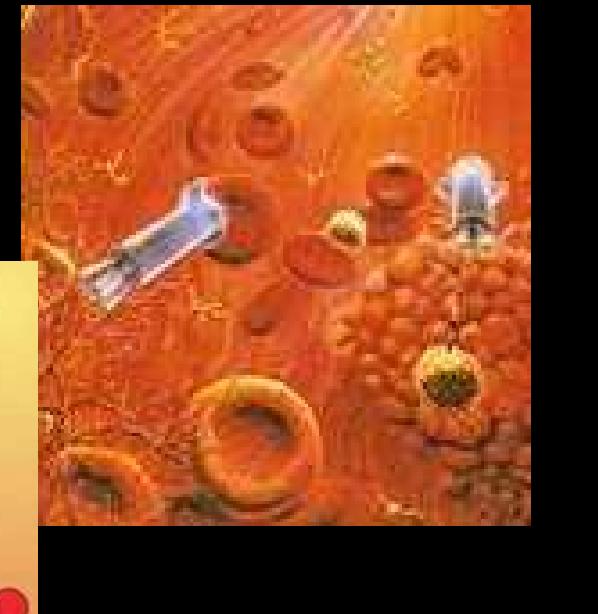
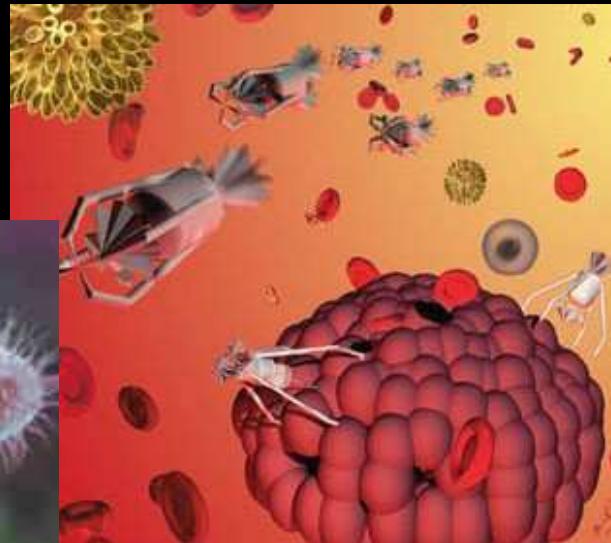
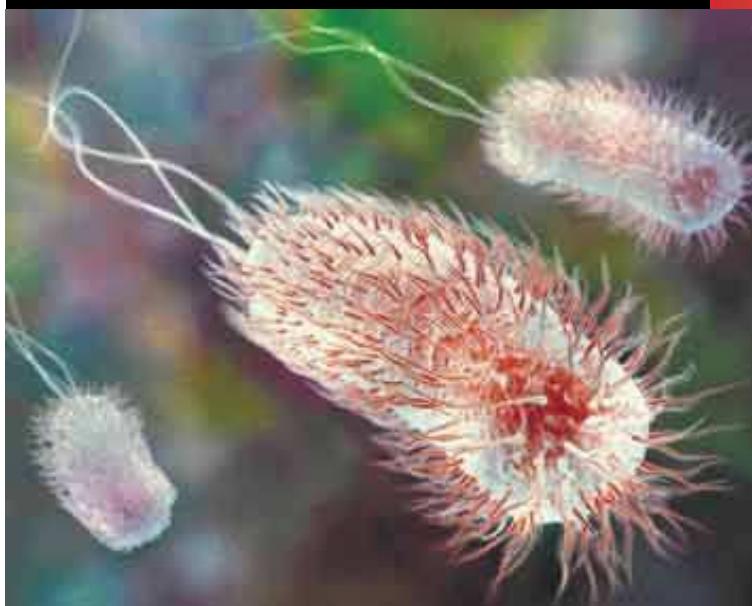
Synthetic Biology . . .

How far will this paradigm go?

Artificial Immune System

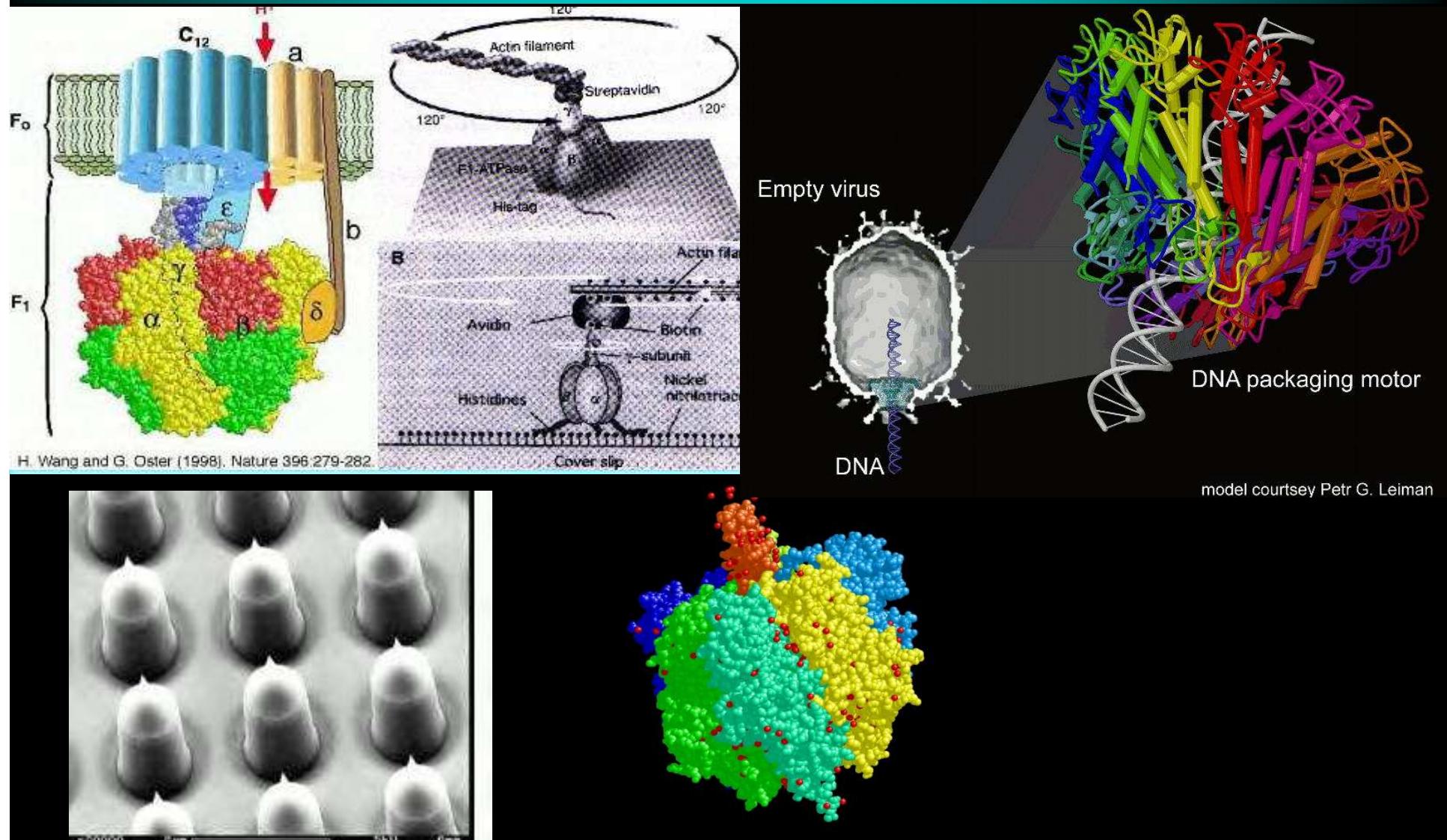
Synthetic Antibodies

Bionic Cells



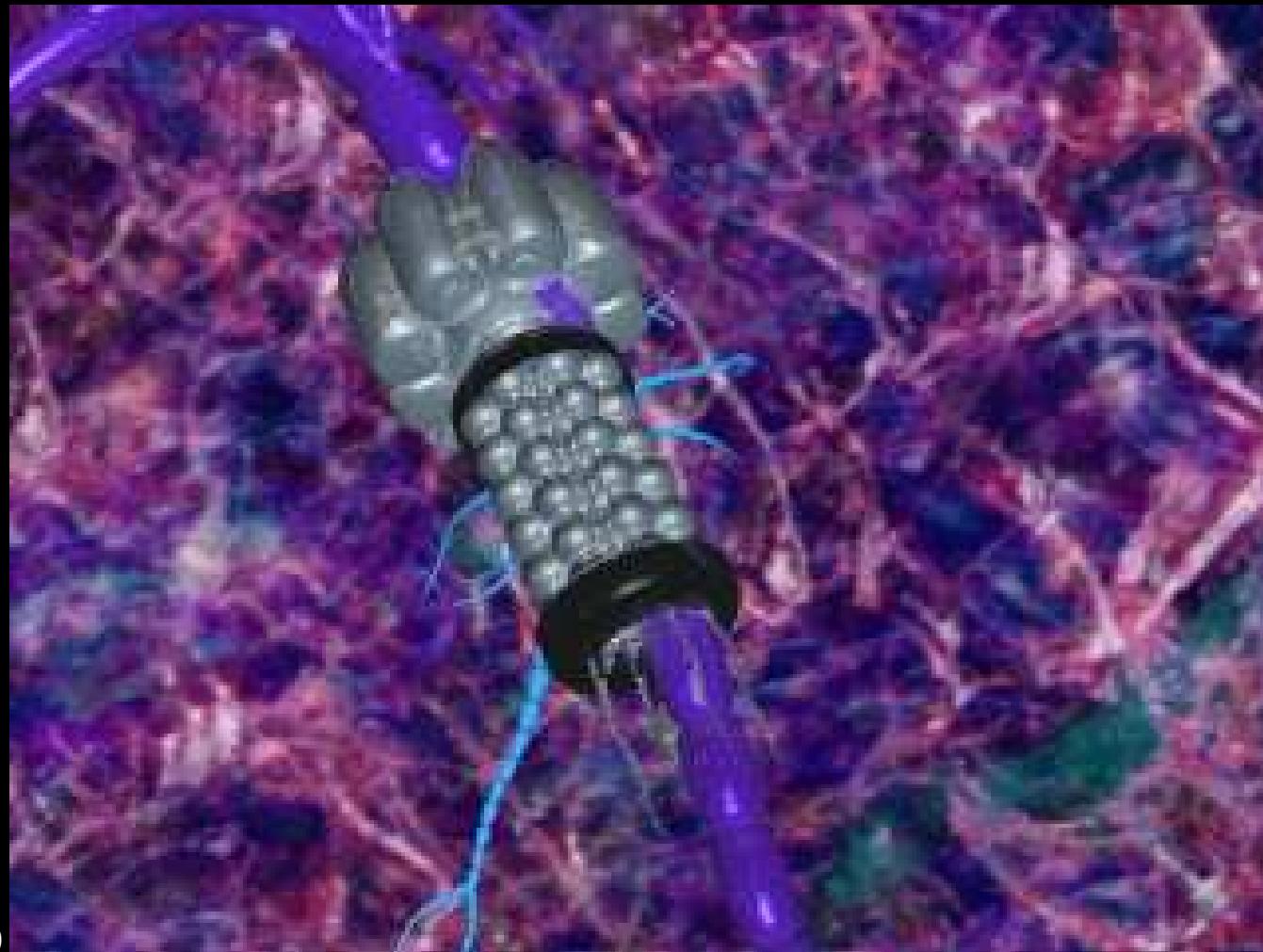
Synthetic Biology . . .

How far will this paradigm go?



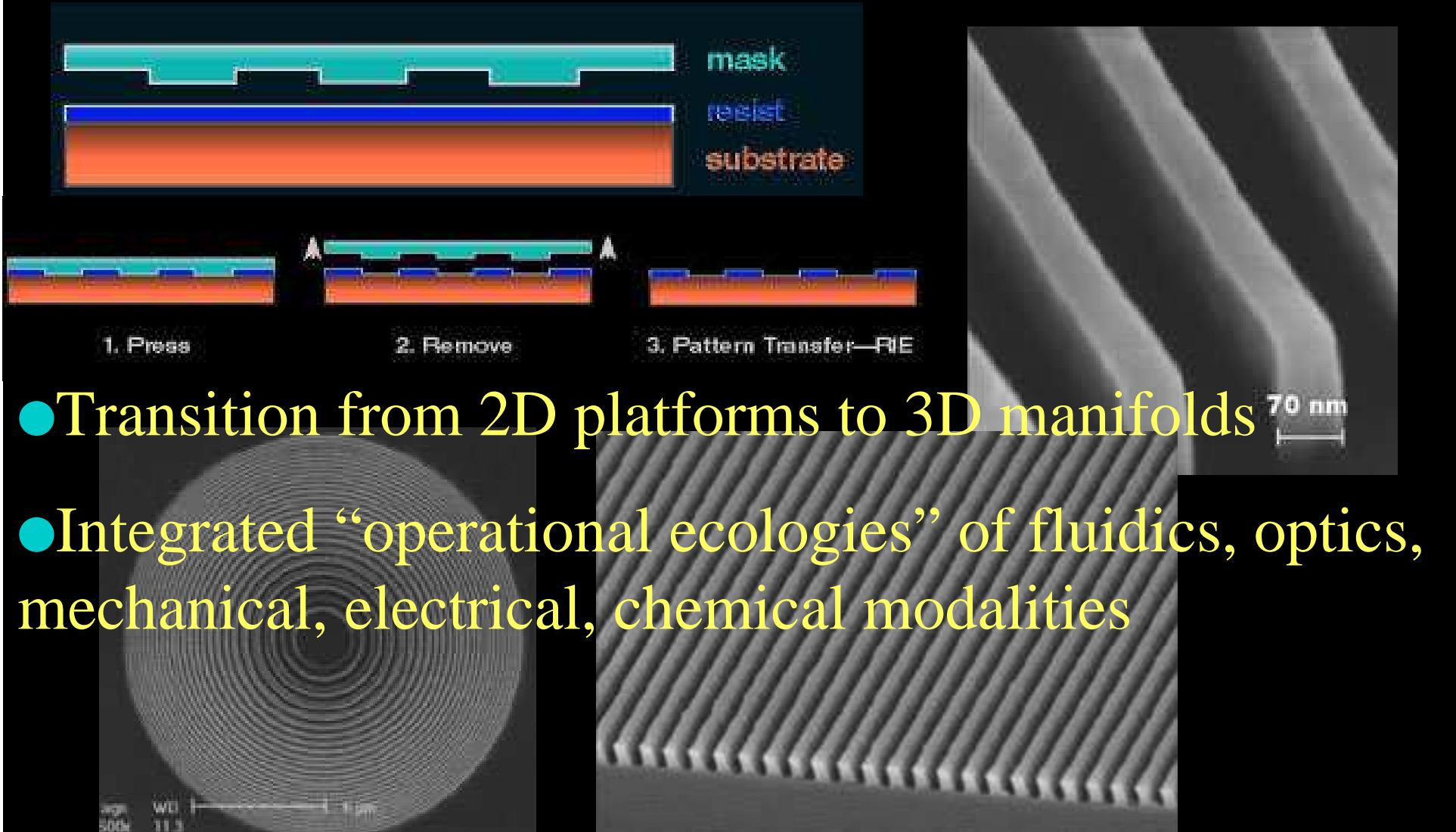
Synthetic Biology . . .

How far will this paradigm go?



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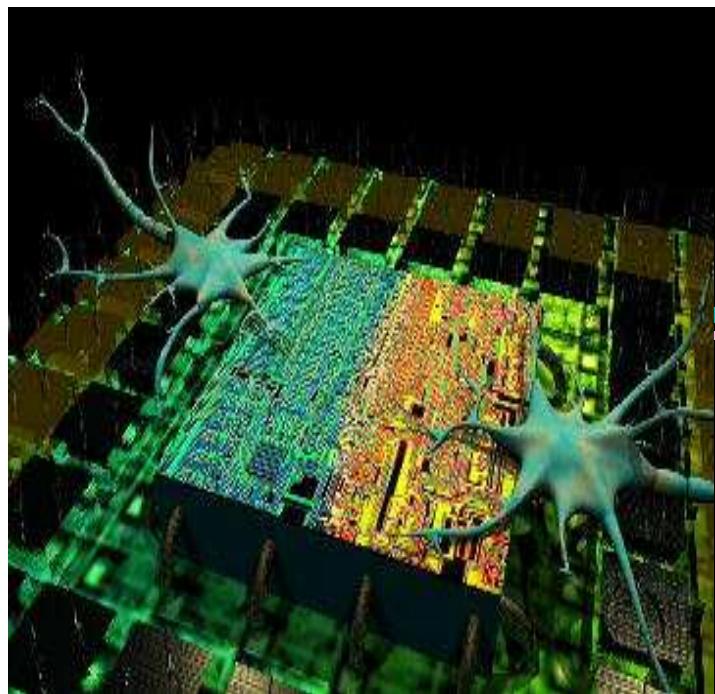
Synergistically Enabling Foundry Processes in Photonics, Electronics, Fluidics – NanoImprinting



- Transition from 2D platforms to 3D manifolds
- Integrated “operational ecologies” of fluidics, optics, mechanical, electrical, chemical modalities

Biopathogen Detection – Live Cells as Sensors





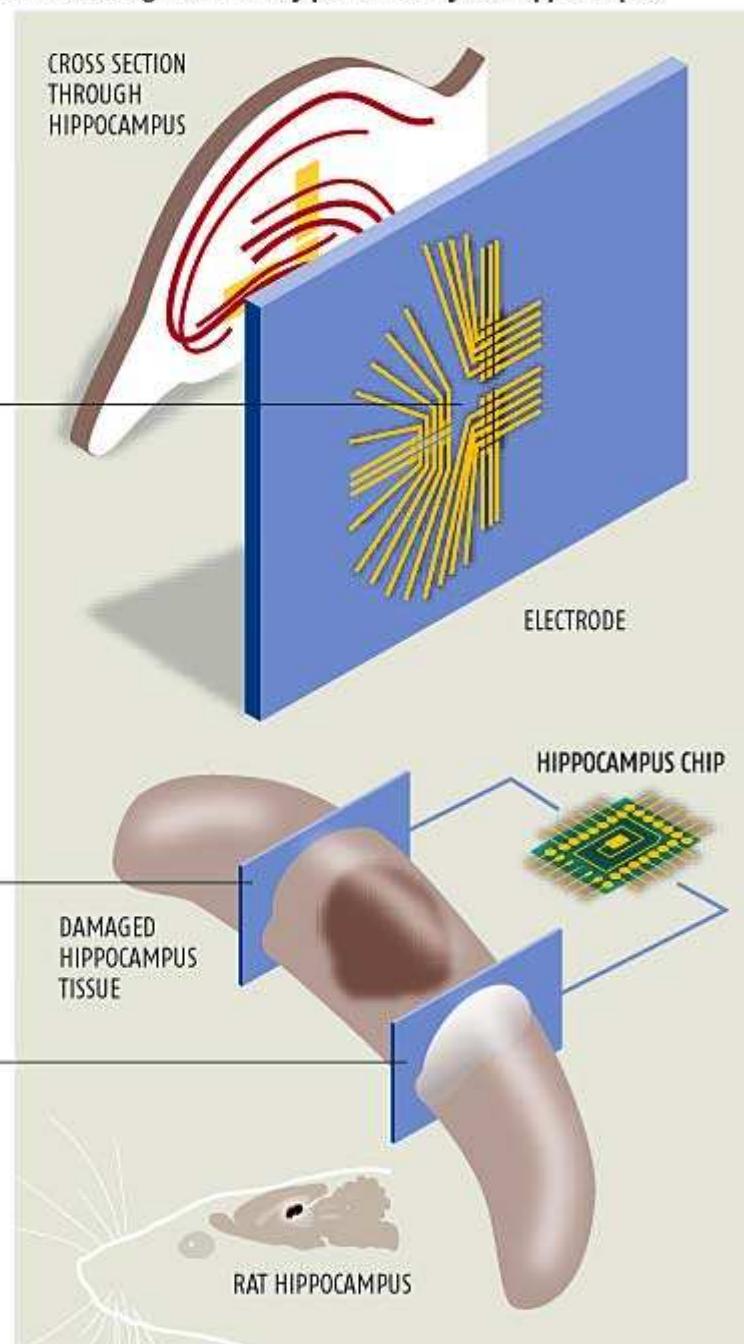
HIPPOCAMPUS REPLACEMENT

Chip takes over the processing of nervous signals normally performed by the hippocampus

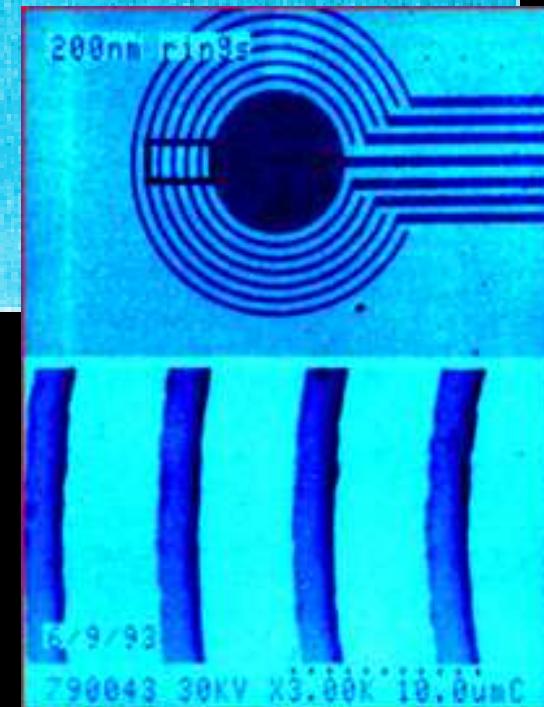
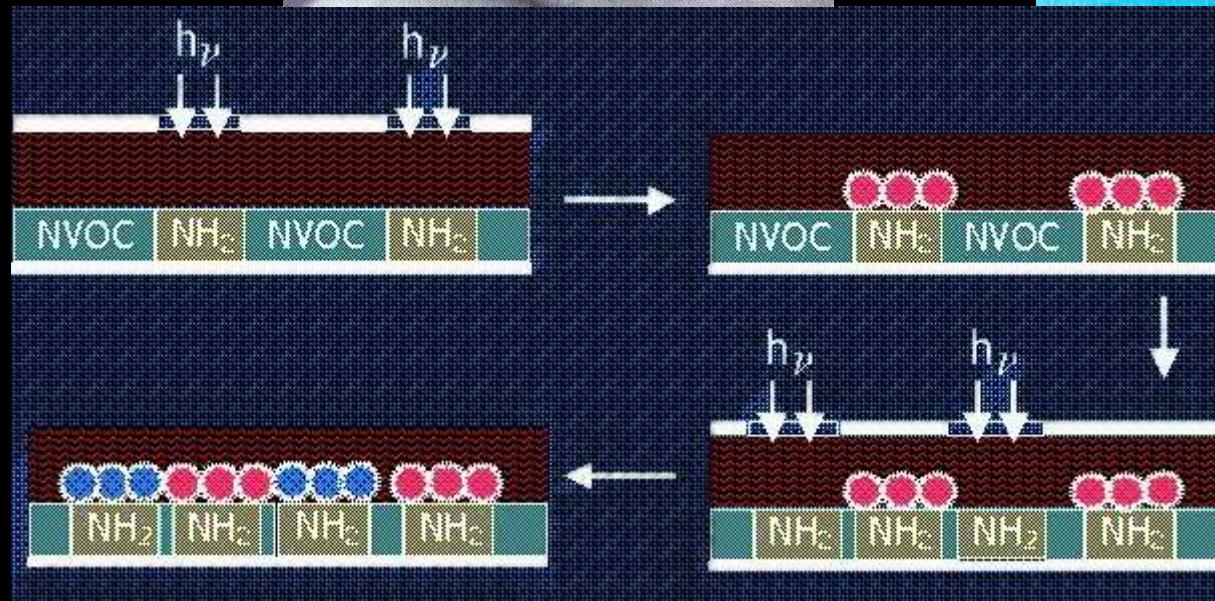
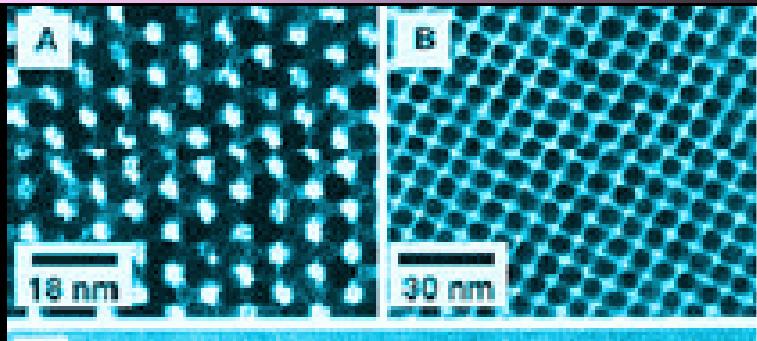
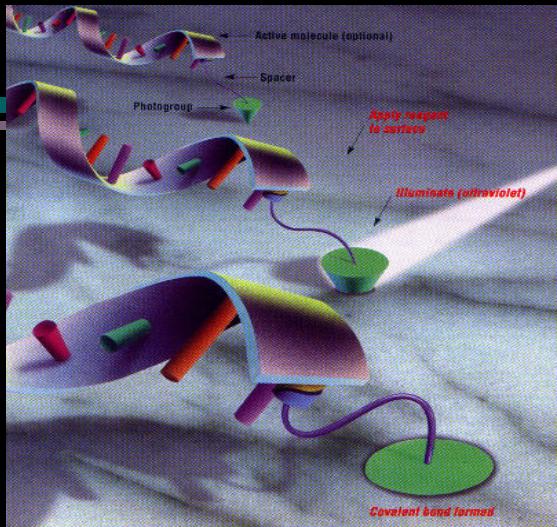
Multiple electrodes are placed on each array. They are positioned to mimic the structure of nerve tissue within a slice of the hippocampus, and make contact with other parts of the brain

Recording electrode array "listens" to neuron activity coming into the hippocampus and feeds it to the chip

Stimulating electrode array delivers the appropriate electrical output to the rest of the brain



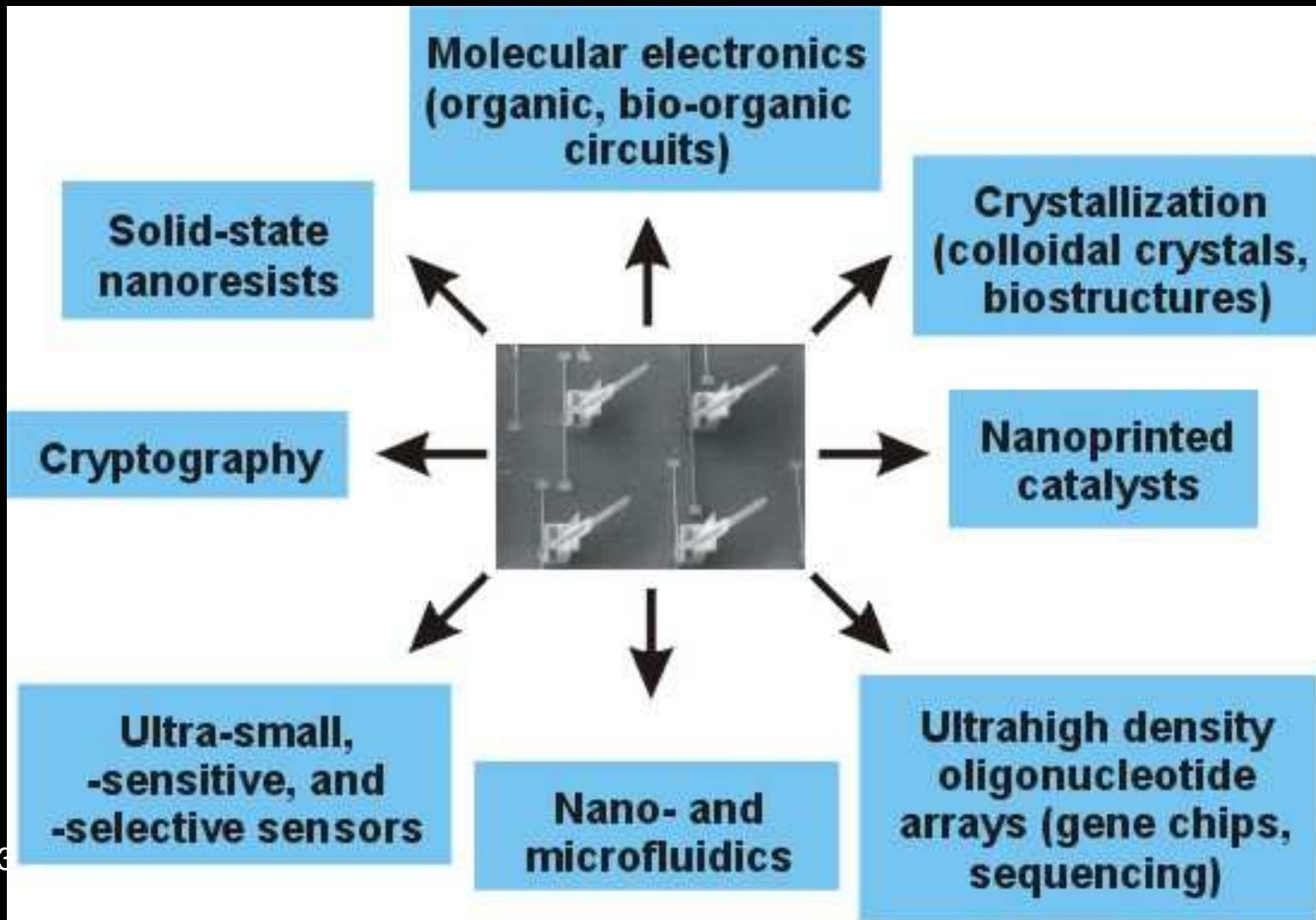
Biolithography – Directed Biochemical Assembly



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Value Proposition is in Synergistic Opportunity

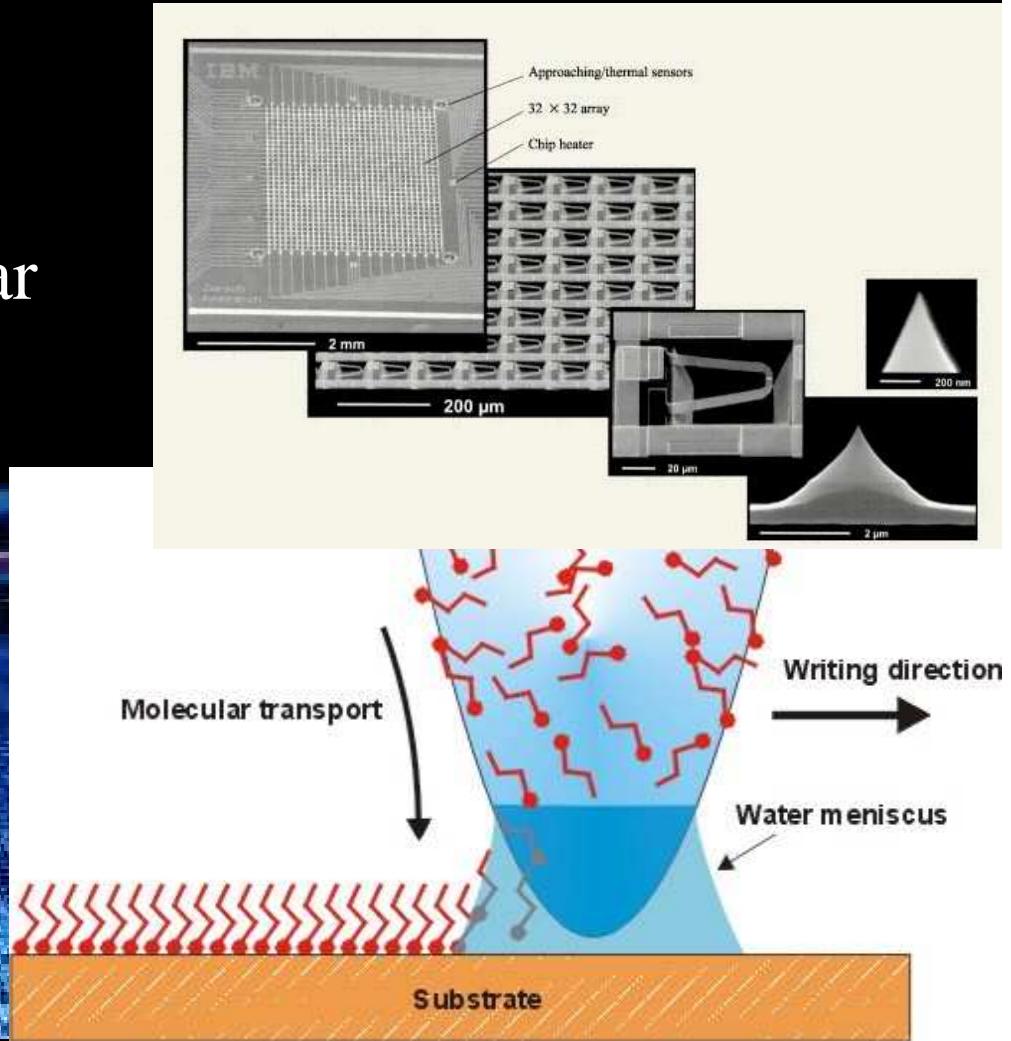
Example - AFM arrays



Value Proposition is in Synergistic Opportunity

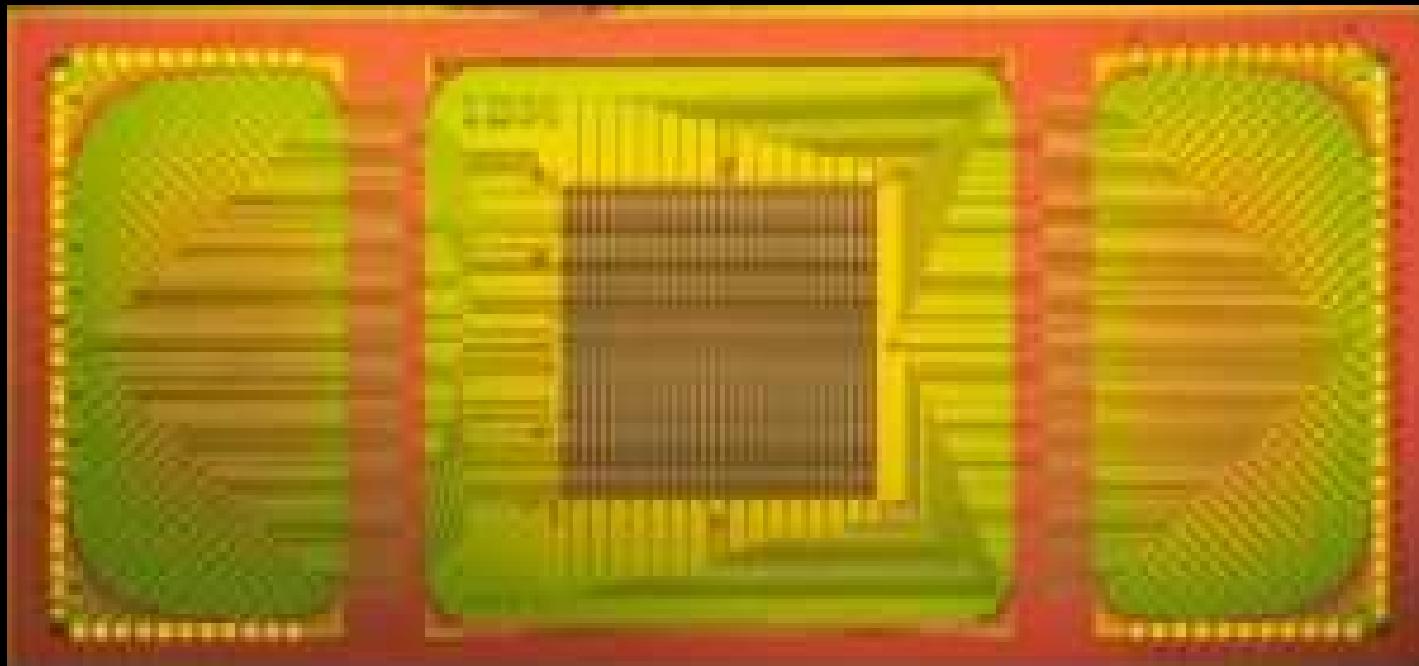
Example - AFM arrays

- Enabling platform for data storage
- Massively parallel molecular deposition



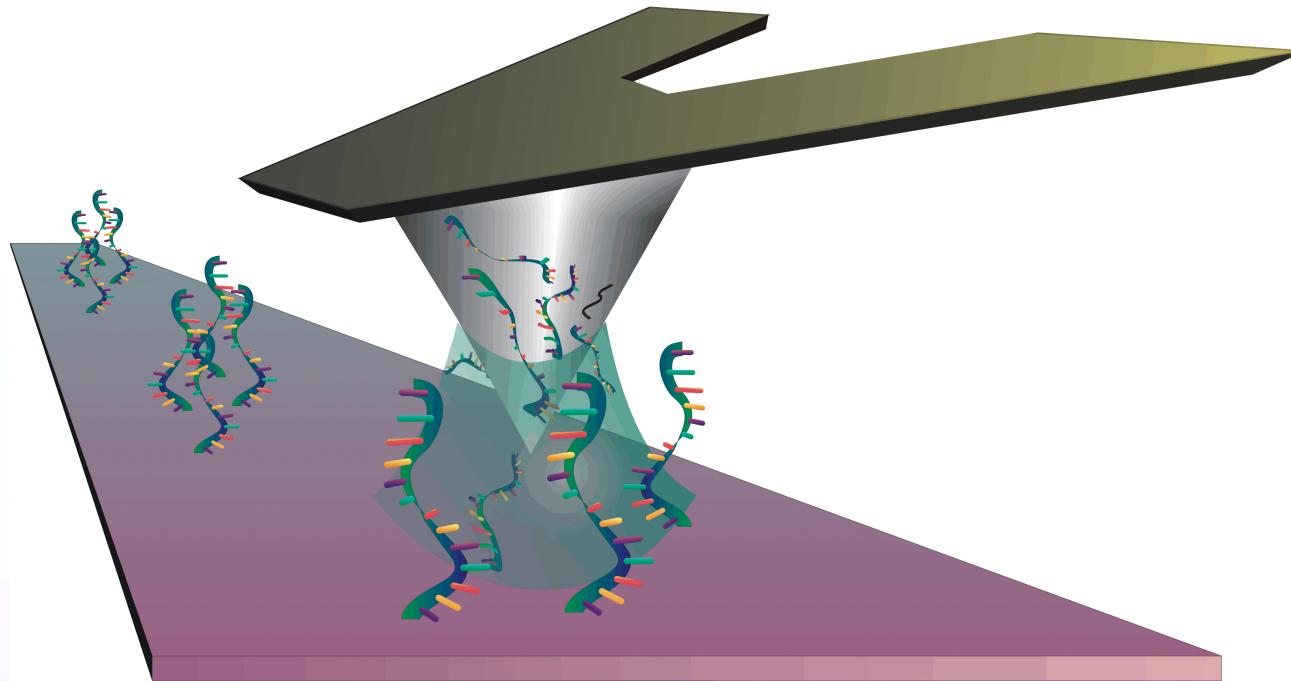
Value Proposition is in Synergistic Opportunity

Example - AFM arrays



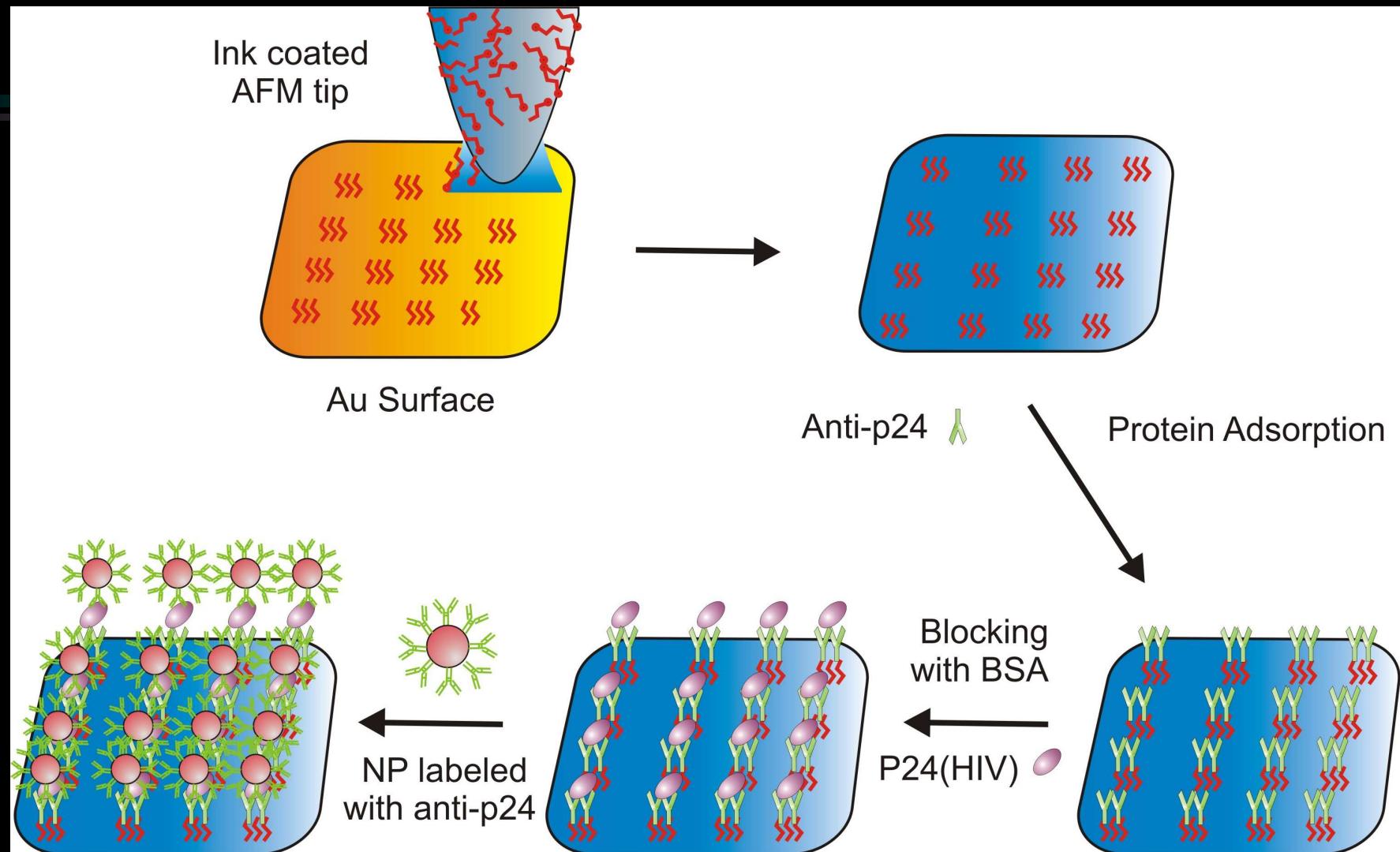
The Millipede chip: showing
electrical wiring for 1,024 tips
etched out in a 3x3mm square.

Biomolecular Nanoarrays via Direct-Write DPN



- More than just miniaturization with higher density
- New opportunities for biodetection and studying biorecognition
- Small sample volumes required
- Higher sensitivity
- New readout capabilities (eg. probeless detection)

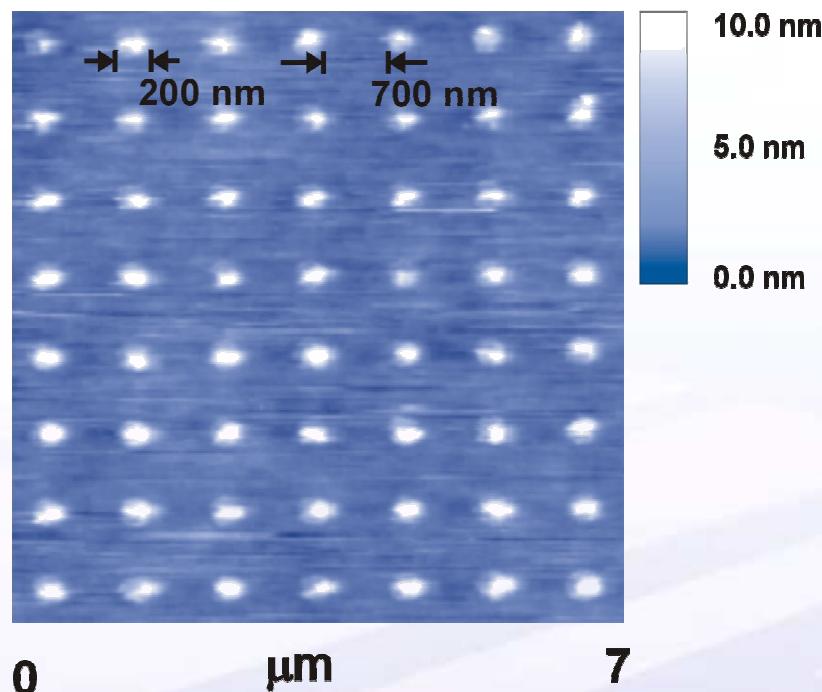
Nanoarrays for Antigen-Based Detection of HIV



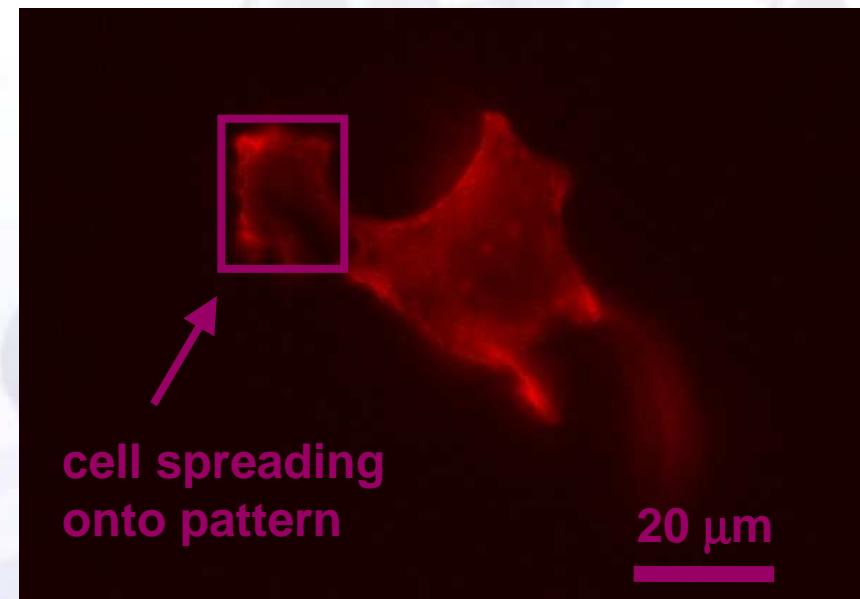
3/26/2010

Protein Nanoarrays for Cell Adhesion Studies

DPN arrays of Retronectin
(AFM topography)



Fluorescence Micrograph of Cell Spreading onto DPN Pattern



with J. C. Smith and M. Mrksich at U. of Chicago

Lee, K.-B. *Science* 295, 1702 (2002).

NANOINKTM INC. | get small™

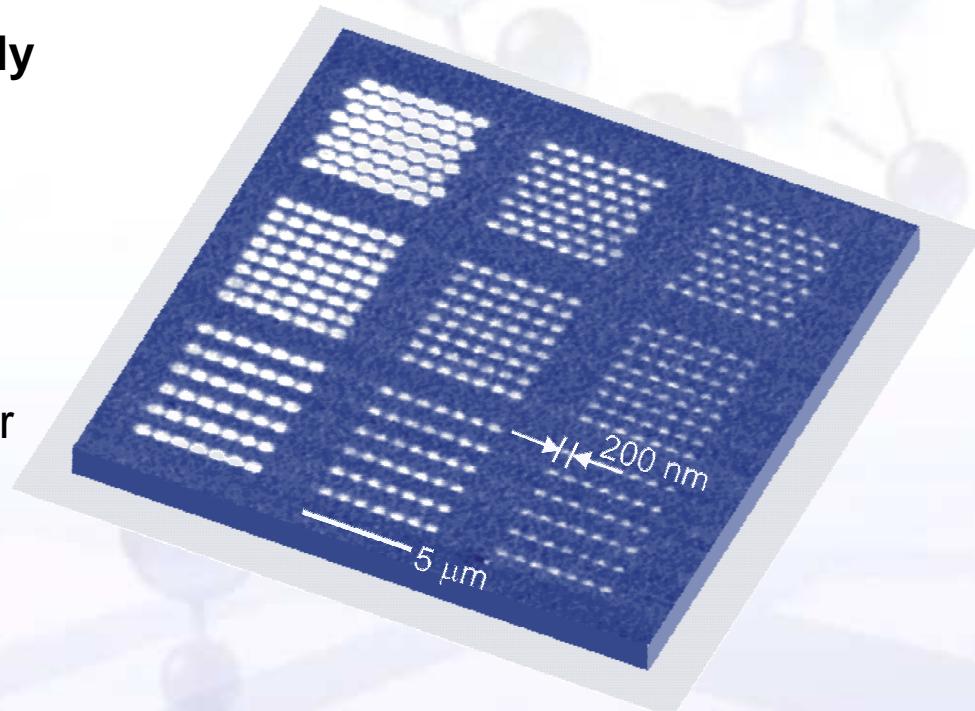
Combinatorial DPN

DPN enables one to systematically vary lattice parameters...

- Composition
- Spacing
- Dot size
- Orientation

Applications...

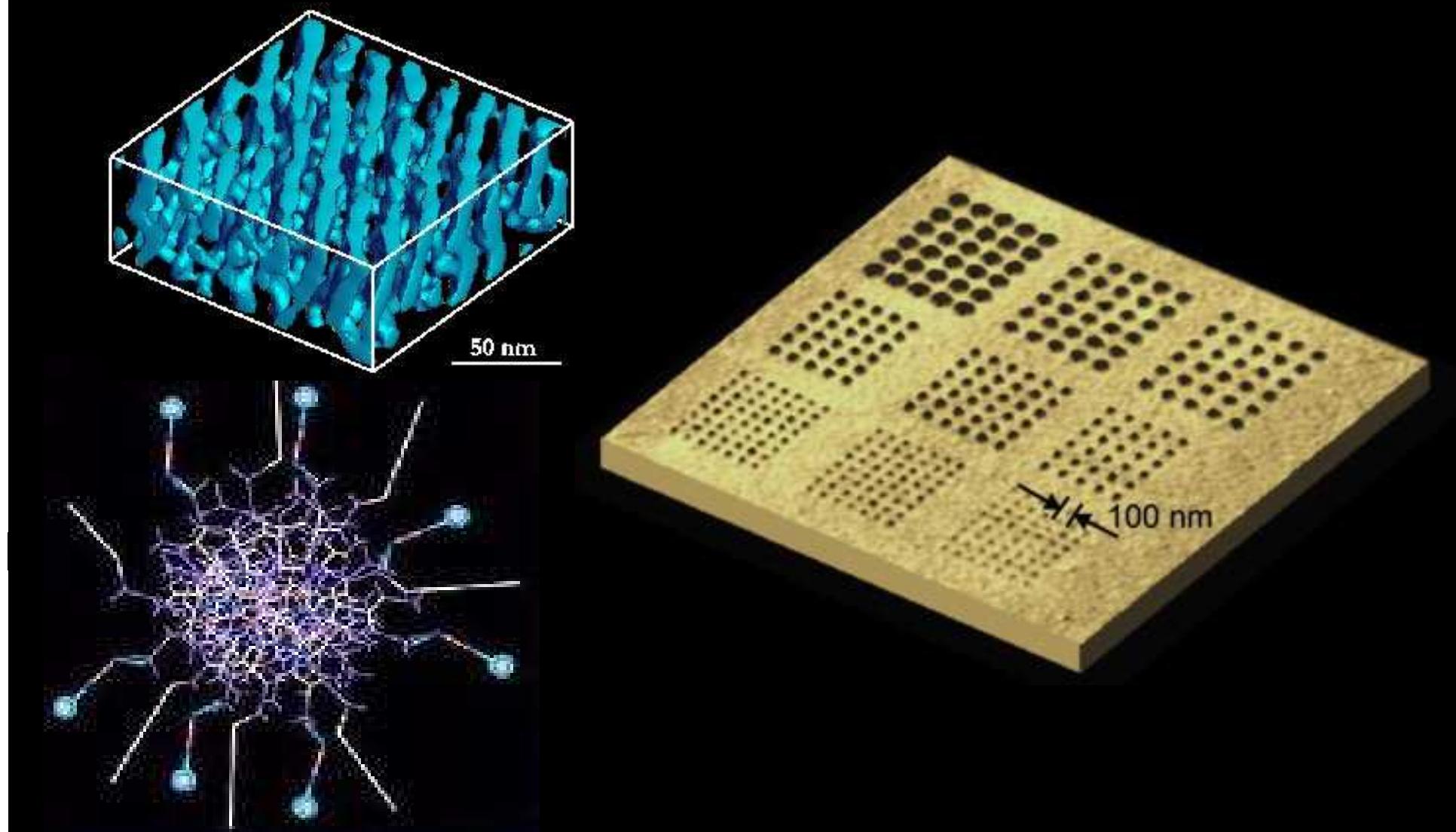
- Magnetic, metallic, and polymer nanoparticle assembly
- Colloidal crystallization
- Catalysis
- Cell adhesion studies
- Photonic materials
- Combinatorial synthesis of materials and biomolecules (DNA, peptides)



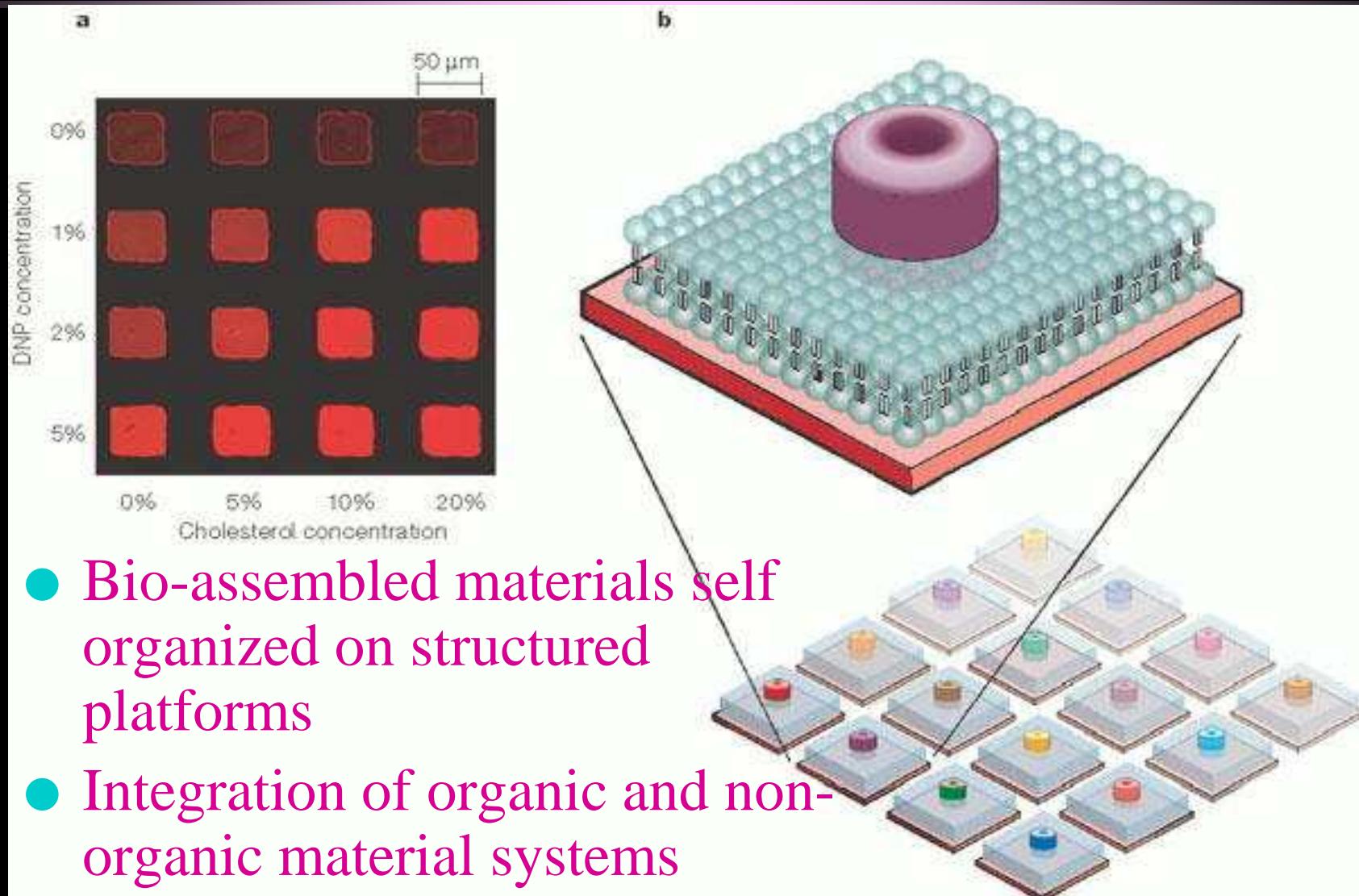
LFM Image of DPN-generated template on Au of 16-mercaptophexadecanoic acid for assembly of (+)charged particles

Demers, L. M. et al *Angew. Chem.* 40, 3069 (2001).

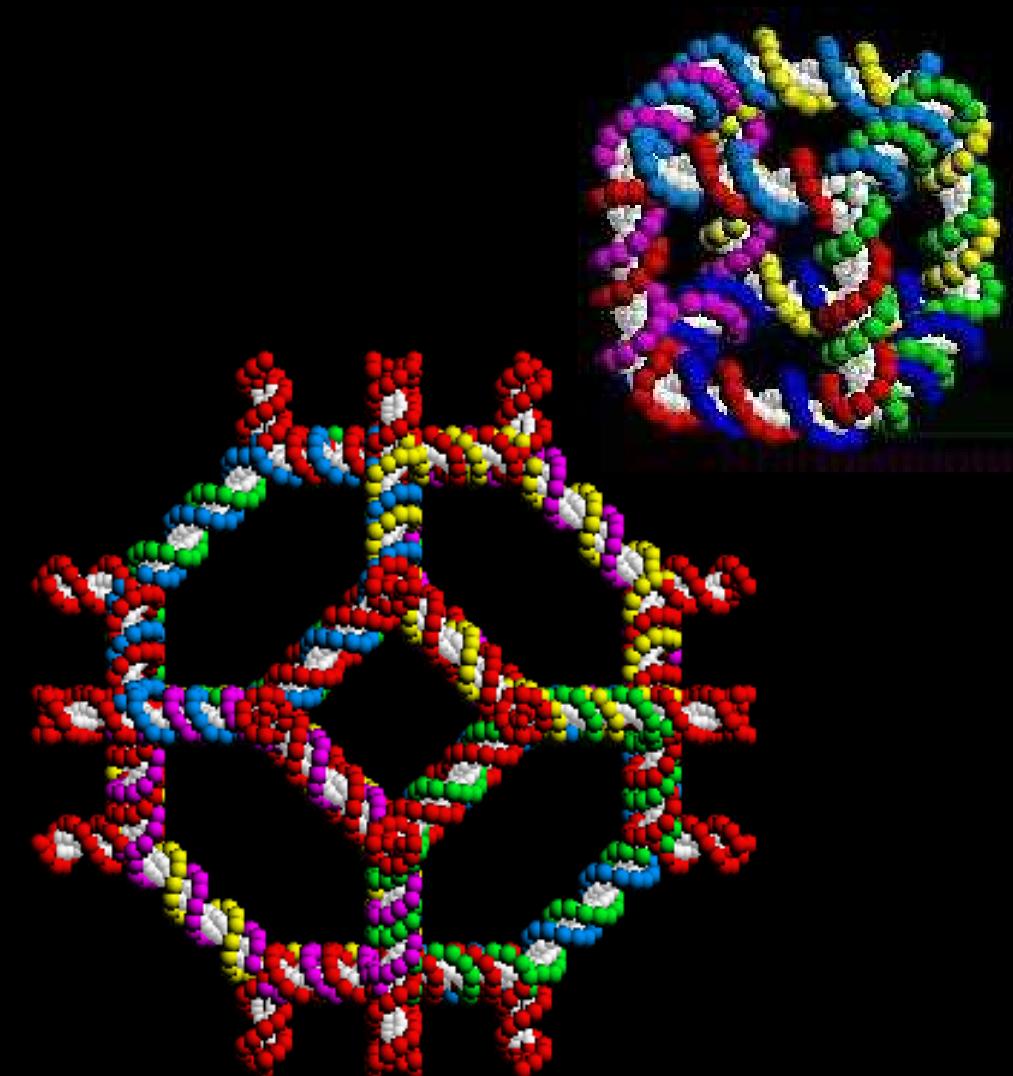
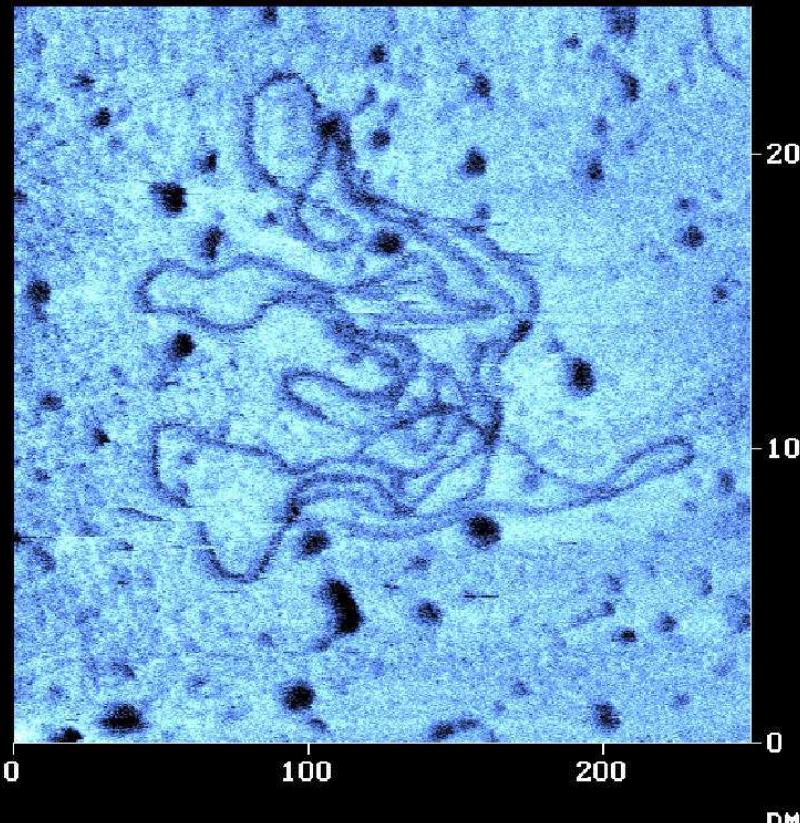
Diversity of Tools – Integration of “traditional” and biologically enabled or inspired processes and materials



Integrated Biofoundry Processes

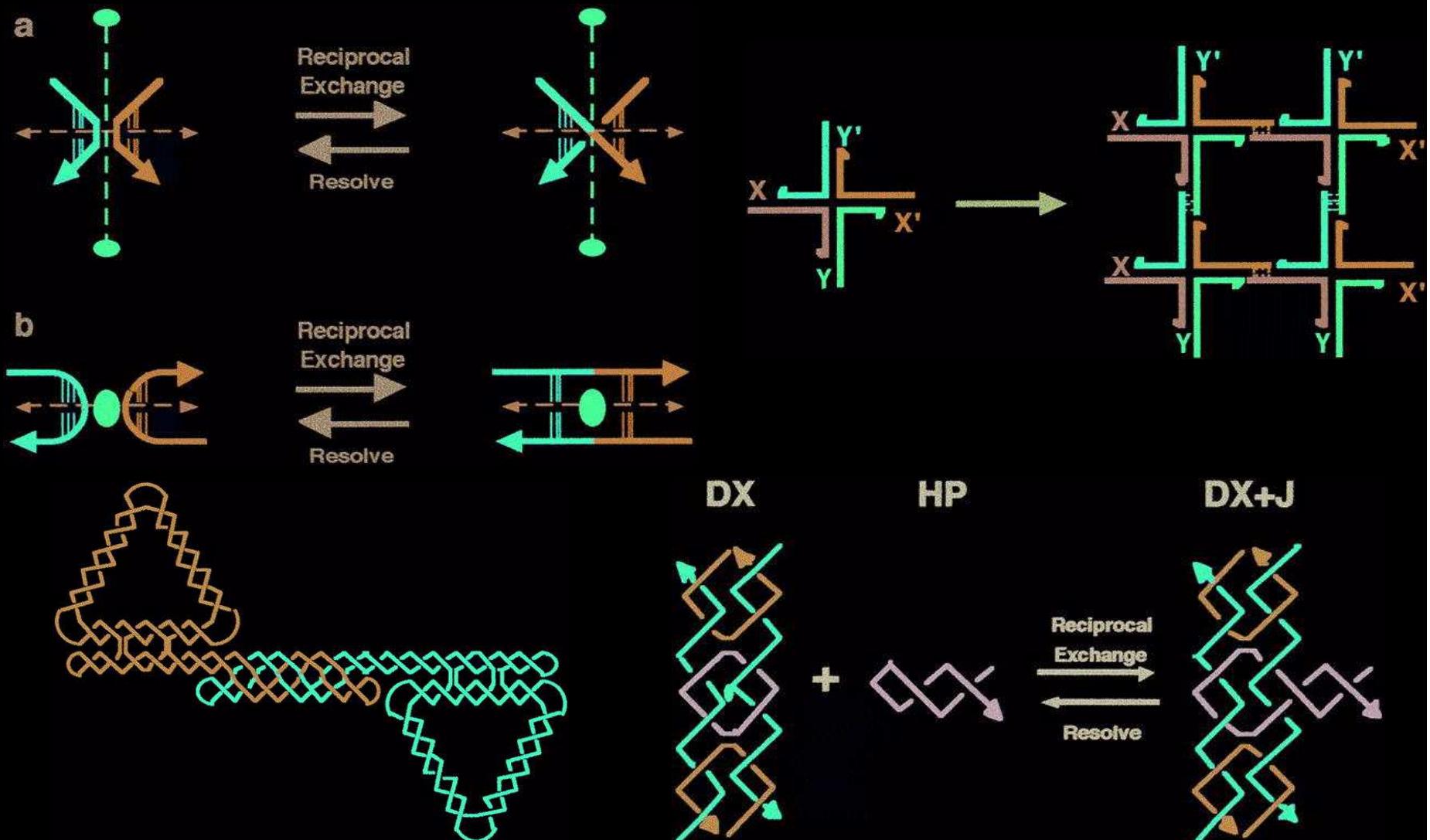


Structural Proteomics - Proteomic Assembly

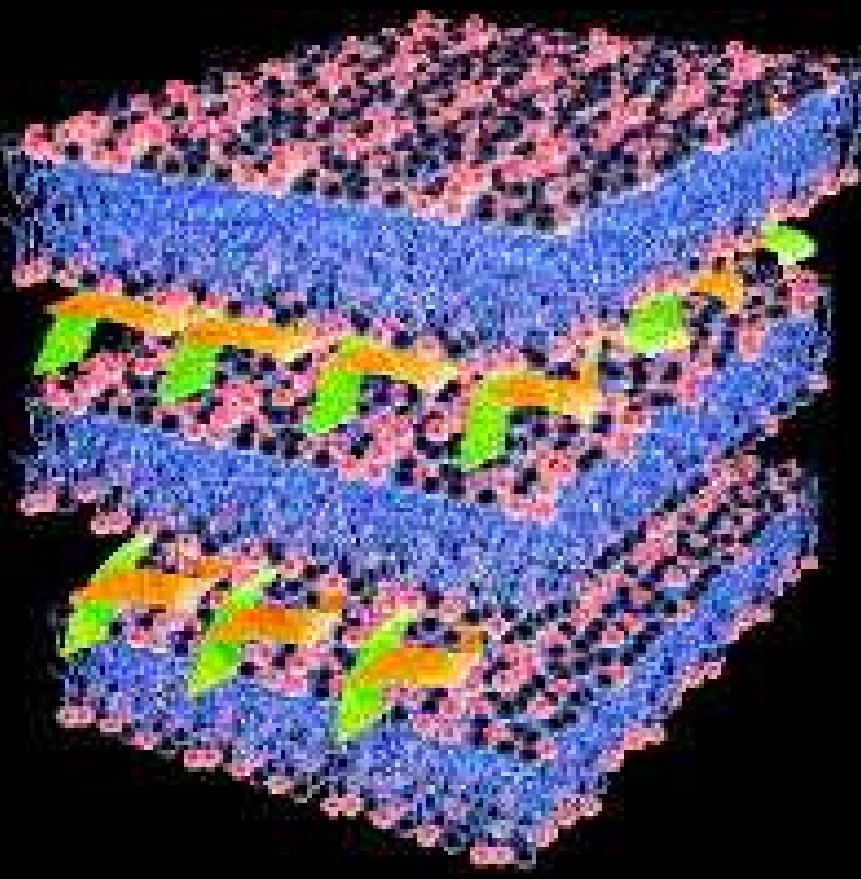
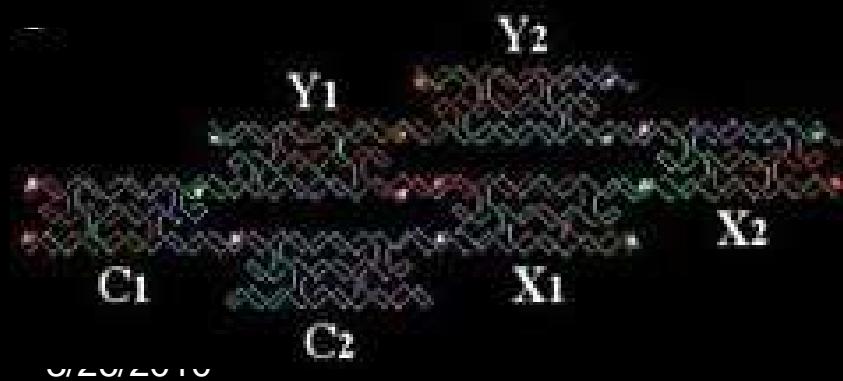


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Structural Proteomics - Proteomic Assembly

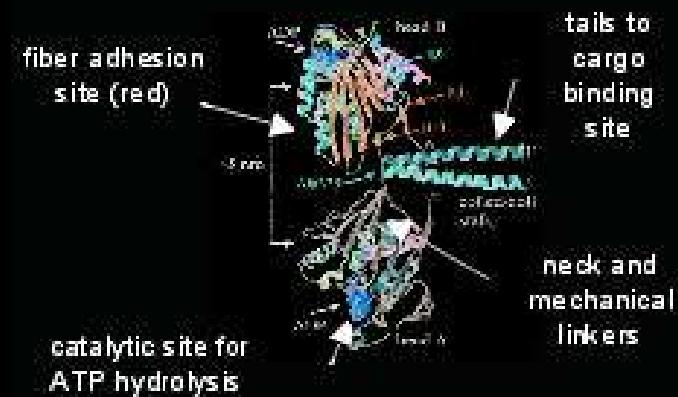


Structural Proteomics - Proteomic Assembly

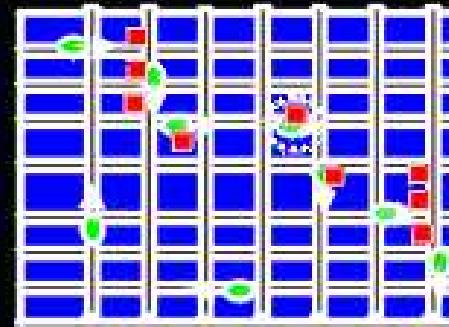


Structural Proteomics - Proteomic Assembly

Modify Proteins



Assemble Fiber Networks



Monitor Protein Function



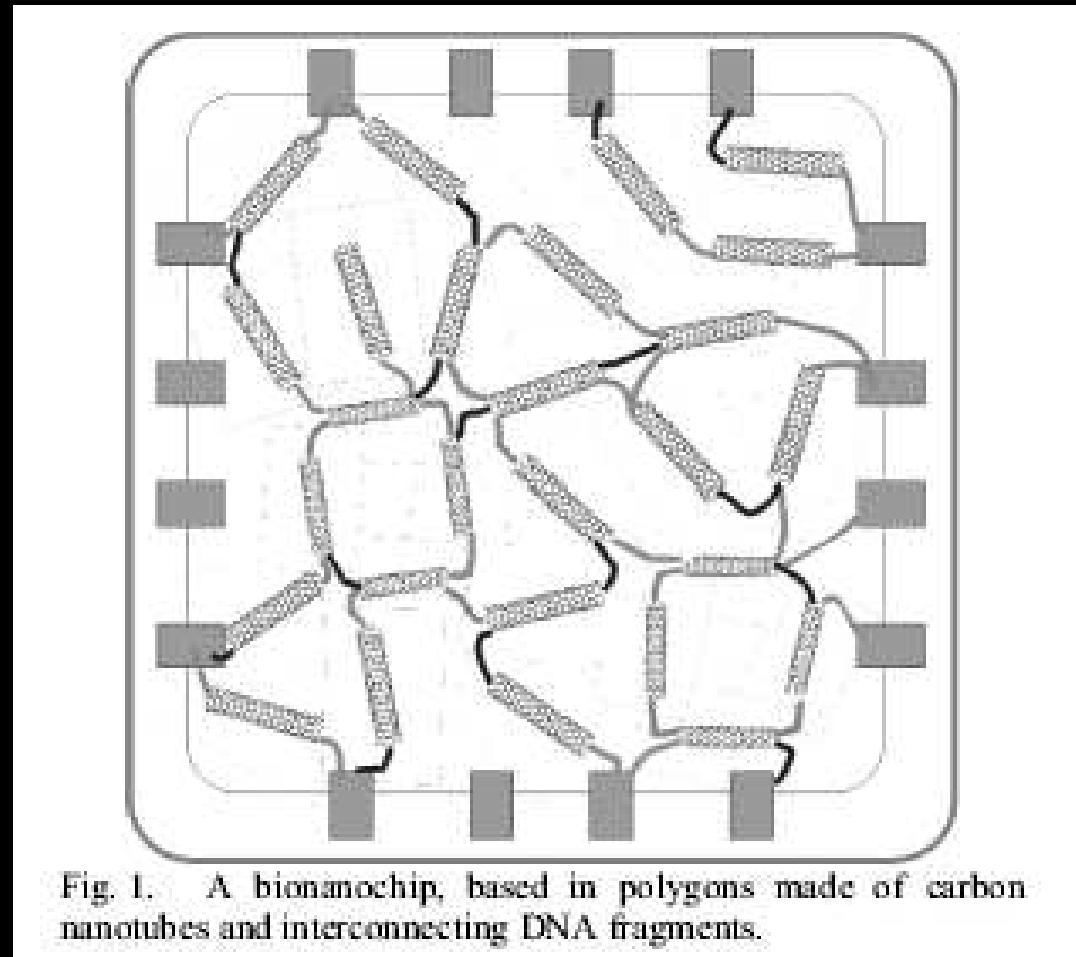
Activate Proteins



Combinatorial / Synergistically Inter-relatable Process Modalities

- Self-assembled DNA / carbon nanotube “nanobiotronic” devices

**U of South Carolina -
Seminario, Agapito,
Figueroa**



Process Dynamics of the Evolutionary Eventstream

Designed Evolution Restoration & Healing Augmentation



Present

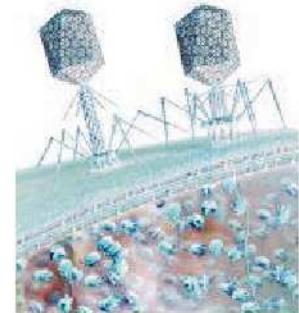
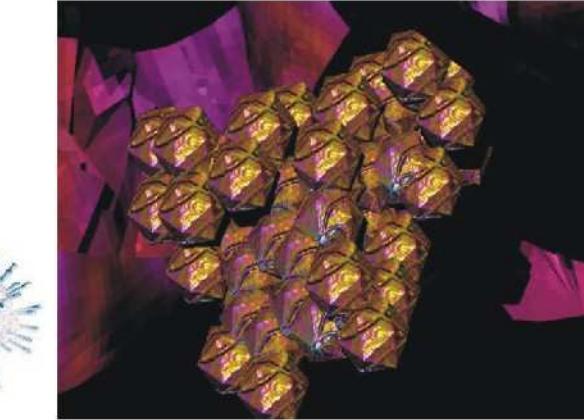
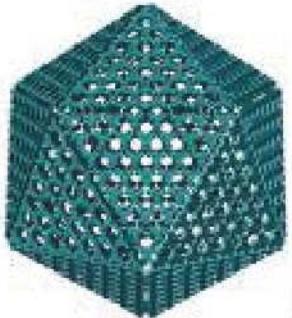
Transition

Future

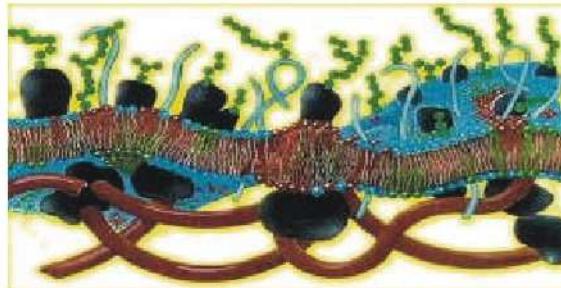
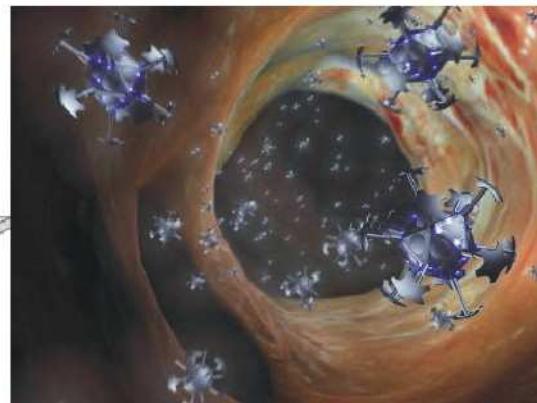
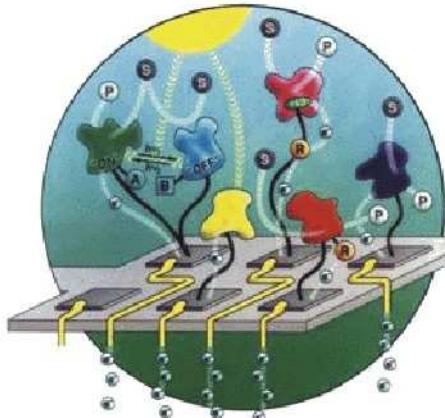
Augmentation

Cognition Enhancement
Physical Enhancement

Parallel Processing Capacity
Complexity Management
Extended Life Productivity

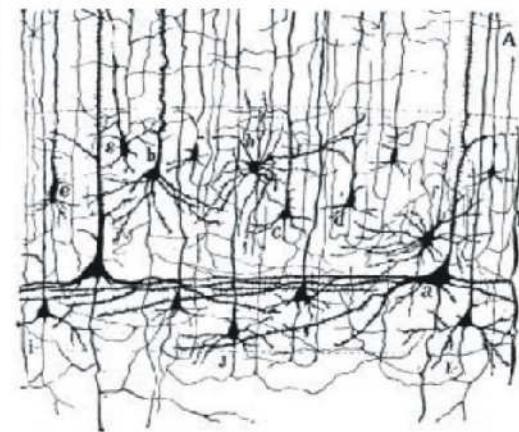
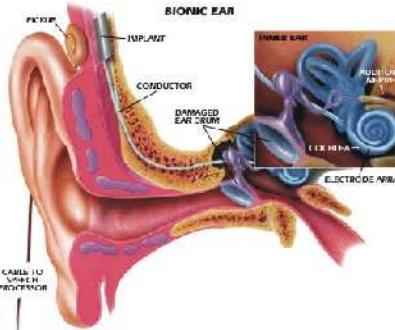
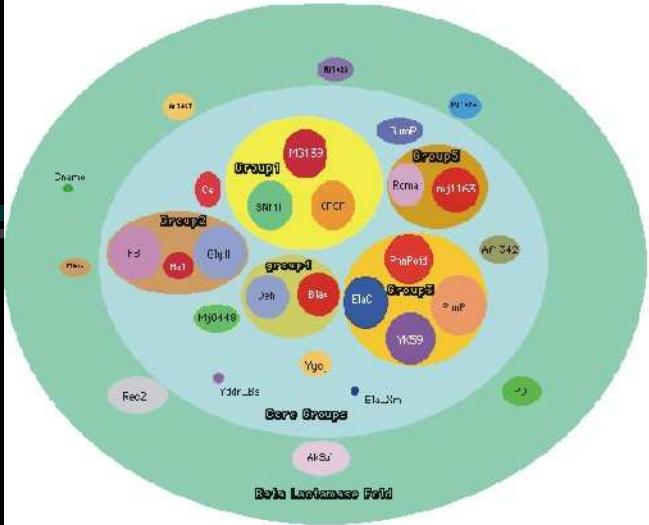


Scenario:
Synthetic Nano-Organisms
Xenomorphic Hunter/Killer Biobots
Hypervirulent Proteomic Targeting



Response:

"Smart" nano-defensive skin /
molecular neutralization
Synthetic immune system "patrol nanites"
Nano-bio sensor implants

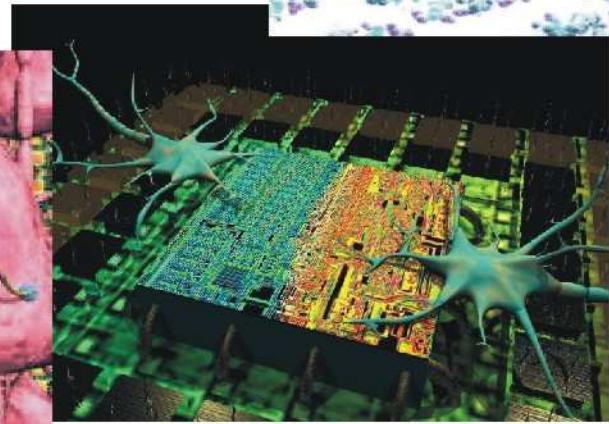
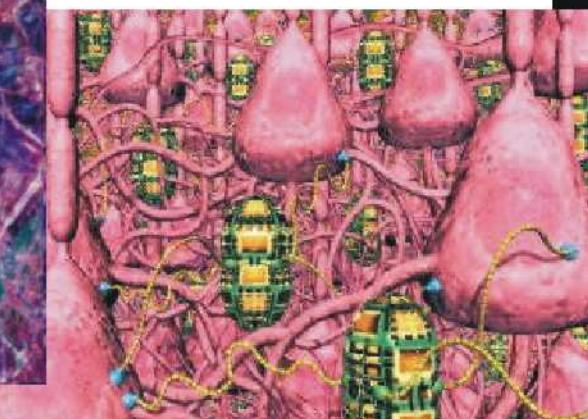
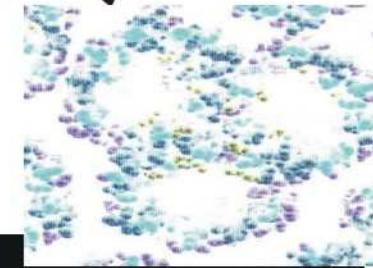


Scenario:

Extended sensory capacities
Extreme "hardened" endurance
Enhanced performance

Solution:

Nano-enhanced tissue
"Smart" healing nano devices
Biochip / integrated implants
Neuro-prosthetics



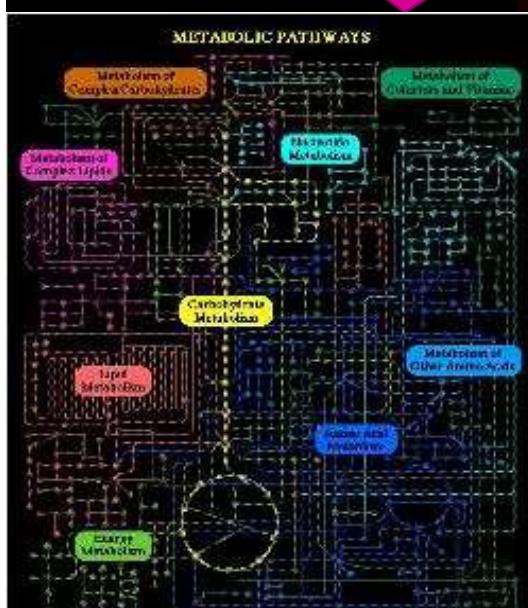
Infotech / Biotech / Nanotech Convergence

Think Different > Think Holographic

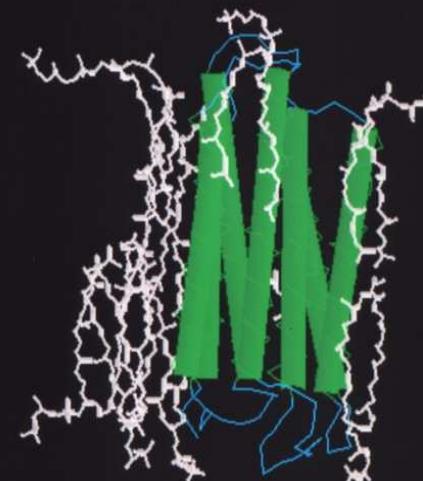
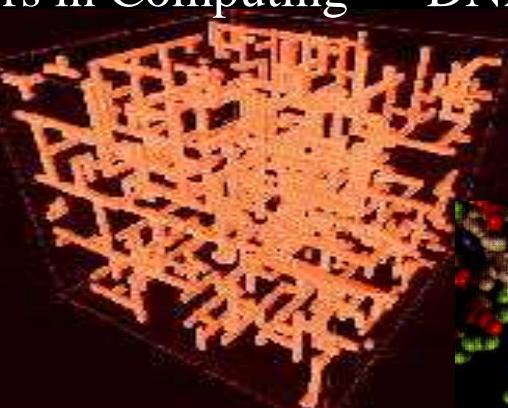
Biological Metaphors in Computing

Bioinfomatics

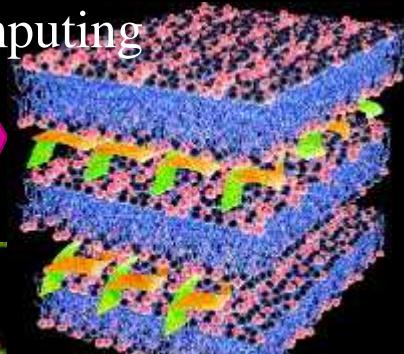
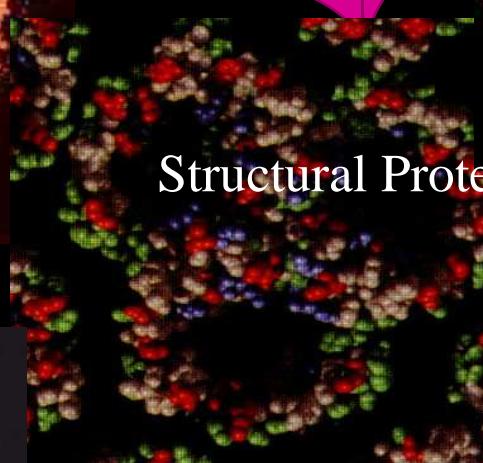
In Silico Biology



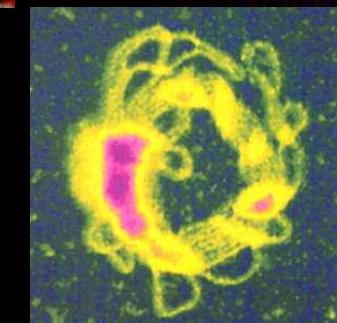
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DNA / Proteomic Computing



Structural Proteomics



Genetic / BioMed Proteomics

Nano Electronics & Photonics Forum

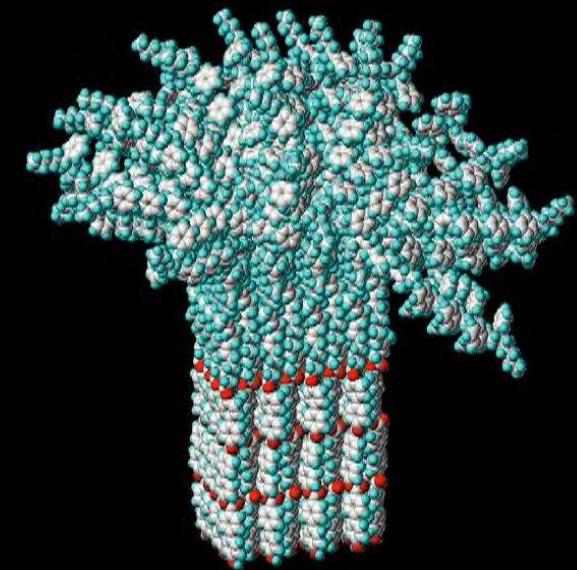


Nano Electronics
& Photonics Forum

Conference Oct 26, 2004, Palo Alto

www.NanoSIG.org/nanoelectronics.htm

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