PI: **XIONG, MOMIAO**	Title: Combined Image and Biomarker Approach to Early Detection of Pancreatic Cancer	
Received: 07/10/2014	FOA: PAR13-189	Council: 01/2015
Competition ID: FORMS-C	FOA Title: IMAGING AND BIOMARKERS FOR EARLY CANCER DETECTION (R01)	
1 R01 CA195601-01	Dual:	Accession Number: 3718569
IPF: 578417	Organization: UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON	
Former Number:	Department: Biostatistics/Human Genetic Ct	
IRG/SRG: ZRG1 SBIB-F (59)R	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 498,352 Year 2: 499,970 Year 3: 486,709 Year 4: 477,183 Year 5: 480,214	Animals: N Humans: Y Clinical Trial: N Current HS Code: 20 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Momiao Xiong PhD	The University of Texas Health Science Center at Houston	PD/PI
Shenying Fang PhD	The University of Texas MD Anderson Cancer Center	Co-Investigator
Donghui Li PhD	The University of Texas MD Anderson Cancer Center	Co-Investigator
Jeffrey Lee MD	The University of Texas MD Anderson Cancer Center	Co-Investigator
Chaan Ng MD	The University of Texas MD Anderson Cancer Center	Co-Investigator
Xiangning Chen	Virginia Commonwealth University	Co-Investigator

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

2. DATE SUBMITTED 2014-07-10

Application Identifier

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION **Organizational DUNS*:** 800771594

Legal Name*: The University of Texas Health Science Center at Houston
Department:
Division:
Street1*: P. O. Box 20036
Street2:
City*: Houston
County: Harris
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 77225-0036

Person to be contacted on matters involving this application

Prefix: First Name*: Krystal Middle Name: Last Name*: Toups Suffix:
Position/Title: Director, Grants
Street1*: P.O. Box 20036
Street2:
City*: Houston
County: Harris
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 77225-0036
Phone Number*: 713-500-3999 Fax Number: 713-383-3746 Email: osp@uth.tmc.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 741761309

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).

❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
93.394
TITLE: Cancer Detection and Diagnosis Research

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Combined Image and Biomarker Approach to Early Detection of Pancreatic Cancer

12. PROPOSED PROJECT

Start Date* Ending Date*
04/01/2015 03/31/2020

13. CONGRESSIONAL DISTRICTS OF APPLICANT
TX-009

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr. First Name*: Momiao Middle Name: Last Name*: Xiong Suffix: PhD

Position/Title: Associate Professor
Organization Name*: The University of Texas Health Science Center at Houston
Department: Biostatistics/Human Genetic Ct
Division: School of Public Health
Street1*: 1200 Herman Pressler Dr., E453
Street2:
City*: Houston
County: Harris
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 77030-3900
Phone Number*: 713-500-9894 Fax Number: 713-500-0900 Email*: Momiao.Xiong@uth.tmc.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$3,860,066.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$3,860,066.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Krystal Middle Name: Last Name*: Toups Suffix:

Position/Title*: Director, Grants
Organization Name*: The University of Texas Health Science Center at Houston
Department: Sponsored Projects
Division:
Street1*: P.O. Box 20036
Street2:
City*: Houston
County: Harris
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 77225-0036
Phone Number*: 713-500-3999 Fax Number: 713-383-3746 Email*: osp@uth.tmc.edu

Signature of Authorized Representative*
Krystal Toups

Date Signed*
07/10/2014

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	The University of Texas Health Science Center at Houston
Duns Number:	800771594
Street1*:	P. O. Box 20036
Street2:	
City*:	Houston
County:	Harris
State*:	TX: Texas
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	77225-0036
Project/Performance Site Congressional District*:	TX-009

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	The University of Texas MD Anderson Cancer Center
DUNS Number:	800772139
Street1*:	1515 Holcombe Boulevard
Street2:	
City*:	Houston
County:	
State*:	TX: Texas
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	77030-4009
Project/Performance Site Congressional District*:	TX-009

Project/Performance Site Location 2

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Virginia Commonwealth University
DUNS Number:	105300446
Street1*:	914 West Franklin Street
Street2:	
City*:	Richmond
County:	
State*:	VA: Virginia
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	23284-3076

Funding Opportunity Number: PAR-13-189. Received Date: 2014-07-10T13:14:47.000-04:00

Project/Performance Site Congressional District*: VA-003

File Name

Additional Location(s)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ❍ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ● **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number FWA-0667

2. Are Vertebrate Animals Used?* ❍ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Abstract1014652922.pdf
8. Project Narrative*	Project_Narrative1014652923.pdf
9. Bibliography & References Cited	Bibliography1014652930.pdf
10.Facilities & Other Resources	Facilities_Resources1014652953.pdf
11.Equipment	Facilities_Resources_Equipment1014652925.pdf

Funding Opportunity Number: PAR-13-189. Received Date: 2014-07-10T13:14:47.000-04:00

Title : Combined Image and biomarker approach to early detection of the pancreatic cancer

Abstract

Ductal adenocarcinoma of the pancreas (pancreatic cancer, PC) is ranked as the 10th most common cause of cancer, and the fourth most common cause of cancer death in the United States. The estimated number of new PC cases in 2014 is 46,420 (23,530 men and 22,890 women), with 39,590 (20,170 men and 19,420 women) deaths. Despite the steady decline in the death rate of many cancers in the US over the past 2 decades, the death rate of pancreatic cancer is actually rising, due in part to the limited strategies available for successful screening, early detection and prevention of PC. At diagnosis more than 80% of PC patients have advanced, unresectable disease for which the only option is palliative systemic therapy. As a result, the five year survival rate of PC remains below 6%. Early detection of PC is essential component of strategies to improve the outcome of patients with PC. Despite of decades of research, diagnostic methods applied for early detection of PC, even in high-risk populations (e.g., patients with intraductal papillary mucinous neoplasia, IPMN),remain relatively crude and based primarily on imaging criteria (size of cysts and similar factors) and results of invasive testing. The overall objective of this application is to address these significant challenges through the development of a framework for integration of raw imaging and blood-based biomarker data derived from miRNA-seq and methylation-seq to develop a low cost, convenient, readily available informational and assay system for early detection of PC with high accuracy while controlling its overdiagnose. We propose to use 400 plasma samples (210 early PC, 90 pre-invasive PC and 100 controls) for genome-wide miRNA and methylation profiling by next-generation sequencing (NGS) to discover a panel of miRNA and methylation markers, and 600 plasma samples (350 early PC, 150 pre-invasive PC and 100 controls) for validation by integrative analysis of imaging, miRNA and methylation biomarker data.

Project Narrative

Ductal adenocarcinoma of the pancreas (pancreatic cancer, PC) is ranked as the 10th most common cause of cancer, and the fourth most common cause of cancer death in the United States. Despite the steady decline in the death rate of many cancers in the US over the past 2 decades, the death rate of pancreatic cancer is actually rising, due in part to the limited strategies available for successful screening, early detection and prevention of PC. To address the great challenges in early detection of PC, overall objective of this application is to discover a panel of circulating miRNA and methylation biomarkers from whole genome micro RNA and methylation profiling in plasma by next-generation sequencing and develop a PC early detection system integrating imaging, miRNA and methylation biomarker data with high accuracy while controlling its overdiagnose.

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10. Facilities & Other Resources

Campus Resources: The University of Texas Health Science Center at Houston (UTHSC-H) includes a Medical School, Dental Branch, School of Public Health, Graduate School of Biomedical Sciences, School of Nursing, and School of Health Information Sciences. In addition, UTHSC-H includes the Center for Clinical and Translational Sciences (CCTS). The goal of the CCTS is to facilitate clinical and translational research at The University of Texas Health Science Center at Houston, The University of Texas M. D. Anderson Cancer Center, and the Memorial Hermann Hospital System. The CCTS is one of the original 12 such centers funded by the National Institutes of Health's Clinical and Translational Science Awards. The University of Texas Health Science Center is part of the large Texas Medical Center in Houston along with the University of Texas M. D. Anderson Cancer Center and Baylor College of Medicine; all are in close proximity. The Texas Medical Center library system offers a full range of library services including computer assisted searches at all component institutions.

Laboratory Resources: The Human Genetics Center, in which Dr. Boerwinkle is the Director and a full time faculty member, is part of the School of Public Health (SPH) at UTHSC-H. The Human Genetics Center laboratory constitutes one of the five top high-throughput academic genotyping laboratories in the country, and has equipment needed to carry out current methodologies in molecular research. The Center's Molecular Genetics Laboratory has over 20 years experience in large collaborative epidemiological studies involving the determination of human genetic variation, and the Center has 10 full time faculty members. The laboratory is experienced in many methods for genotyping large numbers of samples for epidemiological genetic studies. DNA extraction, aliquoting and management of hundreds of thousands of samples from several large population-based projects are routinely performed. Long term liquid nitrogen ultra-low temperature storage facilities and ultra-low freezers are available. All freezers are connected to a call-down alarm system. Duplicate samples are stored in a separate buildings provided by UTHSC-H. Dedicated laboratory space is available for performing DNA isolation protocols and sample handling in a sterile environment. There is approximately 10,000 square feet of dedicated laboratory space.

Computing Resources: The Human Genetics Center (HGC) has a series of interconnected microcomputer resources. All key personnel have late model mobile computers and/or desktop workstations. Researches in HGC operate multiple high-performance multi-CPU Intel workstations with 8GB memory. Two 4-CPU Sun Enterprise 450 servers with 8GB memory and two 2-CPU Sunfire 280 servers are dedicated and maintained for the Human Genetics Center faculty and staff. Additional UNIX resources include two V880, and 4-CPU Sun servers. Dr. Xiong's lab has a DELL PRECISION T5400 sever with 2-CPU and 16GB memory, two DELL OPTIPLEX workstations with multi-core CPU and 8GB memory.

The analyses of exceptionally large amounts of genomic data require sufficient storage space, memory, and numerous multi-core processors. Thus, HGC recently upgraded our computational capacity by creating a computer cluster of the following components: one large server (24Gb memory, 4Tb hard drive) for data storage, data sharing and light data analysis; seven traditional servers (12Gb memory, 500Gb hard drive) for dedicated, computationally intensive analyses; two network storage servers (12 Tb) for data backup; and one GPU based workstation for simulation-based analyses.

Division of Biostatistics has a state-of-the-art Hewlett Packard high performance computing (HPC) cluster. The HPC cluster provides an environment that can accommodate many types of large-scale genetic and genomic computational tasks, as well as database management, with

1164 computing cores of 2.2GHz-2.6GHz CPUs across 35 HP ProLiant DL165 G6 (dual 6-cores) servers , 31 HP ProLiant DL165 G7 (dual 12-cores) servers (computing nodes), a HP ProLiant DL380 G7 server (master node) with dual 6-cores of 3.45GHz CPUs , and a HP ProLiant DL385 G7 server (master node) with dual 12-cores of 2.5GHz CPUs. A HP ProLiant DL385 G6 server (master node) with dual 6-cores of 2.6GHz CPUs as the front end, a Nvidia Tesla S1070-500 System with 960 GPU computing cores, and a large scratch node memory and disk space. The proposed research will utilize this cluster to fully meet the statistical and computing needs for the project. In addition, the cluster is highly expandable and is ready to meet future computational demand.

The HPC cluster has a large node memory and storage space. The master node has 64GB RAM installed. Among all the computing nodes 58 nodes have 16GB RAM each, 8 nodes have 64GB RAM each,1 nodes has 192GB RAM,1 nodes has 96GB RAM, and the GPU node has extra 16GB dedicated shared memory. Each computing node comes with a 160GB hard disk for OS and applications. The master node comes with 2x160GB hard disks configured in RAID for system and applications. Five additional internal hard disks with 500GB, each configured with RAID 5, on the master node provide users with 2TB effective storage space. Additional three internal disk slots are available for future expansion. Recently a new HP StorageWorks MSA60 Array with 12x2TB disks and a new HP P2000 G3 MSA Array system with 12x2TB disks have been added to the cluster installed.

The HPC cluster is managed by HP's Cluster Management Utility (CMU) which administers and monitors the system. The open source resource manager Torque is used for the batch system administration. All computing nodes and the master node in the HPC cluster use SUSE Linux Enterprise Server 11 as the operating system, supporting standard open source GNU compilers and Java SDK, as well as a wide range of statistical and scientific computing softwares, such as R, PLINK, FBAT, MATLAB and the Message Passing Interface (MPI) with R support (Rmpi) for large-scale parallel computing. All the computing nodes are connected and managed in a secured and dedicated private network with Gigabit connection. The master node is in the network security zoon 40 behind the network firewall. It is the frontend of the cluster that only authorized users can access. Users' data can be efficiently and securely transferred by sftp within the UTSPH network. For outside users, the standard VPN connection is required for system access and data transfer. In summary,this cluster will offer the computational capability for carrying out the proposed large-scale genomic and epigenomic data analysis.

The School of Public Health maintains a high speed Local Area Network based on gigabit technology with 100 megabit per second access to each workstation within the building. Advanced network monitoring technologies from Cisco Systems help supply the school with diagnostic and corrective tools to maintain the ever expanding network. The School is interconnected to UTHSC-H through fiber optic cabling providing the highest available bandwidth possible for additional University resources and access to the Internet. This network currently provides access to more than 800 computers in Houston and provides additional computing resources to more than 200 computers located at the school’s remote campuses in Dallas, San Antonio, El Paso, and Brownsville. Between the multiple sites, IT Services provides access to more than 1,600 student, staff, and faculty.

The SPH data center provides for the highest levels of security from both physical and logical penetrations and disasters. All servers containing non-public confidential information are placed within a secured firewall system with only privileged access allowed. The data center itself is protected with both access and surveillance technologies and the latest in fire suppression systems. The data center is protected from power outages with a local battery based

uninterruptible power supply (UPS) protecting all equipment located in the data center. The room has a dual redundant air conditioning systems which protects all equipment, even in the event of total power loss, or loss of chilled water to the primary cooling systems. All mechanical systems are also event monitored by the Facility Operations staff within the Health Science Center. Any abnormal room conditions signal the appropriate staff to take appropriate action.

This project involves state-of-the-art data analysis, The Human Genetics Center, in which Dr. Xiong is a member, has a complete suite of machine learning, bioinformatics and computational biology software tools available. Particularly, Dr. Xiong's lab has developed software GenoMetrix that can perform data quality controls, haplotype inference, imputation, biomarker identification, RNA-seq, miRNA-seq and methylation-seq data analysis, image analysis, image-genetic and image-epigenetic analysis, next-generation sequencing data analysis, genome-wide gene-gene and gene-environment interaction analysis, integrated genomic and epigenomic analysis, functional data analysis and high dimensional data reduction. These tools will ensure the successful completion of the proposed Specific Aims and Work Scope.

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FACILITIES OTHER RESOURCES & EQUIPMENT

Institutional Commitment:
One of the original three Comprehensive Cancer Centers designated by the National Cancer Act in 1971, MD Anderson Cancer Center (MDACC) is one of the world's most respected cancer treatment and research centers with a proven record of providing resources and support early stage investigators. Protected research time is offered to all faculty members and varies from 40% for non-tenure track clinical faculty to 60% for tenure track clinical faculty. Administrative and clinic assistance allows the investigator ample opportunities for education, research, academic work and career development. Many research training courses are available at MDACC, and all investigators have completed courses in the application for NIH grants, as well as human subject's protection workshops. In addition to the resources, the institution provides access to a large patient volume, with many patients who are invested in participating in scientific studies.
Each faculty member is granted funds for travel and attendance to a national conference such as to the American Association for Cancer Research annual meeting and costs for membership to leading societies are included as professional developmental expenses. Resources are also provided towards publications: MDACC offers the institutional editorial committee for review of manuscripts, grants and abstracts. In summary, MDACC is committed to the success of promising investigators and has an exemplary record of providing resources and support for investigators like Drs. Lee, Li, Ng, and Fang.

Description of Institutional Environment

MD Anderson Cancer Center is a fully accredited academic, categorical, NCI-designated Comprehensive Cancer Center devoted exclusively to cancer patient care, research, education, and prevention. MD Anderson is a nonprofit state institution. During fiscal year 2013, MD Anderson treated more than 115,000 patients—10% of the cancer patients in Texas and 1% of all cancer patients in the United States, in addition to a large number of international patients. Owing to an increasing elderly population, the number of new cancer cases diagnosed annually is increasing, which will increase the demand for our services for at least the next 2 decades. MD Anderson investigators have ample access to patients with primary and metastatic solid tumors who are willing to participate in cancer research and clinical trials.

a. **Information Systems for Data Storage, Management, and Computation.** MD Anderson has a comprehensive institution-wide database that includes clinical, socioeconomic, and demographic data. All surviving cancer patients are assessed annually. MD Anderson also has several bioinformatics applications and biological databases and a high-performance computing environment for intensive computation.

b. **UTGSBS and UTSPH.** The University of Texas Graduate School of Biomedical Sciences (UTGSBS) administers MD Anderson's graduate programs. The UTGSBS coordinates and designs its course curriculum and requires the students to participate in the graduate programs at MD Anderson. MD Anderson also collaborates with the The University of Texas School of Public Health (UTSPH) to offer training programs. All clinical and basic science departments maintain active postgraduate training programs in biomedical science and public health. A full-time employee at MD Anderson can register for courses at these schools in a non-degree-granting program, and his/her tuition and fees will be reimbursed through MD Anderson's Tuition Assistance Program. Structured courses in immunology, cancer biology, and genetics are available at the UTGSBS and UTSPH. Courses covering current topics in tumor progression and genetics are also offered at these schools.

c. **Faculty Educational Resources.** MD Anderson provides comprehensive support for the production and distribution of cancer information and education, including the Research Medical Library and the Departments of Scientific Publications, Continuing Medical Education, Conference Services, Academic Information Systems, Telemedicine and Distance Learning, Television Production, and Media Production Resources. These individual programs work in concert to assist faculty with communication and educational challenges. Faculty Development programs provide the supplementary skills and knowledge required of a high-performing faculty. The extensive and highly collaborative programming, events, and seminars offered by the Faculty Development Program cover communication skills and other issues of professional and career development, faculty health and well-being, and the development and enhancement of our faculty as leaders.

d. Research Support Resources. All clinical research activities are supported through the Office of Protocol Research, a central office that comprises four specialized units: Protocol Approval and Regulatory Affairs, the Office of Clinical Research Quality Assurance, the Protocol Data Management System, and Research Finance. The primary functions of this central office are to ensure that the principal investigators comply with federal and institutional regulations, maintain protocol-related information for the institution, provide protocol data management services to investigators, and refine the financial system surrounding clinical research.

The UT MD Anderson Cancer Center also has access to a number of systems dedicated to higher order statistics and statistical genetic analysis:

a. Two (2) SUN Fire V490 servers, equipped with SPARC/Solaris 10, each built with four (4) CPUs, running at 2.1GHz, with 16GB on-board RAM. The system utilizes a network file system which currently renders about 28TB of disk space. We use this system for high through put computation using programs such as Linkage, S.A.G.E., plink, GeneHunter etc.
b. One (1) SUN Fire V240 (SPARC/Solaris 10), with a dual-core (1.5GHz) and 2GB RAM. This is used for system management only, such as internal Web service, identity management, and file management etc.
c. SUN Fire X4200, equipped with four (4) AMD CPUs, each running at 2.8GHz, supported with 32GB of RAM. This system shares the same 28TG disk array, which offers users unified file system. We use this server to process high end statistical analysis in a range of software, such as Linkage, S.A.G.E., plink, and HelixTree for Genowide Association Studies. The system is power by the latest RedHat Enterprise Linux Server V5 operating system.
d. HP Proliant DL385 G5 server, which is running the latest RedHat Enterprise Linux Server V5, on an 8-way CPU (2.3GHz each), 32 GB RAM platform. Other than the standard Linkage programs and the alike, this server is also our main SAS server (SAS for 64-bit). Again, it is attached to the same 28TB file server.
e. HPC, aka High Performance Cluster, a system that is composed of 512 individual nodes, each offers a dual-core AMD O280 processor (2.4GHz), with 16GB on board RAM. This effectively offers us up to 1024 CPUs in a high throughput clustering computational environment. The entire system is power by a HP modified RedHat operating system, and is actively supported by HP.
f. SUN SPARC Enterprise T2000 server, with four (4) CPUs, each running at 2.0GHz, enjoying 32 GB of RAM. This SPARC/Solaris platform is used as the departmental main Web server (http://epi.mdanderson.org) to help with our internal project management and extranet style data sharing with our collaborators. It is built with Apache Web server, complimented by PHP, Oracle, MySQL and other software to offer robust Web services to both internal and external audience.
g. HP 785 proliant server with eight quad core 2.3 MHz processors for a total of 32 cores with 272 GB of RAM. This SPARC/Solaris platform is used as the departmental main Web server (http://epi.mdanderson.org) to help with our internal project management and extranet style data sharing with our collaborators. It is built with Apache Web server, complimented by PHP, Oracle, MySQL and other software to offer robust Web services to both internal and external audience.

All systems are routinely backed up, and include compilers for C, C++, FORTRAN, and Pascal programming languages. The above systems are backed up daily. Data management software includes Visual FoxPro, Visual Basic, Visual Studio.Net, Microsoft Access, Microsoft SQL/Server 2000, SQL server2005 in development and production mode, Verity's Teleforms and LiquidOffice data management applications, MySQL, and several ORACLE developer and designer licenses. Software for statistical analysis includes SAS, SPSS, Stata, S-Plus, Statxact, Logxact and MatLab. To process genome-wide data, we use HelixTree, BeadStudio, PLINK, ProbABEL and Eigenstrat and Partek. For copy number analyses QuantiSNP, WashUHMM, and Penn CNV are available. The SUN SPARC Enterprise T2000 server functions as a host for number of project specific web sites as an Apache web server.

Description of the Department of Surgical Oncology

The Department of Surgical Oncology is one of the premier academic Departments of Surgery in the country, with a deep commitment to collaborative and translational cancer investigation. The Department is at the forefront in managing surgery for patients with cancer and in contributing to new knowledge about cancer through research programs. The department has strong peer-reviewed grant support from multiple federal, state and national agencies, including the National Cancer Institute and the American Cancer Society. Department faculties actively lead research groups and collaborate with a diverse group of investigators representing fields including genetics, epidemiology, molecular biology, immunology, and statistics. MD Anderson faculties have direct access to other components of The University of Texas System, including The University of Texas School of Public Health and The University of Texas Graduate School of Biological Sciences (UTGSBS). Both schools are widely acknowledged as being among the best graduate schools in the country for education and training in basic science, clinical research, and public health. Research is central to MD Anderson's mission to eliminate cancer through outstanding integrated programs in patient care, research, education, and prevention. The institution provides exceptional access to a talented and accomplished group of clinical, translational and basic science investigators for collaboration as well as providing access to laboratory space, established disease-specific, annotated patient databases, integrated tumor and tissue banks, and core research facilities to support his work.

Facilities:
Laboratory –Dr. Lee has a 647 square foot laboratory in the Gimbel building in the hospital complex configured for molecular and cellular biology studies, including a chemical hood. There is an adjacent tissue culture room (100 square feet) with two laminar flow hoods and two insulated CO2 incubators. Dark room and cold storage are available nearby. The following equipments are available in the Dr. Lee's laboratory: laminar flow biohazard hoods for tissue and cell culture; incubators for tissue and cell culture; microscopes; low, high, and ultrahigh speed centrifuges for nucleic acid and protein extractions; shaking water baths, baking and vacuum ovens for nucleic acid and protein blot hybridizations and washes; gel apparatus and power supplies for electrophoresis; thermocycler for PCR applications; HPLC for bimolecular separation; dot-blot filtration manifold; pH meter; balance; circulating water bath; -30^{o}C and -80^{o}C freezers; liquid nitrogen storage; microELISA autoreader; microwave oven, include flow cytometry; laser densitometer; spectrophotometer; cold rooms; warm rooms; a kitchen for media preparation, and cleaning and sterilizing glassware; radioactive and hazardous waste disposal. The following are available in Core Facilities provided by MD Anderson Cancer Center: U.V. crosslinker for covalent crosslinking of nucleic acids to nylon membranes, cesium irradiator for irradiating cells, Speed-Vac concentrator for concentrating nucleic acid and protein samples, gel dryer.

Clinical – MD Anderson Cancer Center has 521 inpatient beds, 31 operating rooms, a dedicated Melanoma and Skin Cancer Center with 30 examination rooms, and all disciplines necessary for the comprehensive care of melanoma patients.

Computer –The Department of Surgical Oncology offers access to a variety of major word processing, literature search, graphic and computing and software resources residing in the department and accessible for this research.

Presently, the Division of Surgery, in which the Department of Surgical Oncology resides, has Macintosh desktop computers and desktop workstations able to connect to the servers via a thin wire Ethernet backbone using the TCP/IP protocol. All desktop systems are connected via 100 MB Ethernet to an institution-based HP proliant cluster running in a Microsoft AD environment for general file sharing and database management activities. Members of the department have E-mail communication handled through an enterprise-wide MS Exchange server. The Division operates a series of HP Proliant dl385 application servers running Microsoft Windows 2003 enterprise edition that are used to enhance work productivity and sustain office activities and other data handling functions:

Secretarial support is provided by the Department of Surgical Oncology.

Description of the Division of Diagnostic Imaging

The Division of Diagnostic Imaging (DDI) did 498,299 imaging procedures in FY2012. DDI is organized into the Department of Nuclear Medicine/PET (9 physicians) and the Department of Diagnostic Radiology, with 6 clinical sections (Abdominal Imaging: 43 physicians; Breast Imaging: 14; Interventional Radiology: 14; Musculoskeletal: 7; Neuroradiology: 16; Thoracic Radiology: 13). From a research perspective, DDI is focused on development of new imaging and interventional radiology techniques. In clinical trials, they play essential roles in assessment of efficacy of new therapies, the assessment of pharmacodynamic endpoints using novel functional imaging, and in procurement of tissue specimens for diagnosis and translational research studies .

The Division of Diagnostic Imaging provides a full range of state-of-the-art diagnostic imaging and therapeutic services. MDACC Major clinical equipment includes 11 MRI units (10 clinical operation and 1 research unit), 20 CT scanners, 11 vascular/interventional suites, 17 ultrasound (US) units, 14 Nuclear Medicine gamma cameras (11 multi-head systems, seven of which have SPECT capabilities and 3 of which have CT imaging capabilities), 2 high resolution PET scanner, 2 PET/CT scanners, 7 film screen Mammography units, 4 digital units and 1 mobile coach, 1 dedicated Mammography stereotactic core biopsy system, 8 dedicated digital chest units, 11 portables x-ray units, 4 portable fluoroscopy surgical units, 4 AC5000s for computerized radiology, 1 bone densitometry unit, and 11 R/F diagnostic units.

The Radiology Outpatient Center immediately adjacent to the main building houses 6 MRI units, 4 CT units and 1 Chest unit.

The Emergency Center located in the main hospital, has 1 CT scanner.

Bellaire, the off campus outpatient center, has 1 mobile MRI unit and one CT scanner.

The new ACB (connected to the Main Building by elevated walkway) includes 4 chest rooms, 3 Rad rooms, 1 fluoroscopy room, 5 MRI scanners, 6 CT scanners, 7 US units, 4 PET/CT scanners, 11 Nuclear Medicine cameras, 6 Breast Diagnostic units, 6 Breast US units, 1 stereotactic core biopsy room, 2 angiography suites, 1 interventional CT scanner, 1 interventional MRI scanner, and 1 interventional US unit.

Description of Dr. Donghui Li's Research Facilities and Resources

Facilities and Resources available to this project in Dr. Li's lab and department are outlined below.
Laboratory:
The Clinical Translational Research Center (CTRC) and the CTRC laboratory form the designated MDACC site for the delivery of outpatient clinical patient drug development research trials. The CTRC implements novel, innovative, and "first-in-man" drug programs and complies with mandated regulatory and monitor oversight requirements. The laboratory provides pharmacokinetic (PK) collection, processing and shipping, and is located within the CTRC. The laboratory processing area can accommodate up to seven phlebotomists at a given time for the handling and management of multiple PK samples. Another room with two phlebotomy recliners allows for fast-track PK collection of blood specimens. The laboratory staff processes, labels, documents, tracks, stores, ships and performs quality control measures of PK specimens for compliance with protocols, accuracy and specimen integrity.
Donghui Li has a laboratory at the South Campus Research Building II (SCRB2) of MDACC. Dr. Li's laboratory has a 1200 square foot bench space and a tissue culture room, a radioactive work room and a

shared cold room, chemical room and darkroom. The entire second floor of this building host about 10 PIs that are all involved in GI cancer research, including faculties for the Department of GI Medical Oncology, Pathology, GI Medicine & Nutrition, Cancer Biology and Clinical Cancer Prevention. The third floor hosts the Kleberg Biomarker Center led by Dr. Gordon Mills and on the top floor locate the Molecular Pathology group and the Proteomics Core. The Kleberg Biomarker Center has a Sequenom system and Dr. Li's group has full access to it. There is frequent shuttle service between this building and the main campus. The Immune Monitoring Core Lab has the required instrument and experience to perform the multiple Bead-based assays on cytokines.

Clinical:

MDACC is a flagship component of the University of Texas System, and its largest institution. MDACC is one of the 37 health institutions in the Texas Medical Center, a 500-acre campus south of downtown Houston. More than 700,000 cancer patients have been treated at MDACC 1944. The CTRC provides a cohesive, dedicated research unit in contiguous space with common focus in new drug development. The newly designed unit is 6,150 square feet and consists of 15 private rooms. Laboratory and administrative offices are strategically placed to facilitate the acquisition and processing of blood specimens and the oversight of unit personnel. The CTRC is adjacent to the Ambulatory Treatment Center (ATC) to maximize nursing care, laboratory support and staff utilization. It is in close proximity to the Emergency Center and Outpatient Pharmacy.

Computer:
Dr. Li has a Dell Optiplex desktop in her office, as well as a Dell Dimension laptop. There is telephone access to the M.D. Anderson main frame. There is substantial software including MS Word, MS Excel, MS PowerPoint, MS Access, Adobe Photoshop, Adobe Acrobat, SPSS and Statistica. The MD Anderson Data Center supports direct patient care and research activities throughout the MDACC campus. MDACC provides desktop systems, servers and mainframes connected through a 10MBPS network; Ethernet (DECNET, TCP/IP) LAN with VAX cluster, IBM3090, Solbourn 5 multi-CPU SPARC-compatible UNIX server running GCG and other software. Microsoft Outlook is used for email throughout the institution, and the system supports numerous databases and forms for research and clinical application and information. Faculty and investigators' offices are equipped with state-of-the-art computer technology, which is overseen by a dedicated MDACC IT support team. In addition, through the Clinical Translational Research Laboratory, Dr. Li has access to the Computerized Accountability Software-IDRx Electronic drug accountability system that tracks investigational agents by drug, protocol, manufacturer and lot numbers. The system provides online assistance with drug and protocol information, and generates reports in the NCI-approved format. She also has access to Freezerworks, a configurable laboratory data management software which allows tracking of samples and freezer inventory.
Office:
Dr. Li has 100 sq. ft office in the Faculty Center, across the street from the main complex. Faculty are supported by administrative assistants or executive assistants based on faculty rank. These offices are equipped with state-of-the-art computer technology, which is overseen by a dedicated institutional IT support structure. Administrative services are available for grant preparation and management.
Other:
MDACC has a Cancer Center Support Grant (CCSG) provides partial funding for shared resources that are available to all cancer center members. These include a variety of instruments and services to facilitate research. In prioritizing use of these facilities, precedence will be given to peer-reviewed investigators.
The Shared Resources available through MDACC include, but are not limited to, tissue procurement & banking facility, research histopathology facility, flow cytometry and cellular imaging facility, biostatistics and data management, bioinformatics, clinical trials support resource, clinical and translational research center, protocol review and monitoring and the molecular cytogenetics facility.
The MD Anderson Science Park Next-Generation Sequencing (NGS) Facility within the Molecular Biology Facility Core (MB Core) has an Illumina HiSeq 2000, an Illumina MiSeq, an Illumina cBot, a Covaris S220 sonication instrument for DNA shearing, a Beckman Coulter SPRI-TE SPRIworks Fragment Library System, an Agilent Technologies TapeStation 2200, an Invitrogen Fluorometer Qubit 2.0, a HP DL585 and a HP DL385 compute servers, a HP P2000 Data Storage Array. The Gene Expression Analysis Laboratory within the MB Core has a Tecan HS 400 Pro automated hybridization station, a GenePix 4200A (Axon Instrument) for microarray data acquisition and analysis, an Agilent 2100 Bioanalyzer, ABI 3130xl Genetic Analyzer, ABI 7900HT Fast Real Time PCR System, 7300 Real Time PCR System, a Beckman Coulter Biomek 2000 Laboratory Automation Station, a complete set of WaferGen Biosystems (including a SmartChip Cycler, a SmarChip Multisample Nanodispenser, and a Nanodispenser for a single sample). The Protein Analysis Laboratory within the MB Core houses a complete Shimadzu LC-10AD VP HPLC system (including pumps, auto injector, both UV-Vis spectrophotometric and fluorescence detectors, fraction collector), a GE AKTApurifier FPLC, a Zoom □ IEF Fractionator (Invitrogen), several apparatuses for protein gel electrophoresis including two PROTEAN Isoelectric Focusing Cells, three Criterion Electrophoresis Cells, one Criterion Dodeca Cell (Bio-Rad Laboratories), as well as refrigerators, freezers, an incubator, a sonicator, centrifuges, vortexes, stir plates, orbital shakers, water baths, necessary for protein sample preparation and 2-dimensional electrophoresis. Image analysis equipment includes a GE Typhoon 9410 Variable Mode Imager and a GE ImageQuant LAS 4000 Gel Documentation System.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. First Name*: Momiao Middle Name Last Name*: Xiong Suffix: PhD

Position/Title*:	Associate Professor
Organization Name*:	The University of Texas Health Science Center at Houston
Department:	Biostatistics/Human Genetic Ct
Division:	School of Public Health
Street1*:	1200 Herman Pressler Dr., E453
Street2:	
City*:	Houston
County:	Harris
State*:	TX: Texas
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	77030-3900

Phone Number*: 713-500-9894 Fax Number: 713-500-0900 E-Mail*: Momiao.Xiong@uth.tmc.edu

Credential, e.g., agency login: MXIONG

Project Role*: PD/PI Other Project Role Category:

Degree Type: PhD Degree Year: 1993

	File Name
Attach Biographical Sketch*:	Xiong_Biosketch_20141014540099.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Shenying Middle Name Last Name*: Fang Suffix: PhD

Position/Title*:	Assistant Professor
Organization Name*:	The University of Texas MD Anderson Cancer Center
Department:	Surgical Oncology
Division:	
Street1*:	1400 Pressler Street
Street2:	
City*:	Houston
County:	
State*:	TX: Texas
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	77030-4009

Phone Number*: 713-745-4702 Fax Number: E-Mail*: sfang@mdanderson.org

Credential, e.g., agency login: SFANG01

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	FangBiosketch1014652737.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Donghui Middle Name Last Name*: Li Suffix: PhD

Position/Title*: Professor
Organization Name*: The University of Texas MD Anderson Cancer Center
Department: Gastrointestinal Medical Oncol
Division:
Street1*: 1400 Pressler Street
Street2:
City*: Houston
County:
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 77030-4009

Phone Number*: 713792-74 Fax Number: E-Mail*: dli@mdanderson.org

Credential, e.g., agency login: dongli

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

File Name

Attach Biographical Sketch*: LiBiosketch1014652739.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Jeffrey Middle Name E. Last Name*: Lee Suffix: MD

Position/Title*: Professor, Department Chair
Organization Name*: The University of Texas MD Anderson Cancer Center
Department: Surgical Oncology
Division: Surgery
Street1*: 1400 Pressler Street
Street2:
City*: Houston
County:
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 77030-4009

Phone Number*: 713-792-7218 Fax Number: 713-745-5068 E-Mail*: jelee@mdanderson.org

Credential, e.g., agency login: LEFREY

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

File Name

Attach Biographical Sketch*: LeeBiosketch1014652741.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Chaan Middle Name Last Name*: Ng Suffix: MD

Position/Title*: Professor
Organization Name*: The University of Texas MD Anderson Cancer Center
Department: Diagnostic Radiology
Division:
Street1*: 1400 Pressler Street
Street2:
City*: Houston
County:
State*: TX: Texas
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 77030-4009

Phone Number*: 713-792-6759 Fax Number: E-Mail*: cng@mdanderson.org

Credential, e.g., agency login: CHAANNG

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	NgBiosketch1014652743.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Xiangning Middle Name Last Name*: Chen Suffix:

Position/Title*:
Organization Name*: Virginia Commonwealth University
Department:
Division:
Street1*: 800 E. Leigh Street
Street2:
City*: Richmond
County:
State*: VA: Virginia
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 23284-3076

Phone Number*: 804-828-8124 Fax Number: 804-828-1471 E-Mail*: xchen@vcu.edu

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	Chen_Biosketch1014652691.pdf
Attach Current & Pending Support:	

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Xiong, Momiao	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) mxiong	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Fudan University, Shanghai, P.R. China	B.S.	1963-1968	Applied Mathematics Mathematics
University of Georgia, Athens, Georgia	Ph.D.	1988-1993	Statistical Genetics
University of Southern California, Los Angeles, California	Post-doctoral	1993-1995	Computational Molecular Biology

A. Personal Statement

The goal of this proposal is to discover a panel of circulating miRNA and methylation biomarkers from whole genome micro RNA and methylation profiling in plasma by next-generation sequencing and develop a PC early detection system integrating imaging, miRNA and methylation data with high accuracy. I am trained in statistical genetics, computational biology and machine learning. I have been working in high dimensional data reduction, feature selection, data mining, image analysis, genome-wide association studies, sequence data analysis, gene-gene and gene-environment interaction analysis, pathway and network analysis, and computational systems biology. As PI or co-Investigator on several previous NIH-funded grants, I prepared the ground work for the proposed research by developing methods for the discovery of clinically significant and actionable genetic and epigenetic variants, selection of treatment, and prediction of clinical outcomes with millions of variables and novel statistical methods for integrative analysis of imaging, genomic and epigenomic data. I have developed skills in communication among project members and working out realistic research plans and timelines. The current application is a logical development of my previous work. I will work closely with Drs. Jeffrey E Lee and Shenying Fang from the Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Dr. Donghui Li from the Department of Gastrointestinal (GI) Medical Oncology, The University of Texas MD Anderson Cancer Center, Dr. Rongfu Wang from the Center for Inflammation and Epigenetics, the Houston Methodist Research Institute and Dr. Xiangning Chen, the Virginia Institute for Psychiatric and Behavioral Genetics, the Virginia Commonwealth University to use functional data analysis, sparse sufficient dimension reduction and matrix subset selection algorithms for developing novel algorithms that can efficiently identify biomarkers for early detection of pancreatic cancer from high volume of imaging and whole genome miRNA-seq and methylation-seq profiles. Dr. Xiong will also supervise a postdoctoral to develop an automatic PC early detection system integrating image, miRNA and methylation data with high accuracy.

B. Positions and Employment

1995-1996 Visiting Assistant Research Scientist, Department of Biostatistics, The University of Michigan
1997-1997 Visiting Assistant Professor, Division of Epidemiology,The University of Minnesota
1997-2001 Assistant Professor (Non-tenure Track), Human Genetics Center, School of Public Health, The University of Texas Health Science Center at Houston (UTHSC-Houston)
2001-2007 Assistant Professor (Tenure Track), Human Genetics Center, UTHSC-Houston
2007-2011 Associate Professor (Tenured), Division of Biostatistics, School of Public Health, UTHSC-Houston
2011-Present Professor, Division of Biostatistics, School of Public Health, UTHSC-Houston

C. Honors:

1989	Junior Best Student Award, University of Georgia
1990	Senior Best Student Award, University of Georgia
1994	Best paper Award, Neural Networks with Hidden Markov Process, Artificial Neural Networks in Engineering Conference, 1994, St. Louis, Missouri
2006	Highly Cited Researcher (Biological science)
2007	Highly Cited Researcher (Biological science)
2012	EJHG 1st Prize of the paper for the paper “Gene and pathway-based second wave analysis of genome-wide association studies” as the top cited article in the first calendar year following its publication.
2013	Supervised postdoctoral fellow Futao Zhang was awarded outstanding postdoctoral fellow in 2013 ASHG meeting
2014	The first place of poster award in the UT GSBS human and molecular genetics symposium The Second place of poster award in the UT GSBS human and molecular genetics symposium. The third place of poster award in the UT GSBS human and molecular genetics symposium.

D. Selected peer-reviewed publications (Selected from 156 peer-reviewed publications**).**

1. Zhang F, Boerwinkle E and Xiong MM. (2014). Epistasis Analysis for Quantitative Trait with Next-generation Sequencing Data. Genome Research. 2014 May 6. [Epub ahead of print]
2. Hong, S, Chen X, Jin L and Xiong MM (2013) Canonical Correlation Analysis for RNA-seq Co-expression Networks. Nucleic Acids Research. 41(8):e95 .
3. Zhu Y and Xiong MM (2012) Family-Based Association Studies for Next-Generation Sequencing. Am J Human Genet. 90(6):1028-1045.
4. Luo L, Zhu Y and Xiong MM (2013) Penalized functional principal component analysis for sequence-based association studies. Eur J Hum Genet. 21(2):217-24
5. Luo L, Zhu Y and Xiong MM. (2012). Quantitative trait locus (QTL) for next-generation sequencing with the functional linear models. J Medical Genetics. 49(8):513-24.
6. Shugart YY, Zhu Y, Guo W, Xiong MM (2012) Weighted Pedigree-based Statistics for Testing the Association of Rare Variants. BMC Genomics, 13:667.
7. Wei S, Wang LE, McHugh MK, Han Y, Xiong M, Amos CI, Spitz M, Wei Q. (2012) Genome-wide gene-environment interaction analysis for asbestos exposure in lung cancer susceptibility. Carcinogenesis. 33(8):1531-7
8. Luo L, Boerwinkle E and Xiong MM (2011) Association studies for next-generation sequencing. Genome Research, 21(7):1099-108.
9. Dong H, Luo L, Hong S, Siu H, Xiao Y, Jin L, Chen R, Xiong MM. (2010) Integrated analysis of mutations, miRNA and mRNA expression in glioblastoma. BMC Syst Biol. 4(1):163. PMC3002314
10. Luo L, Peng G, Zhu Y , Dong H, Amos C, and Xiong MM(2010) Genome-wide Gene and Pathway Analysis. Eur J Hum Genet. 18:111-117.
11. Wu X, Dong H, Luo L, Zhu Y, Peng G, Reveille JD**,** Xiong MM**.** (2010) A novel statistic for genome-wide interaction analysis. Plos Genetics. 6 (9), e1001131. PMCID: PMC2987176
12. Dong H, Luo L, Hong S, Siu H, Xiao Y, Jin L, Chen R**,** Xiong MM. (2010) Integrated analysis of mutations, miRNA and mRNA expression in glioblastoma. BMC Syst Biol. 4(1):163. PMCID: PMC3002314
13. Zhao J, Jin L, Xiong MM (2006) Test for interaction between two unlinked loci. Am J Hum Genet 79:831-845. [PDF] PMCID: PMC1698572
14. Zhang H, Yu C-Y, Singer B, Xiong MM. (2001) Recursive partitioning for tumor classification with gene expression microarray data. Proc Natl Acad Sci U S A. 98: 6730-6735.
15. Xiong MM, Fang X and Zhao JY. (2001) Biomarker identification by feature wrappers. Genome Res. 11:1878-1887.

E. Research Support

Ongoing Research Support

1R01HL106034-01 (Xiong) 01/10/2011 - 12/31/2014
NIH
Statistical Methods for Finding Missing Heritability.
Use genome continuum model as a general principle for developing novel and powerful statistical methods for studying rare variants and gene-gene interactions in the context of next-generation sequencing and GWAS data.
Role: Principle Investigator.

1 R01 GM104411-01 (Xiong) 04/01/2013 - 01/31/2017
NIH
Unified Statistical Methods for Sequence-Based Association Studies
This project is to develop novel and powerful statistical methods for sequence-based association studies and QTL (eQTL) analysis unifying family and population-based study designs.
Role: Principle Investigator.

1R01 MH101054 (CHEN & KENDLER) 08/01/2013 - 07/31/2016
NIMH
Understanding the genetic architecture of schizophrenia in Chinese population
This application proposes to study the genetic factors influencing the development of schizophrenia in Han Chinese using exome sequencing.
Role: Investigator.

Pending Research

1 R01 (Huaizhen Qin) **0**4/01/2015 - 03/31/2019
NIH
Multi-ethnic Pleotropic gene mapping for alcohol and nicotine co-addiction.
This project is to develop novel causal inference methods for identifying DNA sequence variants that simultaneously influence multiple diseases in admixed populations
Role: Investigator.

1 R01 (Chris Amos) 04/01/2015 - 03/31/2020
NIH
Methods for integrated omics, physiological, image and clinical data analysis.
The goal of this project is to develop unified frameworks and novel methods for integrated analyzing growing large, complex and diverse genetic, epigenetic, physiological and image data.
Role: Investigator.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Fang, Shenying	Assistant professor
eRA COMMONS USER NAME (credential, e.g., agency login) SFANG01	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YYYY	FIELD OF STUDY
Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei, China	MD	07/1994	Preventive Medicine
The Fourth Military Medical University, Xi'an, Shaanxi, China	MS	07/1999	Epidemiology
The University of Texas School of Public Health, Houston, TX	MS	08/2004	Biostatistics
The University of Texas School of Public Health, Houston, TX	PHD	12/2008	Biostatistics
The University of Texas MD Anderson Cancer Center, Houston, TX	Postdoctoral Fellow	09/2011	Statistical Genetics

A. Personal Statement

Dr. Shenying Fang is an assistant professor in the Department of Surgical Oncology at the University of Texas MD Anderson Cancer Center. He is a biostatistician with a major interest in genetic diseases. He has applied novel statistical models to identify genetic and environmental determinants for susceptibility to melanoma and disease progression. Dr. Fang identified novel loci for familial lung cancer using an innovative approach that allows for etiological heterogeneity. He evaluated the modifying impact of ***P***53 polymorphism on age to onset of cancer among carriers of ***P***53 germline mutation. He also has experience in evaluating the impact of health care service on cancer patients using a large population-based SEER-Medicare merged database. His long term goal is to become an independent investigator in cancer prevention and control, with a focus on identifying tumor-associated biomarkers in melanoma susceptibility and progression and applying these biomarkers to clinical practice.

B. Positions and Honors

Positions and Employment

1994-1996 Editor, Chinese Journal of School of Health, Bengbu, P.R. China
1999-2002 Assistant Professor, Epidemiology (remote sensing and global positioning systems in field epidemiology), Beijing Institute of Microbiology and Epidemiology, Beijing, P.R. China
2003-2006 Graduate Research Assistant (lung cancer and SEER-Medicare data analysis), The University of Texas MD Anderson Cancer Center, Houston, TX
2007-2009 Statistical Analyst (SEER-Medicare data analysis), Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX
2011-2012 Instructor, Department of Genetics, The University of Texas MD Anderson Cancer Center, Houston, TX
2012-present Assistant Professor, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Other Experience and Professional Memberships

2008-2010 Member, American Statistical Association
2009-present Member, American Society of Human Genetics

Honors

1992 First prize in student practicum, Tongji Medical University
1993 Class scholarship, Tongji Medical University
2010 POSTER FINALIST, Trainee Research Day 2010, The University of Texas MD Anderson Cancer Center

C. Selected Peer-reviewed Publications (from among 41 peer-reviewed publications)

Most relevant to the present application

1. Barrett JH, Iles MM, Harland M, Taylor JC, Aitken JF, Andresen PA, Akslen LA, Armstrong BK, Avril MF, Azizi E, Bakker B, Bergman W, Bianchi-Scarrà G, Bressac-de Paillerets B, Calista D, Cannon-Albright LA, Corda E, Cust AE, Debniak T, Duffy D, Dunning AM, Easton DF, Friedman E, Galan P, Ghiorzo P, Giles GG, Hansson J, Hocevar M, Höiom V, Hopper JL, Ingvar C, Janssen B, Jenkins MA, Jönsson G, Kefford RF, Landi G, Landi MT, Lang J, Lubinski J, Mackie R, Malvehy J, Martin NG, Molven A, Montgomery GW, van Nieuwpoort FA, Novakovic S, Olsson H, Pastorino L, Puig S, Puig-Butille JA, Randerson-Moor J, Snowden H, Tuominen R, Van Belle P, van der Stoep N, Whiteman DC, Zelenika D, Han J, **Fang S**, Lee JE, Wei Q, Lathrop GM, Gillanders EM, Brown KM, Goldstein AM, Kanetsky PA, Mann GJ, Macgregor S, Elder DE, Amos CI, Hayward NK, Gruis NA, Demenais F, Bishop JA, Bishop DT, GenoMEL Consortium. Genome-wide association study identifies three new melanoma susceptibility loci. Nature Genetics 43:1108-1113 (2011). PMCID: PMC3251256.
2. Amos CI, Wang LE, Lee JE, Gershenwald JE, Chen WV, **Fang S**, Kosoy R, Zhang M, Qureshi AA, Vattathil S, Schacherer CW, Gardner JM, Wang Y, Bishop DT, Barrett JH, GenoMEL Investigators, MacGregor S, Hayward NK, Martin NG, Duffy DL, Q-Mega Investigators, Mann GJ, Cust A, Hopper J, AMFS Investigators, Brown KM, Grimm EA, Xu Y, Han Y, Jing K, McHugh C, Laurie CC, Doheny KF, Pugh EW, Seldin MF, Han J, Wei Q. Genome-wide association study identifies novel loci predisposing to cutaneous melanoma. Human Molecular Genetics 20:5012-5023 (2011). PMCID: PMC3298855.
3. **Fang S**, Fang X, Xiong M. Psoriasis prediction from genome-wide SNP profiles. BMC Dermatology 11:1 (2011). PMCID: PMC3022824.
4. Iles MM, Law MH, Stacey SN, Han J, **Fang S**, Pfeiffer R, Harland M, Macgregor S, Taylor JC, Aben KK, Akslen LA, Avril MF, Azizi E, Bakker B, Benediktsdottir KR, Bergman W, Scarrà GB, Brown KM, Calista D, Chaudru V, Fargnoli MC, Cust AE, Demenais F, de Waal AC, Debniak T, Elder DE, Friedman E, Galan P, Ghiorzo P, Gillanders EM, Goldstein AM, Gruis NA, Hansson J, Helsing P, Hocevar M, Höiom V, Hopper JL, Ingvar C, Janssen M, Jenkins MA, Kanetsky PA, Kiemeney LA, Lang J, Lathrop GM, Leachman S, Lee JE, Lubinski J, Mackie RM, Mann GJ, Martin NG, Mayordomo JI, Molven A, Mulder S, Nagore E, Novakovic S, Okamoto I, Olafsson JH, Olsson H, Pehamberger H, Peris K, Grasa MP, Planelles D, Puig S, Puig-Butille JA, Randerson-Moor J, Requena C, Rivoltini L, Rodolfo M, Santinami M, Sigurgeirsson B, Snowden H, Song F, Sulem P, Thorisdottir K, Tuominen R, Van Belle P, van der Stoep N, van Rossum MM, Wei Q, Wendt J, Zelenika D, Zhang M, Landi MT, Thorleifsson G, Bishop DT, Amos CI, Hayward NK, Stefansson K, Bishop JA, Barrett JH, GenoMEL Consortium, Q-MEGA and AMFS Investigators. A variant in FTO shows association with melanoma risk not due to BMI. Nature Genetics 45:428-432, 432e1 (2013). PMCID: PMC3640814.
5. Park JY, Amankwah EK, Anic GM, Lin HY, Walls B, Park H, Krebs K, Madden M, Maddox K, Marzban S, **Fang S**, Chen W, Lee JE, Wei Q, Amos CI, Messina JL, Sondak VK, Sellers TA, Egan KM. Gene variants in angiogenesis and lymphangiogenesis and cutaneous melanoma progression. Cancer Epidemiology, Biomarkers & Prevention 22:827-834 (2013). PMCID: PMC3708315.
6. **Fang S**, Han J, Zhang M, Wang L, Wei Q, Amos CI, Lee JE. Joint effect of multiple common SNPs predicts melanoma susceptibility. PLoS One 8:e85642 (2013). doi:10.1371/journal.pone.0085642. PMCID:PMC3877376.
7. **Fang S**, Wang Y, Chun YS, Liu H, Ross MI, Gershenwald JE, Gardner JM, Schacherer CW, Reveille JD, Chen W, Sui D, Bassett Jr. RL, Wang L, Wei Q, Amos CI, Lee JE. The relationship between blood IL-12p40 level and melanoma progression. In press.

Additional Recent Publications of Importance to the Field (in chronological order)

1. Du XL, Lairson DR, Begley CE, **Fang S**. Temporal and geographic variation in the use of hematopoietic growth factors in older women receiving breast cancer chemotherapy: findings from a large population-based cohort. Journal of Clinical Oncology 23:8620-8628 (2005). PMCID: PMC2572993.
2. Srokowski TP, **Fang S**, Hortobagyi GN, Giordano SH. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. Journal of Clinical Oncology 27:2170-2176 (2009). PMCID: PMC2674004.
3. **Fang S**, Pinney SM, Bailey-Wilson JE, de Andrade MA, Li Y, Kupert E, You M, Schwartz AG, Yang P, Anderson MW, Amos CI. Ordered subset analysis identifies loci influencing lung cancer risk on chromosomes 6q and 12q. Cancer Epidemiology, Biomarkers & Prevention 19:3157-3166 (2010). PMCID: PMC3249234.
4. **Fang S**, Krahe R, Bachinski LL, Zhang B, Amos CI, Strong LC. Sex-specific effect of the TP53 PIN3 polymorphism on cancer risk in a cohort study of TP53 germline mutation carriers. Human Genetics

130:789-794 (2011). PMID: 21688173.
5. Gorlov IP, Logothetis CJ, **Fang S**, Gorlova OY, Amos CI. Building a statistical model for predicting cancer genes. PLoS One 7:e49175 (2012). doi:10.1371/journal.pone.0049175. PMCID: PMC3499550.
6. Bodelon C, Pfeiffer RM, Bollati V, Debbache J, Calista D, Ghiorzo P, Fargnoli MC, Bianchi-Scarra G, Peris K, Hoxha M, Hutchinson A, Burdette L, Burke L, **Fang S**, Tucker MA, Goldstein AM, Lee JE, Wei Q, Savage SA, Yang XR, Amos CI, MariLandi MT. On the interplay of telomeres, nevi and the risk of melanoma. PLoS One 7:e52466 (2012). doi:10.1371/journal.pone.0052466. PMCID: PMC3531488.

D. Research Support

Ongoing Research Support

5R03 CA173792-02 Fang (PI) 1/1/2013-12/31/2014
NIH/NCI
Genetic determinants of Breslow tumor thickness and their impact on melanoma progression
To identify common genetic variants and gene expression patterns associated with Breslow tumor thickness and melanoma progression
Role: Investigator

Completed Research Support

5 P50 CA093459 08(DRP) Fang (PI) 9/1/2012-4/30/2014
NIH/NCI
C-reactive protein and melanoma outcomes
To accumulate preliminary data on genetic variants of C-reactive protein blood levels that are linked with melanoma progression
Role: Investigator

5 P50 CA093459 07(PC-CDP 3) Fang (PI) 9/1/2011-8/31/2012
NIH/NCI
Genetic polymorphisms of IL-12p35 and IL-23p19 in melanoma progression
To accumulate preliminary data on genetic variants of inteleukin-12 p35 and interleukin-23 p19 that are linked with melanoma progression
Role: Principal Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Donghui Li	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) dongli	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Beijing Medical University	B.S.	08/78	Public Health
University of Texas School of Public Health	M.S.	05/86	Environmental Science
University of Texas School of Public Health	Ph.D.	01/89	Environmental Science
Baylor College of Medicine	Postdoctoral	09/91	Carcinogenesis

A. Personal Statement

I am an established molecular epidemiologist with 16 years of experience in research on pancreatic cancer. I was the PI of a NIH supported large scale case control study of pancreatic cancer conducted at MD Anderson Cancer Center during 2004 to 2009. Our study made specific contributions to the field by demonstrating the role of obesity, diabetes and antidiabetic therapy in modifying the risk of pancreatic cancer. I was also the PI of one of the major projects of the pancreatic cancer SPORE grant during 2004 to 2009. Our study has shown genetic variation in drug metabolism, DNA repair, glucose metabolism, and IGF signaling pathways was significantly associated with patients' response to anticancer therapy and overall survival. I have played a leading role in the investigation on genetic susceptibility to pancreatic cancer through candidate gene approach, genome-wide association study (GWAS), as well as post GWAS pathway and gene-environment interaction analysis. I have also collaborated with many investigators in biomarker studies for early detection of pancreatic cancer using the proteomics, metabolomics, and miRNA approach. I believe my knowledge and research experience will serve well for the proposed study in this grant application.

B. Positions and Honors

1991-1993 Research Assistant Professor, Department of Pharmacology, Baylor College of Medicine, Houston, TX
10/93-10/98 Assistant Cell Biologist/Assistant Professor, Department of Clinical Investigation, University of Texas M.D. Anderson Cancer Center, Houston, TX
10/98-8/03 Assistant Cell Biologist/Assistant Professor, Department of Gastrointestinal Medical Oncology and Digestive Diseases, University of Texas M.D. Anderson Cancer Center, Houston, TX
9/03-8/08 Associate Professor, Department of Gastrointestinal Medical Oncology and Department of Carcinogenesis, University of Texas M.D. Anderson Cancer Center, Houston, TX
9/08-current Professor, Department of Gastrointestinal Medical Oncology and Department of Carcinogenesis, University of Texas M.D. Anderson Cancer Center, Houston, TX

Other Experience and Professional Memberships

1989- Member, American Association for Cancer Research
1999- Member, Molecular Epidemiology Working Group

Honors

1986 Student Intercouncil Presidential Scholarship, UT School of Public Health
2006 Texas Federation of Business and Professional Women

C. Selected Peer-reviewed Publications (Selected from 150 peer-reviewed publications)

Most relevant to the current application

1. Tang H, Dong X, Hassan M, Abbruzzese JL, **Li D**. Body mass index, obesity and diabetes-associated gene and risk of pancreatic cancer. *Cancer Epidemiol Biomark Prev*, 20(5) 779-92, 2011. PMID: 21357378.
2. Tang H, Wei P, Duell EJ, Risch HA, Olson SH, Bueno-de-Mesquita HB, Gallinger S, Holly EA, Petersen G, Bracci PM, McWilliams RR, JenabM, Riboli E, Tjønneland A, Boutron-Ruault MC, Kaaks R, Trichopoulos D, Panico S, Sund M, Peeters PHM, Khaw KT, Amos CI, **Li D**. Axonal guidance signaling pathway interacting with smoking in modifying the risk of pancreatic cancer: A gene and pathway-based interaction analysis of GWAS data. Carcinogenesis, 35:1039-45, 2014. PMCID: 4004205.
3. Wang J, Chen J, Chang P, LeBlanc A, **Li D**, Abbruzzesse JL, Frazier ML, Killary AM, Sen S. MicroRNAs in Plasma of Pancreatic Ductal Adenocarcinoma Patients as Novel Blood Based Biomarkers of Disease. Cancer Prev Res (Phila Pa) 2(9):807-13, 2009.
4. Jiao L, Zhu J, Hassan MM, Evans DB, Abbruzzese JL, **Li D**. K-ras mutation and p16 and preproenkephalin promoter hypermethylation in plasma DNA of pancreatic cancer patients: in relation to cigarette smoking. Pancreas 34(1):55-62, 2007. PMCID: PMC1905887.
5. Koomen JM, **Li D**, Xiao LC, Liu TC, Coombes KR, Abbruzzese J, Kobayashi R. Direct tandem mass spectrometry reveals limitations in protein profiling experiments for plasma biomarker discovery. J Proteome Res 4(3):972-81, 2005.

Additional recent publications of importance to the field (in chronological order)

6. Shen J, Person MD, Zhu J, Abbruzzese JL, **Li D**. Protein expression profiles in pancreatic adenocarcinoma compared with normal pancreatic tissue and tissue affected by pancreatitis as detected by two-dimensional gel electrophoresis and mass spectrometry. Cancer Res 64(24):9018-26, 2004.
7. **Li D**, Liu H, Jiao L, Chang DZ, Beinart G, Wolff RA, Evans DB, Hassan MM, Abbruzzese JL. Homologous Recombination DNA Repair Gene Polymorphisms Are Associated with Reduced Survival in Pancreatic Cancer Patients. *Cancer Res*., 66 (6):3323-30, 2006. PMID: 16540687
8. Suzuki H, Jiao L, Li Y, Doll MA, Hein DW, Hassan MM, Day RS, Bondy ML, Abbruzzese JL, and **Li D**. Interaction of the Cytochrome P4501A2, SULT1A1 and NAT Gene Polymorphisms with Smoking and Dietary Mutagen Intake in Modification of the Risk of Pancreatic Cancer. *Carcinogenesis*, 29(6): 1184-1191, 2008. PMID: 18499698
9. Suzuki H, Li Y, Dong X, Hassan M, Abbruzzese JL, **Li D**. Effect of insulin-like growth factor gene polymorphisms alone or in interaction with diabetes on the risk of pancreatic cancer. *Cancer Epi. Biom. Prev*., 17:3467-3473, 2008. PMID: 19064563
10. **Li D**, Morris JS, Liu J, Hassan M, Day RS, Bondy ML, Abbruzzese JL. Body Mass Index and Risk, Age of Onset, and Survival in Pancreatic Cancer Patients. *JAMA*, 301: 2553-2562, 2009. PMID: 19549972
11. Dong X, Jiao L, Li Y, Evans DB, Wang H, Hess KR, Abbruzzese JL, and **Li D**. Significant Associations of Mismatch Repair Gene Polymorphisms with Clinical Outcome of Pancreatic Cancer. *J Clin Oncol*, 27:1592-7, 2009.
12. **Li D**, Yeung SJ, Hassan M, Konopleva M, Abbruzzese JL. Antidiabetic Therapies Affect Risk of Pancreatic Cancer. *Gastroenterology,* 137:482-488, 2009. PMID: 19375425.
13. **Li D**, Suzuki H, Liu B, Morris J, Liu J, Okazaki T, Li Yanan, Chang P, Abbruzzese JL. DNA Repair Gene Polymorphisms and Risk of Pancreatic Cancer. *Clinical Cancer Res*., 15 (2) 740-6, 2009. PMID: 19147782
14. Tang H, Dong X, Day RS, Hassan MM, **Li D.** Antioxidant Genes, Diabetes and Dietary Antioxidants in Association with Risk of Pancreatic Cancer. Carcinogenesis, 31 (4): 607-13, 2010. PMID: 20097730.
15. Dong X, Javle M, Hess K, Shroff R, Abbruzzese JL, **Li D**. Insulin-like Growth Factor Axis Gene Polymorphisms and Clinical Outcome in Pancreatic Cancer. *Gastroenterology,* 139:464–73, 2010. PMID: 20416304.

D. Research Support

Ongoing Research Support

5 R01 CA154823 02 Klein (PI) 4/1/2011-3/31/2015
NIH/NCI
Validation and Fine Mapping of Pancreatic Cancer Susceptibility Loci
Conduct a genome-wide association study on pancreatic cancer and identify risk alleles.
Role: Co-Investigator

1 R01 CA172880-01A1 Jiao (PI) 9/1/2013-8/31/2016
NIH/NCI
Advanced Glycation End-Products and Risk of Pancreatic Cancer
Demonstrate the role of advanced glycation end products and their role in pancreatic cancer.
Role: Co-Investigator

1 R01 CA169122-01A1 Wei (PI) 9/1/2013-8/31/2017
NIH/NCI
Genetic susceptibility and risk model for pancreatic cancer
Conduct gene-environment interaction analysis on GWAS data and test the genetic markers in a risk prediction model
Role: Co-Investigator

1 RO1 CA181244-01 Scheet (PI) 7/1/2014-6/30/2019
NIH/NCI
Discovery of risk loci and genomics of pancreatic cancer throuç xome sequencing
Identify susceptibility genes for pancreatic cancer
Role: Co-investigator

Li, D (PI) 8/1/2013-7/31/2016
Khalifa Bin Zayed Al Nahyan Foundation
Biomarkers for early detection of pancreatic cancer
Identify genetic and non-genetic risk factors for pancreatic cancer.
Role: Principal Investigator

Completed Research Support

CA137803 Li (PI) 9/1/2008-8/31/2011
NIH/NCI
N-nitroso Compounds and Pancreatic Cancer
To demonstrate the role of dietary nitrosamine exposure and risk of pancreatic cancer.
Role: Principal Investigator

Li (PI) 10/1/2010-8/31/2011
Hogan Research Funds
ABO Blood Type, Thrombosis, and Pancreatic Cancer
Role: Principal Investigator

LS2011-00034286LG 01 Li (PI) 12/20/2010-9/20/2012
ImClone
Biomarkers of TGFB Pathway and Pancreatic Cancer
Role: Principal Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Lee, Jeffrey E.	Professor & Chair, Department of Surgical Oncology
eRA COMMONS USER NAME (credential, e.g., agency login)	
LEFREY	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YYYY	FIELD OF STUDY
Dartmouth College, Hanover, NH	BA	4/1979	Biochemistry
Stanford University School of Medicine, Stanford, CA	MD	4/1984	Medicine
Stanford University Medical Center, Stanford, CA	Internship	1984-1985	General Surgery
Stanford University Medical Center, Stanford, CA	Resident	1984-1990	General Surgery
Stanford University School of Medicine, Stanford, CA	Research Fellow	7/1987-6/1989	Immunology
Stanford University Medical Center, Stanford, CA	Chief Resident	1990-1991	General Surgery
The University of Texas MD Anderson Cancer Center, Houston, TX	Fellowship	1991-1993	Surgical Oncology

A. Personal Statement

My laboratory is primarily interested in defining the role of genetic polymorphisms in melanoma disease progression. Our overall goal is to identify molecular markers to elucidate mechanisms of melanoma progression, aid in the development of surveillance strategies, and assist in the selection of patients for systemic therapies. An important potential mechanism regulating melanoma recurrence and progression is variation in the immune and inflammatory response to melanoma; one important way to identify relevant biologic markers is to examine the relationship of human genetic variation (genetic polymorphisms) to disease recurrence and progression. Our investigations have identified specific polymorphisms in human leukocyte antigen (HLA) class I and II, transforming growth factor-beta 1 (TGF-beta1), and vascular endothelial growth factor (VEGF) genes; as well as IL-12 and interferon gamma (IFN-gamma) blood levels; as independent markers of disease progression and prognosis in melanoma patients. HLA polymorphisms regulate melanoma immune responses by differential binding of peptide antigens; TGF-beta1 polymorphisms regulate tumor growth and metastasis by differential expression of TGF-beta1 and by immunomodulation, and IL-12 and IFN-gamma are important immunoregulatory cytokines. We therefore have hypothesized that genetic polymorphisms in these and other immune and inflammatory genes influence host response to melanoma and thereby melanoma progression. We have begun a coordinated investigation of our most promising and mechanistically related polymorphisms in a large cohort of patients with melanoma. In addition to the markers mentioned above, additional genes and proteins under active evaluation include CTLA-4, MC1R, ASIP, TYR, TYRP1, CRP, and vitamin D. Finally, together with our collaborators, we are currently analyzing results of a genome-wide analysis of 1 million single-nucleotide polymorphisms (SNPs) in 2000 melanoma patients to identify candidate loci most strongly linked with melanoma progression. We will use this information to develop a risk model of melanoma progression incorporating clinical, histopathologic, serologic, and genetic prognostic information. Determination of the most important genomic polymorphisms influencing melanoma progression will lead to more accurate identification of high-risk patients for adjuvant therapies, more accurate selection of systemic therapies for patients with recurrence, and suggest novel treatments.

B. Positions and Honors

Positions and Employment

1997-2010 Medical Director, Ben Love/El Paso Corporation Melanoma and Skin Center, Melanoma and Skin Center, The University of Texas MD Anderson Cancer Center, Houston, TX

2003-present Professor, Department of Surgical Oncology, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX

2010-present Department Chair, Department of Surgical Oncology, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX

Honors

1994	Gillson Longenbaugh Foundation Award
1996	American College of Surgeons, Fellow
1998	Outstanding Teacher Award, M.D. Anderson Department of Surgical Oncology Fellows
2001	Castle Connolly Top Doctor in America
2004	America's Top Surgeons
2010-present	Irving and Nadine Mansfield and Robert David Levitt Cancer Research Chair, UT MD Anderson Cancer Center, Houston, TX
2011	Outstanding Teacher Award, M.D. Anderson Department of Surgical Oncology Fellows

C. Selected Peer-reviewed Publications (Selected from 332 peer-reviewed publications)
Most relevant to the current application

1. **Lee JE**, Lu M, Mansfield PF, Platsoucas CD, Reveille JD, Ross MI. Malignant melanoma: relationship of the human leukocyte antigen class II gene DQB1*0301 to disease recurrence in American Joint Committee on Cancer Stage I or II. Cancer 78:758-63, 1996. PMID: 8756369.
2. Porter GA, Abdalla J, Lu M, Smith S, Montgomery D, Grimm E, Ross MI, Mansfield PF, Gershenwald JE, **Lee JE**. Significance of plasma cytokine levels in melanoma patients with histologically negative sentinel lymph nodes. Ann Surg Oncol 8(2):116-22, 3/2001. PMID: 11258775.
3. Mittendorf EA, Lim SJ, Schacherer CW, Lucci A, Cormier JN, Mansfield PF, Gershenwald JE, Ross MI, **Lee JE**. Melanoma adrenal metastasis: natural history and surgical management. Am J Surg 195(3):363-8; discussion 368-9, 3/2008. e-Pub 1/2008. PMID: 18206850.
4. Eton O, Ross MI, East MJ, Mansfield PF, Papadopoulos N, Ellerhorst JA, Bedikian AY, **Lee JE**. Autologous tumor-derived heat-shock protein peptide complex-96 (HSPPC-96) in patients with metastatic melanoma. J Transl Med 8(9):9, 2010. e-Pub 1/2010. PMCID: PMC2835652.
5. Xing Y, Bronstein Y, Ross MI, Askew RL, **Lee JE**, Gershenwald JE, Royal R, Cormier JN. Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a Meta-analysis. J Natl Cancer Inst 103(2):1-14, 1/2011. e-Pub 11/2010. PMCID: PMC3022618.
6. Nan H, Xu M, Zhang J, Zhang M, Kraft P, Qureshi AA, Chen C, Guo Q, Hu FB, Rimm EB, Curhan G, Song Y, Amos CI, Wang LE, **Lee JE**, Wei Q, Hunter DJ, Han J. Genome-wide association study identifies nidogen 1 (NID1) as a susceptibility locus to cutaneous nevi and melanoma risk. Hum Mol Genet 20(13):2673-9, 7/2011. e-Pub 4/2011. PMCID: PMC3110001.
7. Nan H, Xu M, Kraft P, Qureshi AA, Chen C, Guo Q, Hu FB, Curhan G, Amos CI, Wang LE, **Lee JE**, Wei Q, Hunter DJ, Han J. Genome-wide association study identifies novel alleles associated with risk of cutaneous basal cell carcinoma and squamous cell carcinoma. Hum Mol Genet 20(18):3718-24, 9/2011. e-Pub 6/2011. PMCID: PMC3159556.
8. Amos CI, Wang LE, **Lee JE**, Gershenwald JE, Chen WV, Fang S, Kosoy R, Zhang M, Qureshi AA, Vattathil S, Schacherer CW, Gardner JM, Wang Y, Bishop DT, Barrett JH, GenoMEL Investigators, MacGregor S, Hayward NK, Martin NG, Duffy DL, Q-Mega Investigators, Mann GJ, Cust A, Hopper J, AMFS Investigators, Brown KM, Grimm EA, Xu Y, Han Y, Jing K, McHugh C, Laurie CC, Doheny KF, Pugh EW, Seldin MF, Han J, Wei Q. Genome-wide association study identifies novel loci predisposing to cutaneous melanoma. Hum Mol Genet 20(24):5012-23, 12/2011. e-Pub 9/2011. PMCID: PMC3298855.
9. Song F, Qureshi AA, Zhang J, Zhan J, Amos CI, **Lee JE**, Wei Q, Han J. Exonuclease 1 (EXO1) gene variation and melanoma risk. DNA Repair (Amst) 11(3):304-9, 3/2012. e-Pub 1/2012. PMCID: PMC3274568.
10. Liu H, Wei Q, Gershenwald JE, Prieto VG, **Lee JE**, Duvic M, Grimm EA, Wang LE. Influence of single nucleotide polymorphisms in the MMP1 promoter region on cutaneous melanoma progression. Melanoma Res 22(2):169-75, 4/2012. e-Pub 12/2011. PMCID: PMC3296883.
11. Shoag J, Haq R, Zhang M, Liu L, Rowe GC, Jiang A, Koulisis N, Farrel C, Amos CI, Wei Q, **Lee JE**, Zhang J, Kupper TS, Qureshi AA, Cui R, Han J, Fisher DE, Arany Z. PGC-1 coactivators regulate MITF and the tanning response. Mol Cell 49(1):145-57, 1/2013. e-Pub 11/2012. PMID: 23201126.
12. Li X, Liang L, Zhang M, Song F, Nan H, Wang LE, Wei Q,**Lee JE**, Amos CI, Qureshi AA, Han J. Obesity-related genetic variants, human pigmentation, and risk of melanoma. Hum Genet. e-Pub 3/2013. PMID: 23539184, PMCID 3683389.
13. Zhang M, Song F, Liang L, Nan H, Zhang J, Liu H, Wang LE, Wei Q, **Lee JE**, Amos CI, Kraft P, Qureshi AA, Han J. Genome-wide association studies identify several new loci associated with pigmentation traits and skin cancer risk in European Americans. Hum Mol Genet. e-Pub 4/2013. PMID: 23548203, PMCID

3690971.
14. Fang S, Han J, Zhang M, Wang LE, Wei Q, Amos CI, **Lee JE**. Joint effect of multiple common SNPs predicts melanoma susceptibility. PLoS One 8(12):e85642, 2013. e-Pub 12/2013. PMCID: PMC3877376.
15. Xiao F, Ma J, Cai G, Fang S, **Lee JE**, Wei Q, Amos CI. Natural and orthogonal model for estimating gene-gene interactions applied to cutaneous melanoma. Hum Genet 133(5):559-74, 5/2014. e-Pub 11/2013. PMID: 24241239.

Additional recent publications of importance to the field (in chronological order)

1. **Lee JE**, Abdalla J, Porter GA, Bradford L, Grimm EA, Reveille JD, Mansfield PF, Gershenwald JE, Ross MI. Presence of the human leukocyte antigen class II gene DRB1*1101 predicts interferon gamma levels and disease recurrence in melanoma patients. Ann Surg Oncol 9(6):587-93. Accompanying editorial: Sondak VK, Chang AE. Melanoma and human leukocyte antigen status: the missing link? Ann Surg Oncol. 2002;9(8):723-724., 7/2002. PMID: 12095976.
2. Wei Q, **Lee JE**, Gershenwald JE, Ross MI, Mansfield PF, Strom SS, Wang LE, Guo Z, Qiao Y, Amos CI, Spitz MR, Duvic M. Repair of UV light-induced DNA damage and risk of cutaneous malignant melanoma. J Natl Cancer Inst 95(4):308-15, 2/2003. PMID: 12591987.
3. Aloia TA, Gershenwald JE, Andtbacka RH, Johnson MM, Schacherer CW, Ng CS, Cormier JN, **Lee JE**, Ross MI, Mansfield PF. Utility of computed tomography and magnetic resonance imaging staging before completion lymphadenectomy in patients with sentinel lymph node-positive melanoma. J Clin Oncol 24(18):2858-65, 6/2006. PMID: 16782925.
4. Cornett WR, McCall LM, Petersen RP, Ross MI, Briele HA, Noyes RD, Sussman JJ, Kraybill WG, Kane JM, 3rd, Alexander HR, **Lee JE**, Mansfield PF, Pingpank JF, Winchester DJ, White RL, Jr, Chadaram V, Herndon JE, 2nd, Fraker DL, Tyler DS. Randomized multicenter trial of hyperthermic isolated limb perfusion with melphalan alone compared with melphalan plus tumor necrosis factor: American College of Surgeons Oncology Group Trial Z0020. J Clin Oncol 24(25):4196-201, 9/2006. PMID: 16943537.
5. Cormier JN, Xing Y, Ding M, Cantor SB, Salter KJ, **Lee JE**, Mansfield PF, Gershenwald JE, Ross MI. Cost effectiveness of adjuvant interferon in node-positive melanoma. J Clin Oncol 25(17):2442-8, 6/2007. PMID: 17557957.

D. Research Support

Ongoing Research Support

2P30 CA016672 38 DePinho (PI) 9/4/1988-6/30/2018
NIH/NCI
To provide support for shared resources that have facilitated and enhanced research productivity. To enhance faculty recruitment, to provide seed support for multi-investigator grants and to develop a limited number of new shared resources.
Role: Co-Leader

5 T32 CA009599-26 Meric-Bernstam (PI) 2/1/2008-1/31/2018
NIH/NCI
Training of Academic Surgical Oncologists
To train academic surgical oncologists who will be excellent clinical surgeons as well as productive investigators.
Role: Mentor

5P01CA12891304 Hwu (PI) 9/10/2008-8/31/2014
NIH/NCI
Activation of Plasmacytoid Dendritic Cells (pDC's) to Induce Antitumor Activity
Activation of plasmacytoid dendritic cells using TLR agonists will result in an inflammatory cascade that will lead to both improved T-cell priming as well as enhanced migration to and function at the tumor site. Four integrated projects and three cores are proposed to evaluate the role of plasmacytoid dendritic cells in antitumor immunity and identify methods to improve vaccine strategies. These projects represent a systematic evaluation of this issue from laboratory to clinical endpoints.
Role: Collaborator

5 P50 CA093459 06 Grimm (PI) 9/15/2010-8/31/2015
NIH/NCI
UT M. D. Anderson Cancer Center SPORE in Melanoma - Core A

The overall goal of the U.T. M.D. Anderson SPORE in Skin Cancer is to facilitate innovative research in the prevention, detection and treatment of melanoma. The goal of the Administrative Core is to organize SPORE-related research efforts.
Role: Co-director

5 P50 CA093459 06 Grimm (PI) 9/15/2010-8/31/2015
NIH/NCI
UT M. D. Anderson Cancer Center SPORE in Melanoma - DRP
The goal of the SPORE Development Research Program is to promote new ideas directed toward the SPORE translational melanoma research. SPORE guidelines mandate diligent efforts to identify and fund pilot projects by providing a formal developmental Research Program (DRP) that will highlight and support new research endeavors, whether collaborative among scientists within one or more SPOREs, or with new scientists outside the SPORE environment, that may eventually reduce the incidence and morbidity or increase the survival of melanoma patients.
Role: Co-director

5 P50 CA093459 06 Grimm (PI) 9/15/2010-8/31/2015
NIH/NCI
UT M. D. Anderson Cancer Center SPORE in Melanoma - Project 5
The overall goal of the UT M. D. Anderson SPORE in Skin Cancer is to facilitate innovative research in the prevention, detection and treatment of melanoma. The goal of Project 5 is to determine the genetic polymorphisms most strongly linked to melanoma progression, and to incorporate these polymorphisms into an integrated risk model of melanoma disease progression.
Role: Leader

5 P50 CA093459 06 Grimm (PI) 9/15/2010-8/31/2015
NIH/NCI
UT MD Anderson Cancer Center SPORE in Melanoma - CDP
The goal of the Melanoma SPORE Career Development Program (CDP) is to develop an integrated cadre of investigators at all levels of training dedicated to translational research on human melanoma.
Role: Co-Director

5 R03 CA173792 02 Fang (PI) 1/1/2013-12/31/2014
NIH/NCI
Genetic determinants of Breslow tumor thickness and their impact on melanoma progression
To determine common genetic variants and gene expression patterns associated with Breslow tumor thickness and melanoma progression
Role: Contributor

Completed Research Support
None

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Ng, Chaan S.	Professor of Radiology
eRA COMMONS USER NAME (credential, e.g., agency login) CHAANNG	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YYYY	FIELD OF STUDY
Christ's College, University of Cambridge, Cambridge, United Kingdom	BA	1/1979	Engineering
Christ's College, University of Cambridge, Cambridge, United Kingdom	MA	1/1983	Chemical Engineering
Royal Free Hospital School of Medicine, University of London, London, United Kingdom	MBBS	1/1989	Medicine
Christ's College, University of Cambridge, Cambridge, United Kingdom	MEng	1/1993	Chemical Engineering

A. Personal Statement

I am a radiologist specializing in Body Imaging (Abdomen and Pelvis), with extensive experience in CT, MRI and PET. I am actively involved in the development and evaluation of functional imaging techniques, including DCE-CT. I lead the imaging aspects of several clinical trials involving targeted imaging agents.

B. Positions and Honors

Positions and Employment

1998-2001 University Lecturer (Assistant Professor Equivalent), School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom
1999-2001 College Teaching Fellow, Wolf Fellow, and Supervisor, Christ's College, Cambridge, United Kingdom
2001-2006 Assistant Professor, Department of Diagnostic Radiology, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX
2006-2011 Associate Professor, Department of Diagnostic Radiology, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX
2008-2010 Assistant Professor, Department of Diagnostic and Interventional Imaging, The University of Texas Medical School at Houston, Houston, TX
2010-present Associate Professor, Department of Diagnostic and Interventional Imaging, The University of Texas Medical School at Houston, Houston, TX
2011-present Professor, Department of Diagnostic Radiology, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX

Honors

1985 William Marsden Scholarship and Medal, Royal Free Hospital School of Medicine, University of London
1989 Distinction in Clinical Pharmacology and Therapeutics in Final M.B.B.S., University of London
1999 Cum Laude Poster Presentation, "MR Imaging of tumors involving the perineum: imaging anatomy, diagnosis and staging, treatment evaluation, and surgical correlation," European Congress of Radiology
2002 Best Scientific Paper and Prize Oral Presentation, "A prospective randomised study of early abdominopelvic computed tomography (CT) in the management of patients with acute abdominal pain of indeterminate aetiology," European Congress of Radiology
2002 Robert and Elma Kemp Harper Prize for Best Paper in Gastrointestinal Radiology in Clinical Radiology, "Caecal carcinomas in the elderly: serosal margin blurring and terminal ileal wall thickening, useful signs in minimal preparation CT," Royal College of Radiologist
2007 Cum Laude Educational Exhibition, "Papillary renal cell carcinoma: radiologic-pathologic correlation and spectrum of disease," Radiological Society of North America
2008 Robert and Elma Kemp Harper Prize for Best Paper in Gastrointestinal Radiology in Clinical

Radiology, "Minimal-preparation abdominopelvic CT in frail and elderly patients: prognostic value of colonic and extracolonic findings," Royal College of Radiologists

2010 Shipley Award for Best Abstract Presented, "Results of adopting posterior retroperitoneoscopic adrenalectomy into surgical care," Southern Surgical Association

C. Selected Peer-reviewed Publications (Selected from 129 peer-reviewed publications)

Most relevant to the current application

1. Coleman RL, Duska LR, Ramirez PT, Heymach JV, Kamat AA, Modesitt SC, Schmeler KM, Iyer RB, Garcia ME, Miller DL, Jackson EF, **Ng CS**, Kundra V, Jaffe R, Sood AK. Phase 1-2 study of docetaxel plus aflibercept in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer. Lancet Oncol 12(12):1109-17, 11/2011. PMCID: PMC3444811.
2. Kurzrock R, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, Pfister DG, Cohen EE, Janisch L, Nauling F, Hong DS, **Ng CS**, Ye L, Gagel RF, Frye J, Müller T, Ratain MJ, Salgia R. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. J Clin Oncol 29(19):2660-6, Jul, 2011. e-Pub 5/2011. PMCID: PMC3646303.
3. Naing A, Kurzrock R, Burger AM, Gupta S, Lei X, Busaidy NL, Hong DS, Chen HX, Doyle L, Heilbrun LK, Rohren E, **Ng C**, Chandhasin C, Lorusso PM. Phase I trial of Cixutumumab combined with Temsirolimus in patients with advanced cancer. Clin Cancer Res 17(18):6052-60, Sept, 2011. PMCID: PMC3176947.
4. **Ng CS**, Chandler AG, Wei W, Herron DH, Anderson EF, Kurzrock R, Charnsangavej C. Reproducibility of CT perfusion parameters in liver tumors and normal liver. Radiology 260(3):762-70, Sept, 2011. e-Pub 7/2011. PMCID: PMC3156998.
5. **Ng CS**, Chandler A, Wei W, Anderson EF, Herron DH, Charnsangavej C, Kurzrock R. Reproducibility of perfusion parameters obtained from perfusion CT in lung tumors. AJR Am J Roentgenol 197(1):113-121, Jul, 2011. PMID: 21701018.
6. Davies MA, Fox PS, Papadopoulos NE, Bedikian AY, Hwu WJ, Lazar AJ, Prieto VG, Culotta KS, Madden TL, Xu Q, Huang S, Deng W, **Ng CS**, Gupta S, Liu W, Dancey JE, Wright JJ, Bassett RL, Hwu P, Kim KB. Phase I study of the combination of Sorafenib and Temsirolimus in patients with metastatic melanoma. Clin Cancer Res. e-Pub 2/2012. PMID: 22223528.
7. Chandler A, Wei W, Anderson EF, Herron DH, Ye Z, **Ng CS**. Validation of motion correction techniques for liver CT perfusion studies. Br J Radiol. e-Pub 2/2012. PMCID: PMC3587085.
8. Bronstein Y, **Ng CS**, Rohren E, Ross MI, Lee JE, Cormier J, Johnson VE, Hwu WJ. PET/CT in the Management of Patients With Stage IIIC and IV Metastatic Melanoma Considered Candidates for Surgery: Evaluation of the Additive Value After Conventional Imaging. AJR Am J Roentgenol 198(4):902-8, 4/2012. PMID: 22451559.
9. Jain RK, Lee JJ, **Ng C**, Hong D, Gong J, Naing A, Wheler J, Kurzrock R. Change in tumor size by RECIST correlates linearly with overall survival in phase I oncology studies. J Clin Oncol. e-Pub 6/2012. PMCID: PMC3413279.
10. **Ng CS**, Waterton JC, Kundra V, Brammer D, Ravoori M, Han L, Wei W, Klumpp S, Johnson VE, Jackson EF. Reproducibility and comparison of DCE-MRI and DCE-CT perfusion parameters in a rat tumor model. Technol Cancer Res Treat 11(3):279-88, 6/2012. e-Pub 3/2012. PMCID: 22417064.
11. **Ng CS**, Chandler AG, Wei W, Anderson EF, Herron DH, Kurzrock R, Charnsangavej C. Effect of dual vascular input functions on CT perfusion parameter values and reproducibility in Liver Tumors and Normal liver. J Comput Assist Tomogr 36(4):388-93, 7/2012. PMID: 22805665.
12. **Ng CS**, Chandler A, Wei W, Herron DH, Anderson EF, Kurzrock R, Charnsangavej C. Effect of sampling frequency on perfusion values in CT perfusion of lung tumors. AJR 200(2):W155-62, 2/2013. PMID: 23345379.
13. Grubbs EG, Rich TA, **Ng C**, Bhosale PR, Jimenez C, Evans DB, Lee JE, Perrier ND. Long-term outcomes of surgical treatment for hereditary pheochromocytoma. J Am Coll Surg 216(2):280-9, 2/2013. PMID: 23317575.
14. **Ng CS**, Hobbs BP, Chandler AG, Anderson EF, Herron DH, Charnsangavej C, Yao J. Metastases to the Liver from Neuroendocrine Tumors: Effect of Duration of Scan Acquisition on CT Perfusion Values. Radiology 269(3):758-67, 12/2013. PMID: 23824990.
15. **Ng C,** Chandler AG, Yao J, Herron DH, Anderson EF, Charnsangavej C, Hobbs BP. Effect of pre-enhancement set-point on CT perfusion values in normal liver and metastases to the liver from neuroendocrine tumors. JCAT. In Press. PMID: 23317575.

D. Research Support

Ongoing Research Support

5 U01 CA062461 Yao (PI) 3/1/1994-2/28/2015
NIH/NCI
Phase I studies of targeted anti-cancer therapies.
Goals: To determine the effects of NCI-CTEP derived anti-cancer agents in both hematological malignancies/solid tumors using correlative studies with the development of cellular targets.
Role: **Significant Contributor**

P50CA093459 Grimm (PI) 6/1/2010-8/1/2015
NIH/NCI
UT MD Anderson Cancer Center SPORE in melanoma
Project 4: A Phase I Study of PAR-1 (or IL-8) Gene Targeting using Neutral Liposomal Small Interfering RNA Delivery in Refractory Advanced Melanoma.
Goals: To evaluate PAR-1 (or IL-8) siRNA packaged in neutral liposomes as a possible therapeutic modality for advanced melanoma alone and/or in combination with chemotherapy.
Role: **Co-Investigator**

DICRC-02-2010 Ng (PI) 12/1/2010-present
DICRC
Pilot study assessing the technical efficacy of computed tomography urography (CTU) vs. intravenous urography (IVU), with particular focus on patients at risk of urothelial tumors.
Goals: Comparison of accuracy of CTU vs. IVU for lesion detection.
Role: **Principal Investigator**

5 U01 CA080098 12 Ng (PI) 1/1/2011-present
ACRIN 6695
Perfusion CT Imaging to evaluate treatment response in patients participating in GOG-0262, a phase III trial of every 3-weeks paclitaxel Versus dose dense weekly paclitaxel in combination with carboplatin with or without concurrent and consolidation bevacizumab in the treatment of primary stage II, III or IV epithelial ovarian, peritoneal or fallopian tube cancer.
Goals: To assess CT perfusion as an early biomarker in ovarian cancer therapy.
Role: **Principal Investigator**

Davies (PI) 10/10/2012-10/11/2015
Genentech, Inc.
Patterns and outcomes of treatment sequencing in metastatic melanoma.
Goals: To assess patterns and outcomes of treatment sequencing with ipilimumab and vemurafenib in metastatic melanoma.
Role: **Collaborator**

Completed Research Support

Charnsangavej (PI) 10/1/2003-10/1/2008
GE Medical Systems
Quantitative CT perfusion in the liver.
Goals: To assess the technique and reproducibility of CT perfusion in the liver.
Role: **Co-Investigator**

Ng (PI) 1/1/2004-12/1/2006
Mike Hogg Fund
Reproducibility of functional parameters from dynamic contrast enhancement magnetic resonance imaging (dceMRI), and a comparison with dynamic contrast enhancement computed tomography in lung and liver malignancies.
Goals: To assess the technique and reproducibility of CT perfusion in lung and liver.
Role: **Principal Investigator**

CS2004-00010744HM Ng (PI) 4/1/2004-8/1/2007
Pfizer Pharmaceuticals
Reproducibility of functional and structural imaging parameters from dynamic contrast enhancement magnetic resonance imaging (dceMRI) in lung and liver computed tomography (dceCT) parameters in lung malignancies
Goals: To assess the technique and reproducibility of MRI and CT perfusion in the lung and liver.
Role: **Principal Investigator**

LS2006-00016301PP-6 Bast (PI) 7/1/2005-7/1/2010
AstraZeneca
Objective evaluation of DCE-CT and DCE-MRI in assessing tumor perfusion and permeability changes with AZ drugs in the angiogenesis biological effect area in an animal model.
Goals: To assess the technique and reproducibility of MRI and CT perfusion in an animal model.
Role: **Project Leader**

Li (PI) 12/1/2005-6/1/2009
MDACC, Technology Review Committee
Pg-Gd: a novel MRI blood-pool agent with wide applicability to non-invasive vascular and functional imaging and delineation of tissue necrosis.
Goals: To investigate the potential of Pg-Gd to assess tissue necrosis.
Role: **Collaborator**

CS2006-00018400JW Tannir (PI) 5/1/2006-8/1/2007
Pfizer Pharmaceuticals
Phase II trial of sunitinib malate (Sutent) therapy in patients with advanced non-clear cell renal cell carcinoma.
Goals: To investigate sunitinib in a Phase II clinical trial.
Role: **Collaborator**

1 U19 CA121503 Cohen (PI) 9/1/2006-8/1/2010
NIH/NCI
International Center of TCM for Cancer
Goals: To investigate the efficacy of herbal/natural products in cancer treatment.
Role: **Collaborator**

CS2008-00023493MA Ng (PI) 3/1/2008-6/1/2010
GE Healthcare
Pilot study assessing the technical efficacy of computed tomography urography (CTU) vs. intravenous urography (IVU), with particular focus on patients at risk of urothelial tumors.
Goals: Comparison of accuracy of CTU vs. IVU for lesion detection.
Role: **Principal Investigator**

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Chen, Xiangning	Associate Professor
eRA COMMONS USER NAME SAMCHEN	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Houston Univ. Dept. of Biochem & Biophys.	Ph.D.	1989-1994	Genomics/Mol. Biol.
Institute of Genetics, Academia Sinica	M.S.	1983-1986	Genetics/Biochemistry
Guangxi Agricultural Institute, China	B.A.	1977-1982	Agronomy

A. PERSONAL STATEMENT

Dr. Chen was trained in genetics, genomics and molecular biology. In recent years he has established himself as a productive researcher in the field of psychiatric genetics. Dr. Chen has established collaborative relationship with Dr. Momiao Xiong on his schizophrenia exome sequencing project. His specialty covers the genetics of schizophrenia, smoking, nicotine dependence and other substances of abuse, anxiety and depression. One of the areas Dr. Chen focuses on is to integrate genetics, genomics and informatics to study complex human diseases, including cancer. The publications below list his works most directly relevant to this application. His training, working experience and publications demonstrate that he has the expertise, ability and capacity required for this application.

B. POSITION AND HONOR

May 1994 - June 1997. Post-doctoral fellow, Washington University School of Medicine, St. Louis, MO.
April 1996-March 1998. National research service award (NRSA) NIH. 1-F32-HG00156-01.
July 1997 – June 1999. Research Instructor, Washington University School of Medicine, St. Louis, MO.
July 1999-July 2000. Scientist, project leader, Cereon Genomics, LLC, Cambridge, MA.
July 2000-Feb. 2001. Senior Scientist, project leader, CuraGen Corporation, New Haven, CT.
Feb. 2001-2008. Assistant professor, Virginia Institute for Psychiatric and Behavioral Genetics, and Department of Psychiatry, Virginia Commonwealth University, Richmond, VA.
Feb. 2008-present. Associate professor, Virginia Institute for Psychiatric and Behavioral Genetics, and Department of Psychiatry, Virginia Commonwealth University, Richmond, VA.

C. SELECTED PEER-REVIEWED PUBLICATION (FROM OVER 80 PUBLICATIONS)

Most relevant to this application:

1. J Chen, DH Brunzell, K Jackson, A van der Vaart, J-Z. Ma, TJ Payne, R Sherva, LA Farrer, P Gejman, DF Levinson, P Holmans, SH. Aggen, I Damaj, P-H Kuo, BT Webb, R Anton, HR. Kranzler,J Gelernter, MD Li, KS Kendler, **X Chen: 2011**. ACSL6 Is associated with the number of cigarettes smoked and its expressions is altered by chronic nicotine exposure. Plos ONE. 6(12):e28790. PMC3243669.
2. KS Kendler, **X Chen**, D Dick, H Maes, N Gillespie, MC Neale, Riley B. **2012.** Recent advances in the genetic epidemiology and molecular genetics of substance use disorders. Nat Neurosci. 15(2):181-9. PMC3297622.
3. J Ji, K Sundquist, Y Ning, KS Kendler, J Sundquist, **X Chen. 2013**. Incidence of Cancer in Patients With Schizophrenia and Their First-Degree Relatives: A Population-Based Study in Sweden. Schizophr Bull. 39(3):527-36. PMC3627751.
4. KS Kendler, J Myers, IM Mamaj, **X Chen. 2013.** Early age of smoking onset is related to increased risk for subsequent nicotine dependence: A monozygotic co-twin control study. Am J Psychiatry. 170(4):408-13. PMID: 23318372. PMC3615117.
5. Z Zhao, J Xu, J Chen, S Kim, M Reimers, S-A Bacanu, H Yu, C Liu, J Sun, Q Wang, P Jia, F Xu, Y Zhang, KS Kendler, Z Peng, **X Chen. 2014**. Transcriptome Sequencing and Genome-wide Association Analyses Reveal Lysosomal Function and Actin Cytoskeleton Remodeling in Schizophrenia and Bipolar Disorder. Mol Psychiatry, in press. PMCID not available yet.

Additional recent publications of importance to the field (in chronological order)

1. L Zhang, KS Kendler and **X Chen. 2006.** Association of the phosphatase and tensin homolg gene (PTEN) with smoking initiation and Nicotine dependence. Am J Med Genet. 141(1):10-14. PMCID: NA.
2. **X Chen**, VS Williams, SS An, JM Hettema, SH Aggen, MC Neale and KS Kendler. **2008.** The cannabinoid receptor 1 (CNR1) gene association with nicotine dependence. Arch Gen Psychiatry. 65:816-24. PMC2733353.
3. CM Middeldorp, JM Vink, JM Hettema, EJ de Geus, KS Kendler, G Willemsen, MC Neale, DI Boomsma, **X Chen. 2010.** An association between Epac-1 gene variants and anxiety and depression in two independent samples. Am J Med Genet B Neuropsychiatr Genet. 153B:214-219. PMCID: NA.
4. KJ Jackson, Chen Q, Chen J, Aggen SH, Kendler KS, **Chen X. 2010.** Association of histidine-triad nucleotide binding protein 1 (HINT1) gene variants with nicotine dependence. Pharmacogenomics. 11(4):251-7. PMCID: NA.
5. KJ. Jackson, MJ. Marks, RE. Vann, **X Chen**, TF. Gamage, JA. Warner, MI. Damaj. 2010. The role of alpha5 nicotinic acetylcholine receptors in the pharmacological and behavioral effects of nicotine in mice. J Pharmacol Exp Ther. 334(1):137-46. PMCID: NA.
6. KJ Jackson, **X Chen**, MF Miles, J Harenza, MI Damaj. 2011. The neuropeptide galanin and variants in the GalR1 gene are associated with nicotine dependence. Neuropsychopharmacology. 36 (11):2339-48. PMCID: NA.
7. HH Maes, MC Neale, **X Chen**, J Chen, CA Prescott, KS Kendler 2011. A twin association study of nicotine dependence with markers in the CHRNA3 and CHRNA5 genes. Behav Genet. 41(5):680-90. PMC3400498.
8. NL Saccone, RC Culverhouse, T-H Schwantes-An, DS Cannon, **X Chen**, S Cichon et al: **2010.** Multiple independent loci at chromosome 15q25.1 affect smoking quantity: a meta-analysis and comparison with lung cancer and COPD. PloS Genetics, 6: e1001053. PMC2916847.
9. KJ Jackson JB Wang, E Barbier, **X Chen,** MI Damaj. **2012.** Acute behavioral effects of nicotine in male and female HINT1 knockout mice. Genes Brain Behav. In press. PMCID: NA.
10. SM Hartz, SE Short, NL Saccone, R Culverhouse, L Chen, TH Schwantes-An, H Coon, Y Han, SH Stephens, J Sun, **X Chen**, F Ducci, N Dueker et al: 2012. Increased Genetic Vulnerability to Smoking at CHRNA5 in Early-Onset Smokers. *Arch Gen Psychiatry.* **2012**. 69(8):854-60. PMC2912049.

C. RESEARCH SUPPORT

Current

R01 MH101054 (Chen & Kendler) 09/13—08/16
NIMH
Understanding the genetic architecture of schizophrenia in Chinese population
This project uses exome sequencing to discover rare mutations in Chinese family samples.
Role: PI

R01 DA032246 (Damaj) 01/13 – 12/17
NIDA
Genes and molecular pathways in nicotine dependence and withdrawal
This project uses mouse model to identify and characterize genes involved in nicotine dependence and withdrawal.
Role: Co-I

R01 DA025109 (Maes) 03/10 - 01/15
NIDA
Developmental Genetic Epidemiology of Smoking
This project aims to explore the etiology, development, heterogeneity and comorbidity of smoking.
Role: Co-I

R01MH087646 (Hettema) 08/10-07/15
NIMH
The role of genes and environment in anxiety spectrum disorders
This study aims to identify genes involved in anxiety disorders.
Role: Co-I

R01LM011177 (Zhao) 04/12-03/15
NLM
MAPPING THE GENETIC ARCHITECTURE OF COMPLEX DISEASE VIA RNA-SEQ AND GWAS DATA
This study uses RNA seq and GWAS data to map and understand the genetic architecture of schizophrenia.
Role: PI (subcontract)

Completed

Independent Investigator Award (Chen) 11/08-10/13
NARSAD
A comparative study of transcriptome of schizophrenia patients and controls by Solexa sequencing
This project proposes to conduct high-throughput, deep-coverage sequencing of brain transcriptomes of schizophrenia patients and controls.
Role: PI

R21DA027070 (Chen) 10/09-09/13
NIDA
Variants in CHRNA5/CHRNA3/CHRNB4 locus and nicotine dependence
This project uses in vitro and in vivo methods to study how polymorphisms in the CHRNA5/CHRNA3/CHRNB4 locus affect the function of nicotinic receptors, leading to the development of nicotine dependence.
Role: PI

Young Investigator Award (Chen) 05/02-04/05
NARSAD
Using biological haplotypes to identify susceptible genes for schizophrenia
We proposed to use haploid cell lines to construct haplotypes for a few high density schizophrenia families over a large range on chromosome 5 that was indicated by whole genome scan. The goal was to compare the haplotype structures between the affected and controls and associate them to the disease condition.
Role: PI

RO1MH41953 (Kendler) 4/99-2/09
NIMH
The Genetic Epidemiology of Schizophrenia in Ireland
This is a competitive renewal that seeks support to critically extend the Irish Study of High Density Schizophrenia Families by collecting 500 proband-parent triads for family-based association studies.
Role: Co-I

Tobacco settlement foundation, Contract# 5100004ST (Martin) 07/06-06/10
The genetics of smoking and nicotine dependence
This research grant is from the Tobacco settlement foundation of Virginia Commonwealth, and we proposed to conduct genetic studies to identify susceptibility genes to tobacco smoking and nicotine dependence.
Role: Co-I

Stanley Medical Research Institute (Chen) 01/08-02/11
Association studies of T helper cell interleukins and schizophrenia
This project proposes to study interleukins involved in T helper cell differentiation for their roles in schizophrenia.
Role: PI

K01DA019498 (Chen) 09/06-08/12
NIDA
Genetics of nicotine and other abused substances
This application proposes to study the genetics of nicotine and other abused substances.
Role: PI

R03DA027619 (Chen) 09/09-08/12
NIDA
Variants in nicotinic receptors and pharmacogenetics
This project studies the impacts of genetic variants in the nicotinic receptors on subjective and physiologic responses of smokers and non-smokers and tests the utility of these responses as endophenotypes for nicotine dependence.
Role: PI

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2015 **End Date*:** 03-31-2016 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Momiao		Xiong	PhD	PD/PI	140,492.00	3.6			42,148.00	10,116.00	52,264.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **52,264.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12			50,000.00	15,000.00	65,000.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**65,000.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**117,264.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2015 **End Date*:** 03-31-2016 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	
Total Travel Cost	**5,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2015 **End Date*:** 03-31-2016 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	4,000.00
2. Publication Costs	4,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	587,170.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**595,170.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**717,434.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Research On_Campus	54	180,264.00	97,343.00
		Total Indirect Costs	**97,343.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Arif Karim, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**814,777.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: Budget_Justification1014652841.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2016 **End Date*:** 03-31-2017 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Momiao		Xiong	PhD	PD/PI	140,492.00	3.6			42,148.00	10,116.00	52,264.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **52,264.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12			50,000.00	15,000.00	65,000.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**65,000.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**117,264.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2016 **End Date*:** 03-31-2017 **Budget Period: 2**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	
Total Travel Cost	**5,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2016 **End Date*:** 03-31-2017 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	3,000.00
2. Publication Costs	4,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	591,163.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**598,163.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**720,427.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Research On_Campus	54	129,264.00	69,803.00
		Total Indirect Costs	**69,803.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Arif Karim, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**790,230.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: Budget_Justification1014652841.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Momiao		Xiong	PhD	PD/PI	140,492.00	3.6			42,148.00	10,116.00	52,264.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **52,264.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12			50,000.00	15,000.00	65,000.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**65,000.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**117,264.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 3**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	
Total Travel Cost	**5,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	4,000.00
2. Publication Costs	4,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	563,302.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**571,302.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**693,566.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Research On_Campus	54	130,264.00	70,343.00
		Total Indirect Costs	**70,343.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Arif Karim, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**763,909.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: Budget_Justification1014652841.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Momiao		Xiong	PhD	PD/PI	140,492.00	3.6			42,148.00	10,116.00	52,264.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **52,264.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12			50,000.00	15,000.00	65,000.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**65,000.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**117,264.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 4**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	
Total Travel Cost	**5,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 4**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	4,000.00
2. Publication Costs	4,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	542,657.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**550,657.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**672,921.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Research On_Campus	54	130,264.00	70,343.00
		Total Indirect Costs	**70,343.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Arif Karim, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**743,264.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: Budget_Justification1014652841.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Momiao		Xiong	PhD	PD/PI	140,492.00	3.6			42,148.00	10,116.00	52,264.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **52,264.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12			50,000.00	15,000.00	65,000.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**65,000.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**117,264.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 5**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	
Total Travel Cost	**5,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 800771594

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: The University of Texas Health Science Center at Houston

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	4,000.00
2. Publication Costs	4,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	547,279.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**555,279.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**677,543.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Research On_Campus	54	130,264.00	70,343.00
		Total Indirect Costs	**70,343.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Arif Karim, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**747,886.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: Budget_Justification1014652841.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

PERSONNEL:

Momiao Xiong (3.6 cal mo/year), Ph. D., Professor, Division of Biostatistics, Human Genetics Center, at the School of Public Health at The University of Texas Health Science Center at Houston, will devote 30% of effort to the proposed research as Principle Investigator. He has developed numerous statistical methods for data mining, biomarker identification, genetic studies of complex diseases involved in both qualitative and quantitative traits, DNA sequence analysis, detection of gene-gene interaction and gene-environment interaction, gene expression data analysis, pathway analysis, characterization and construction of genetic networks and metabolic networks, and computational systems biology. Dr. Xiong will have overall responsibility for directing all aspects of the research and for communicating critical issues with the entire investigative team. He will interact on a regular basis with Drs. Jeffrey E Lee and Shenying Fang from the Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Dr. Donghui Li from the Department of Gastrointestinal (GI) Medical Oncology, The University of Texas MD Anderson Cancer Center, and Dr. Xiangning Chen, the Virginia Institute for Psychiatric and Behavioral Genetics, the Virginia Commonwealth University. Dr. Xiong will have primary responsibility for performing genome-wide circulating miRNA and methylation profiling by next-generation sequencing, identifying miRNA and methylation biomarkers for early detection of pancreatic cancer from high volume of imaging and whole genome miRNA-seq and methylation-seq profiles and developing an automatic PC early detection system integrating image, miRNA and methylation data with high accuracy. Dr Xiong will supervise a postdoctoral fellow for developing software to implement the developed algorithms and real data analysis to discover miRNA and methylation biomarkers for early detection of PC.

TBA (12.00 cal mo/year), Ph.D., Postdoctoral Fellow, will devote 100% of effort to the proposed research for developing statistical methods, conducting simulations and real data analysis. This fellow will be primary responsible for developing statistical methods for the discovery of clinically significant and actionable epigenetic variants of clinical utility with millions of variables from the integrative analysis of imaging, whole genome miRNA-seq and methylation-seq data. This fellow will also responsible for modelling the imaging intensity of a pixel as a two variate function of its location, the number of methylated reads at the CpG site as a function of genomic position and the position-level number of reads of miRNA as a function of genomic position, and developing mathematical formulation of multiscale integration of imaging, miRNA-seq and methylation-seq data as a feature selection problem. In addition, he will assist Dr. Xiong to develop innovative approaches to large-scale classification and cluster analysis to combine imaging, miRNA and methylation data for early detection of pancreatic cancer. This fellow will assist with writing of research reports and articles.

The salary support requested for all personnel is equal to the level of effort contributed to the project.

Travel ($5,000/year):
Travel for the Principal Investigator and Postdoctoral Fellow ($2,500 each) to attend and present research findings at a scientific/research conference once per year.

Supplies ($4,000/year):
Computer Media and Printer Supplies ($1,000); Software ($3,000)

Other Expense ($4,000/year):
Publication Fees ($4,000)

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		**261,320.00**
Section B, Other Personnel		**325,000.00**
Total Number Other Personnel	5	
Total Salary, Wages and Fringe Benefits (A+B)		**586,320.00**
Section C, Equipment		
Section D, Travel		**25,000.00**
1. Domestic	25,000.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		**2,870,571.00**
1. Materials and Supplies	19,000.00	
2. Publication Costs	20,000.00	
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs	2,831,571.00	
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1		
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		**3,481,891.00**
Section H, Indirect Costs		**378,175.00**
Section I, Total Direct and Indirect Costs (G + H)		**3,860,066.00**
Section J, Fee		

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2015 **End Date*:** 03-31-2016 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Jeffrey	E.	Lee	MD	Co-Investigator	181,500.00	0.6			9,075.00	2,541.00	11,616.00
2 .	Dr.	Shenying		Fang	PhD	Co-Investigator	68,170.00	4.8			27,268.00	7,635.00	34,903.00
3 .	Dr.	Donghui		Li	PhD	Co-Investigator	181,500.00	1.2			18,150.00	5,082.00	23,232.00
4 .	Dr.	Chaan		NG	MD	Co-Investigator	181,500.00	0.6			9,075.00	2,541.00	11,616.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **81,367.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Investigator - Yanan Li, Ph.D.	6			25,397.00	7,111.00	32,508.00
1	Study Coordinator - Catalina Ortega	6			19,371.00	5,423.00	24,794.00
1	TBN, Research Scientist	6			31,500.00	8,820.00	40,320.00
3	**Total Number Other Personnel**					**Total Other Personnel**	**97,622.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**178,989.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2015 **End Date*:** 03-31-2016 **Budget Period: 1**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2015 **End Date*:** 03-31-2016 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	164,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Instrument Maintenance Fee	1,000.00
9 . Shipping and Handling	500.00
Total Other Direct Costs	**165,500.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**344,489.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	60	344,489.00	206,693.00
		Total Indirect Costs	**206,693.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Arif Karim, 415-437-7820

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**551,182.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: Justification1014652735.pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2016 **End Date*:** 03-31-2017 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Jeffrey	E.	Lee	Dr.	Co-Investigator	181,500.00	0.6			9,075.00	2,541.00	11,616.00
2 .	Dr.	Shenying		Fang	PhD	Co-Investigator	68,170.00	4.8			27,268.00	7,635.00	34,903.00
3 .	Dr.	Donghui		Li	PhD	Co-Investigator	181,500.00	1.2			18,150.00	5,082.00	23,232.00
4 .	Dr.	Chaan		Ng	MD	Co-Investigator	181,500.00	0.6			9,075.00	2,541.00	11,616.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **81,367.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Investigator - Yanan Li	6			25,397.00	7,111.00	32,508.00
1	Study Coordinator - Catalina Ortega	6			19,371.00	5,423.00	24,794.00
1	TBN, Research Scientist	6			31,500.00	8,820.00	40,320.00
3	**Total Number Other Personnel**					**Total Other Personnel**	**97,622.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**178,989.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2016 **End Date*:** 03-31-2017 **Budget Period: 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2016 **End Date*:** 03-31-2017 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	164,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Instrument Maintenance Fee	1,000.00
9 . Shipping and Handling	500.00
Total Other Direct Costs	**165,500.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**344,489.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	60	344,489.00	206,693.00
		Total Indirect Costs	**206,693.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Arif Karim, 415-437-7820

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**551,182.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: Justification1014652735.pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Jeffrey	E.	Lee	MD	Co-Investigator	181,500.00	0.6			9,075.00	2,541.00	11,616.00
2 .	Dr.	Shenying		Fang	PhD	Co-Investigator	181,500.00	4.8			27,268.00	7,635.00	34,903.00
3 .	Dr.	Donghui		Li	PhD	Co-Investigator	181,500.00	1.2			18,150.00	5,082.00	23,232.00
4 .	Dr.	Chaan		Ng	MD	Co-Investigator	181,500.00	0.6			9,075.00	2,541.00	11,616.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **81,367.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Investigator - Yanan Li	0.24			10,159.00	2,844.00	13,003.00
1	Study Coordinator - Catalina Ortega	6			19,371.00	5,423.00	24,794.00
1	TBN, Research Scientist	6			31,500.00	8,820.00	40,320.00
3	**Total Number Other Personnel**					**Total Other Personnel**	**78,117.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**159,484.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	102,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Instrument Maintenance Fee	1,000.00
9 . Shipping and Handling	500.00
Total Other Direct Costs	**103,500.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**262,984.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	60	262,984.00	157,790.00
		Total Indirect Costs	**157,790.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Arif Karim, 415-437-7820

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**420,774.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: Justification1014652735.pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Jeffrey	E.	Lee	MD	Co-Investigator	181,500.00	0.6			9,075.00	2,541.00	11,616.00
2 .	Dr.	Shenying		Fang	PhD	Co-Investigator	68,170.00	4.2			23,860.00	6,681.00	30,541.00
3 .	Dr.	Donghui		Li	PhD	Co-Investigator	181,500.00	1.08			16,335.00	4,574.00	20,909.00
4 .	Dr.	Chaan		Ng	MD	Co-Investigator	181,500.00	0.6			9,075.00	2,541.00	11,616.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **74,682.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Investigator - Yanan Li	6			25,397.00	7,111.00	32,508.00
1	Study Coordinator - Catalina Ortega	3			9,686.00	2,711.00	12,397.00
1	TBN, Research Scientist	6			31,500.00	8,820.00	40,320.00
3	**Total Number Other Personnel**					**Total Other Personnel**	**85,225.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**159,907.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 4**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 4**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	20,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Instrument Maintenance Fee	1,000.00
9 . Shipping and Handling	500.00
Total Other Direct Costs	**21,500.00**

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	**181,407.00**

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . MTDC	60	181,407.00	108,844.00
		Total Indirect Costs	**108,844.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Arif Karim, 415-437-7820

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	**290,251.00**

J. Fee	**Funds Requested ($)***

K. Budget Justification* File Name: Justification1014652735.pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Jeffrey	E.	Lee	MD	Co-Investigator	181,500.00	0.6			9,075.00	2,541.00	11,616.00
2 .	Dr.	Shenying		Fang	PhD	Co-Investigator	68,170.00	4.2			23,860.00	6,681.00	30,541.00
3 .	Dr.	Donghui		Li	PhD	Co-Investigator	181,500.00	1.08			16,335.00	4,574.00	20,909.00
4 .	Dr.	Chaan		Ng	MD	Co-Investigator	181,500.00	0.6			9,075.00	2,541.00	11,616.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **74,682.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Investigator - Yanan Li	6			25,397.00	7,111.00	32,508.00
1	Study Coordinator - Catalina Ortega	3			9,686.00	2,711.00	12,397.00
1	TBN, Research Scientist	6			31,500.00	8,820.00	40,320.00
3	**Total Number Other Personnel**					**Total Other Personnel**	**85,225.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**159,907.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 5**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 8007721390000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The University of Texas MD Anderson Cancer Center

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	20,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Instrument Maintenance Fee	1,000.00
9 . Shipping and Handling	500.00
Total Other Direct Costs	**21,500.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**181,407.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	60	181,407.00	108,844.00
		Total Indirect Costs	**108,844.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Arif Karim, 415-437-7820

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**290,251.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: Justification1014652735.pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

Jeffrey E. Lee, Principal Investigator (0.6 calendar months or 5% effort). Dr. Lee is a clinical surgeon and chair of the Department of Surgical Oncology at MD Anderson. His major research interest involves investigating the role of genetic polymorphisms in melanoma progression and other cancer progression. He has an established molecular immunology and genetics laboratory research program with a focus on clinical translation. He will provide expertise in the clinical staging of pancreatic cancer and interpretation of image data. He will also provide samples, laboratory space, and experimental equipment for data storage. Dr. Lee will advise the data analyst on the extract of imaging and clinical data. Dr. Lee will be responsible for overseeing the study design, monitoring study progress, and reviewing the research findings, grant proposals and manuscripts. Dr. Xiong will meet with Dr. Lee each month during the award period.

Donghui Li, PhD. Co-Investigator (1.2 calendar months or 10% effort, years 1-3), (1.08 calendar months or 9% effort, years 4-5). Dr. Li is a professor of medicine at the Department of Gastrointestinal Medical Oncology at MD Anderson. She was the principal investigator of a previously conducted case control study of pancreatic cancer supported by NIH grant RO1 CA098380. She has extensive experience in molecular epidemiology research including biomarker studies using proteomics, metabolomics, plasma circulating DNA mutation and DNA methylation, miRNA, DNA adduct and micronuclei assays. She will oversee the design, case control matching, coordination, blood sample processing and extraction of RNA and DNA from plasma samples in this project. She will work closely with the PI and Co-PI in the sequencing data analysis and interpretation as well as the final data analysis, interpretation and final report preparation.

Chaan Ng, MD, Co-Investigator (0.6 calendar months or 5% effort). Dr. Ng is a professor at the Department of Radiology at MD Anderson. He is a radiologist specializing in Body Imaging (Abdomen and Pelvis), with extensive experience in CT, MRI and PET. He is actively involved in the development and evaluation of functional imaging techniques, including DCE-CT. He also leads the imaging aspects of several clinical trials involving targeted imaging agents. Dr. Ng will provide image data for patients and controls and help interpret image data analysis results. He will contribute 5% of his effort to this project every year.

Shenying Fang, MD, PhD, Co-Investigator (4.82 calendar months or 40% effort, years 1-3, 4.2 calendar months or 35% effort, years 4-5). Dr. Fang is an assistant professor in the Department of Surgical Oncology, he will assist Dr. Lee with the proposed project at MD Anderson. He will seek and maintain approvals for use of human samples including pancreatic cancer, pre-invasive, and pancreatitis blood samples. He will coordinate the proposed research activities-collect image data and blood samples, prepare miRNA and DNA data, deliver the sample to the industry company for miRNA-seq and methylation array study, together with the co-investigators, co-PI and PI. Dr. Fang will also organize lab meeting to discuss data collection and experimental issues raised in the program. He will also oversee the statistical data analysis for this project.

Research Development Support

Yanan Li, Ph.D. Research Investigator (6.0 calendar months or 50% effort, years 1-2, 2.4 calendar months or 20% effort, year 3, 6.0 calendar months or 50% effort, years 4-5). Dr. Li is a very experienced laboratory researcher. He has worked in Dr. Li's laboratory for over 10 years now. He will be conducting all the experiments on blood sample processing, DNA and RNA extraction from plasma samples, concentration measurement and quality control. Salary support is requested at 50% for the first two years (DNA and RNA extraction from 200 samples each year), 20% for year 3 (blood processing only) and 50% for the last two years (RNA and DNA extraction from 300 samples each year and blood processing).

Ortega, Catalina, Study Coordinator (6.0 calendar months or 50% effort, years 1-3, 3.0 calendar months or 25% effort, years 4-5). Catalina has been working with Dr. Li for her study involving patient recruitment and blood sample collection over a year now. She has been trained as a phlebotomist and she is familiar with the clinic setting. She will be responsible for the recruitment of patients and controls from MD Anderson for this project. She will identify the eligible patients and controls, introduce the study and consent the patients, conduct a brief interview, collect the blood sample, register the patients in PDMS, and log in the patient in the research database.

TBN, Research Scientist (6.0 calendar months or 50% effort), The TBN, Research Science will manage and extract patient raw image data from clinical station at MD Anderson Cancer Center. He/She will be responsible for review and interpretation of raw image data and can handle high-throughput clinical image data. He/She will also have knowledge in using computer language to output the data for PI's group to perform analysis. He or she will help interpret the image data analysis results.

Salary support is requested for all personnel and is equal to the level of effort contributed to the project. Fringe benefits are calculated at 28% of the requested salary.

Supplies
DNA extraction from plasma was budgeted at $20/sample including DNA extraction kits, test tubes and disposables. RNA extraction cost $40/sample, including the ExoQuick Plasma prep and Exosome precipitation kit, SeraMir Exosome RNA Purification Column kit, and Small RNA kit (For RNA quality control). Blood processing supplies include test tubes, pipettes, pipette tips, tube labels and disposable. A total of $60,000 (1000 samples x $60/samples) was budgeted and distributed in year 1, 2, 4 and 5.

$2000/year is budgeted for blood collection and processing supplies include blood collection tubes, test tubes, pipettes, pipette tips, tube labels and disposable for all years.

Number of samples sequenced: 400
Each sample: $1,000(including $200 for library and barcoding) for miRNA (4GB data) and methylation (5GBdata). Total cost for 400 observations: $1,000*400=$400,000 (years 1-3 only)

Other Expenses:

$1,000 is budgeted for instrument maintenance cost (years 1-5)
$500 for fright, shipping and handling cost (years 1-5)

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		**393,465.00**
Section B, Other Personnel		**443,811.00**
Total Number Other Personnel	15	
Total Salary, Wages and Fringe Benefits (A+B)		**837,276.00**
Section C, Equipment		
Section D, Travel		
1. Domestic		
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		**477,500.00**
1. Materials and Supplies	470,000.00	
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	5,000.00	
9. Other 2	2,500.00	
10. Other 3		
Section G, Direct Costs (A thru F)		**1,314,776.00**
Section H, Indirect Costs		**788,864.00**
Section I, Total Direct and Indirect Costs (G + H)		**2,103,640.00**
Section J, Fee		

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: Virginia Commonwealth University

Start Date*: 04-01-2015 **End Date*:** 03-31-2016 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Xiangning		Chen		Co-Investigator	107,224.00	0.6			5,361.00	1,828.00	7,189.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **7,189.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Associate	2.4			10,000.00	3,410.00	13,410.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**13,410.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**20,599.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: Virginia Commonwealth University

Start Date*: 04-01-2015 **End Date*:** 03-31-2016 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	1,500.00
2. Foreign Travel Costs	
Total Travel Cost	**1,500.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT11700714 Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: Virginia Commonwealth University

Start Date*: 04-01-2015 **End Date*:** 03-31-2016 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	1,500.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**1,500.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**23,599.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Organized Reseach On_Campus	52.5	23,599.00	12,389.00
		Total Indirect Costs	**12,389.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**35,988.00**

J. Fee	Funds Requested ($)*

K. Budget Justification*	File Name: Justification1014652688.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: Virginia Commonwealth University

Start Date*: 04-01-2016 **End Date*:** 03-31-2017 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	Xiangning		Chen		Co-Investigator	107,224.00	0.6			5,522.00	1,883.00	7,405.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **7,405.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Associate	2.4			10,300.00	3,512.00	13,812.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**13,812.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**21,217.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: Virginia Commonwealth University

Start Date*: 04-01-2016 **End Date*:** 03-31-2017 **Budget Period: 2**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	1,500.00
2. Foreign Travel Costs	
Total Travel Cost	**1,500.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT11700714 Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: Virginia Commonwealth University

Start Date*: 04-01-2016 **End Date*:** 03-31-2017 **Budget Period: 2**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	
2. Publication Costs	1,500.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Micro RNA and Methylation Assays & Supplies	2,000.00
Total Other Direct Costs	**3,500.00**

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	**26,217.00**

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . Organized Reseach On_Campus	52.5	26,217.00	13,764.00
		Total Indirect Costs	**13,764.00**

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	**39,981.00**

J. Fee	**Funds Requested ($)***

K. Budget Justification*	File Name: Justification1014652688.pdf
	(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: Virginia Commonwealth University

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 3**

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 . Dr.	Xiangning		Chen		Co-Investigator	107,224.00	3.6			33,132.00	11,298.00	44,430.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **44,430.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Associate	6			25,750.00	8,781.00	34,531.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**34,531.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**78,961.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: Virginia Commonwealth University

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 3**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	1,500.00
2. Foreign Travel Costs	
Total Travel Cost	**1,500.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT11700714 Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: Virginia Commonwealth University

Start Date*: 04-01-2017 **End Date*:** 03-31-2018 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	1,500.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Micro RNA Assays and supplies	5,000.00
9 . Methylation Assays and supplies	5,000.00
10 . Computer	1,500.00
Total Other Direct Costs	**13,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**93,461.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Organized Reseach On_Campus	52.5	93,461.00	49,067.00
		Total Indirect Costs	**49,067.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**142,528.00**

J. Fee	Funds Requested ($)*

K. Budget Justification*	File Name: Justification1014652688.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: Virginia Commonwealth University

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 4**

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 . Dr.	Xiangning		Chen		Co-Investigator	107,224.00	3.6			34,126.00	11,637.00	45,763.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **45,763.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Associate	9.6			41,200.00	14,049.00	55,249.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**55,249.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**101,012.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: Virginia Commonwealth University

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 4**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	1,500.00
2. Foreign Travel Costs	
Total Travel Cost	**1,500.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT11700714 Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: Virginia Commonwealth University

Start Date*: 04-01-2018 **End Date*:** 03-31-2019 **Budget Period: 4**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	1,500.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Computer	1,500.00
9 . Micro RNA Assays and supplies	30,000.00
10 . Methylation Assays and supplies	30,000.00
Total Other Direct Costs	**63,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**165,512.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Organized Reseach On_Campus	52.5	165,512.00	86,894.00
		Total Indirect Costs	**86,894.00**

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**252,406.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: Justification1014652688.pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: Virginia Commonwealth University

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 5**

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 . Dr.	Xiangning		Chen		Co-Investigator	107,224.00	3.6			35,150.00	11,986.00	47,136.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **47,136.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Associate	9.6			42,436.00	14,471.00	56,907.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**56,907.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**104,043.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: Virginia Commonwealth University

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 5**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	1,500.00
2. Foreign Travel Costs	
Total Travel Cost	**1,500.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 105300446

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: Virginia Commonwealth University

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	1,500.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Computer	1,500.00
9 . Micro RNA Assays and supplies	30,000.00
10 . Methylation Assays and supplies	30,000.00
Total Other Direct Costs	**63,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**168,543.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Organized Reseach On_Campus	52.5	168,543.00	88,485.00
		Total Indirect Costs	**88,485.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**257,028.00**

J. Fee	Funds Requested ($)*

K. Budget Justification*	File Name: Justification1014652688.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

VCU budget justification

A. Personnel

Xiangning Chen, Ph.D., subcontract PI, average effort 2.4 calendar months. The efforts vary across the year (5% to 30%). Dr. Chen will be responsible for the works proposed at VCU site, i.e. verification of promising micro RNA and methylation biomarkers. He will supervise the associate at VCU, plan, design and analyze the results obtained from micro RNA and methylation assays. Dr. Chen will also coordinate efforts with the PI and other investigators of this project, advise them on issues related to the biomarker validation.

Jingchun Chen, M.D., Ph.D., research associate, average effort 6.0 calendar months. The efforts vary across the year (20% - 80%). Dr. J Chen will conduct the validation experiments, analyze the data, summarize and communicate the results to the PI and other investigators.

B. Supplies

Methylation marker validation: $66,000. In the project, we propose to validate at least 10 methylation markers for 800 subjects. The direct cost is estimated at $7.5/subject/marker, total $60,000. We request $6,000 to cover other costs, such as plastic tubes, tips, chemicals etc. over 5 years.

microRNA marker validation: $66,000. In the project, we propose to validate at least 10 methylation markers for 800 subjects. The direct cost is estimated at $7.5/subject/marker, total $60,000. We request $6,000 to cover other costs specific to microRNA assays, such as fluorescent materials, special microplates for real-time PCR, agents for microRNA isolation and reverse transcription.

Personal computer and accessories: $4,500. We request funds to purchase 2 personal computers for VCU people for this project at the price of $1,500/computer. We also request $1,500 over the five years to update computer software and other accessories.

C. Publication fee:

We request $7,500 for publish results obtained from this project for 5 years at $1,500/year.

D. Domestic travel:

We request $7,500 for attending domestic conference on pancreatic related subjects for 5 years at $1,500/year.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		**151,923.00**
Section B, Other Personnel		**173,909.00**
Total Number Other Personnel	5	
Total Salary, Wages and Fringe Benefits (A+B)		**325,832.00**
Section C, Equipment		
Section D, Travel		**7,500.00**
1. Domestic	7,500.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		**144,000.00**
1. Materials and Supplies		
2. Publication Costs	7,500.00	
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	10,000.00	
9. Other 2	65,000.00	
10. Other 3	61,500.00	
Section G, Direct Costs (A thru F)		**477,332.00**
Section H, Indirect Costs		**250,599.00**
Section I, Total Direct and Indirect Costs (G + H)		**727,931.00**
Section J, Fee		

Funding Opportunity Number: PAR-13-189 . Received Date: 2014-07-10T13:14:47.000-04:00

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:	Dr.
First Name*:	Momiao
Middle Name:	
Last Name*:	Xiong
Suffix:	PhD

2. Human Subjects

Clinical Trial?	● No	○ Yes
Agency-Defined Phase III Clinical Trial?*	○ No	○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

● Yes ○ No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount ($)*	Source(s)*

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ❍ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ❍ Yes ❍ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ❍ Yes ❍ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	
2. Specific Aims	Specific_Aim1014652918.pdf
3. Research Strategy*	Research_Strategy1014652952.pdf
4. Progress Report Publication List	
Human Subjects Sections	
5. Protection of Human Subjects	Protection_Human_Subject1014652896.pdf
6. Inclusion of Women and Minorities	Woman___Minorities1014652897.pdf
7. Inclusion of Children	Inclusion_Children1014652898.pdf
Other Research Plan Sections	
8. Vertebrate Animals	
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	Letters_of_Support1014652916.pdf
13. Resource Sharing Plan(s)	Resource_Sharing_PLan1014652900.pdf
Appendix (if applicable)	
14. Appendix	

Specific

Pancreatic ductal adenocarcinoma accounts for 95% of the pancreatic cancer (PC). PC ranks the 10th in incidence but 4th in mortality in the United States. The estimated number of new PC cases in 2014 is 46,420 (23,530 men and 22,890 women), with 39,590 (20,170 men and 19,420 women) deaths. Despite the steady decline in the death rate of many cancers in the US over the past 2 decades, the death rate of pancreatic cancer is actually rising, due in part to the limited strategies available for successful screening, early detection and prevention of PC. At diagnosis more than 80% of PC patients have advanced, unresectable disease for which the only option is palliative systemic therapy. As a result, the five year survival rate of PC remains below 6%. Early detection of PC is essential component of strategies to improve the outcome of patients with PC. Despite of decades of research, diagnostic methods applied for early detection of PC, even in high-risk populations, remain relatively crude and based primarily on imaging criteria and results of invasive testing. The overall objective of this application is to address these significant challenges through the development of a framework for integration of raw imaging and blood-based biomarker data derived from miRNA-seq and methylation-seq to develop a low cost, convenient, readily available informational and assay system for early detection of PC with high accuracy while controlling its overdiagnose. We propose to use 400 plasma samples (210 early PC, 90 pre-invasive PC and 100 controls), for genome-wide miRNA and methylation profiling by next-generation sequencing (NGS) to discover a panel of miRNA and methylation markers, and 600 plasma samples (350 early PC, 150 pre-invasive PC and 100 controls) for the validation by integrative analysis of imaging, miRNA and methylation biomarker data. To accomplish this goal, we plan to address three interrelated specific aims:

Aim1: To use NGS to perform whole genome cell free circulating miRNA and methylation profiling and comprehensively characterize their alternations among early PC, pre-invasive PC and controls in a large cohort of 400 (210 early PC, 90 pre-invasive PC and 100 controls) participants where early PC, benign pancreatic/prepancreatic diseases and healthy controls are included in the cohort.

Aim 2: To use functional principal component analysis (FPCA) to integrate imaging, miRNA-seq and methylation-seq data. To formulate biomarker discovery problem as a sparse sufficient dimension reduction problem where the derived functional principal component (FPC) scores of imaging, miRNA-seq and methylation-seq data are projected to very low dimensional space while preserving all information on clinical outcome information and develop a novel matrix subset selection algorithm for efficiently identifying biomarkers from high volume of imaging and whole genome miRNA-seq and methylation-seq profiles for PC early detection. Verify the expression/methylation detected by sequencing using real time PCR.

Aim 3: To develop multiplex assay for rapid and accurate detection and quantification of circulating miRNA and methylation in plasma. Using the developed multiplex miRNA and methylation assay and machine learning tools, we will develop automatic PC detection system on integration of imaging and the multiplex miRNA and methylation assay and validate their performance for PC early detection in an independent cohorts of 600 (350 early PC, 150 pre-invasive PC and 100 controls) participants.

Millstone: To discover a panel of miRNA and methylation biomarkers and develop a PC early detection system integrating image, miRNA and methylation data with high accuracy and less overdiagnosis.

3. Research Strategy

3.1. Significance.

The significance in this proposal is broad and multi-faceted, and will be addressed by novel methodological and clinical approaches.

3.1.1. Even after decades of research, no non-invasive diagnostic markers have proven clinical practice for PC early detection. Whole genome cell free circulating epigenomic (methylation and miRNA) sequencing profiles from plasma in a cohort of PC studies provides a powerful tool to develop a panel of epigenetic biomarkers for PC early detection, which is expected to dramatically improve the accuracy of PC early diagnosis.

In 2014, approximately 46,420 (23,530 men and 22,890 women) new PC patients and 39,590 (20,170 men and 19,420 women) PC death occurred all over the US[1]. In the US, although the incidence rate of PC is ranked as 10th most common cancer, its death rate is ranked as the fourth most common cancer. Despite there has been a steady decline in the death rate of many cancers over the past 2 decades, the death rate of PC is rising due to limited success for PC early detection[2]. Late onset of symptoms and aggressive physiological features of PC impose limitation on therapeutic intervention[3]. Since most PC is present at the advanced stage, less than 20% of diagnosed PC patients have resectable tumors and 5-year survival rate of the PC patients undergo surgery is just 15-40%, depending on the size of the tumor[4]. The high death rate of PC is primarily caused by the lack of symptoms early in the development of PC[5]. Unlike many other cancers where their symptoms were specific to particular cancer, the symptoms of PC such as abdominal or back pain, weight loss, jaundice, nausea, light stool color, etc are similar to other illness and hence can result in a further delay in the PC detection[2,5]. The most promising strategy to reduce mortality and improve survival of this malignancy is early detection. However, population screening for early detection is neither cost-effective nor practical at present due to the relative low incidence of the disease and lack of effective risk prediction model or sensitive detection method for early disease. Even after many years of research, both imaging techniques and serological markers including carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), are, in general, unable to detect PC early[6]. Due to lack of PC-specific symptoms, reliable imaging techniques and biomarkers for early detection of PC are difficult.

Recently, there is increasing evidence that epigenetics play an important role in pancreatic carcinogenesis[7].Epigenetics involves DNA methylation that represses gene expression by the addition of a methyl group, or a "chemical cap," to part of the DNA molecule and miRNA that is a small non-coding RNA molecule of about 22 nucleotides involved in the regulation of gene expression. Epigenetics is critic in the initiation, progression and metastasis of tumors. Identification of epigenetic alternation offers several remarkable advantages over serological and genetic markers for PC early detection[3,8-10]. First, aberrant epigenetic changes often occur in early-stage pancreatic tumors, causing loss or gain of function in key biological processes. Second, we observe epigenetic alternations more often than genetic changes in tumors. Third, detection of the epigenetic alternations seems more sensitive and simple. Emerging epigenomic technologies that allow the genome scale epigenetic profiles are increasingly applied in cancer diagnosis. Several epigenetic studies have been conducted to evaluate their performance for PC diagnosis (Table 1). Although these studies have produced encouraging results, due to small sample sizes, wide-ranging values for sensitivity and specificity, unreliable accuracy, using methylation and miRNA biomarkers as primary screening tools remains unsatisfactory and clinically challenging[11]. To overcome these limitations, we plan to perform whole genome cell free circulating epigenomic (methylation and miRNA) sequencing profiles from plasma in a large cohort of PC study, conduct joint analysis of methylation and miRNA, develop efficient dimension and feature selection algorithms to discover a panel of epigenetic biomarkers for early diagnosis of PC.

Table 1. Sensitivity and specificity of epigenetic markers for diagnosis of pancreatic cancer

	Sample Size					
	PC	Control	Number of Markers	Sensitivity	Specificity	Referencses
	43	18	5	73%	100%	Ginestà (2013)
	104	60	1	80%	76%	Park (2012)
Methylation	30	30	5	76%	59%	Melnokov (2009)
	30	30	14	91.20%	90.80%	Liggett (2010)
	49	36	4	64%	89%	Wang (2009)
	29	13	1	84.6	65.50%	Ren (2012)
	11	11	3	91%	91%	Ganepola (2014)
miRNA	180	199	4	85%	64%	Schultz (2014)
	180	199	10	85%	85%	Schultz (2014)
	2036	1444	meta-analysis	82%	77%	Ding (2014)

The proposed approach has several remarkable features. First, application of next-generation sequencing (NGS) technology to methylation and miRNA profiling can achieve high resolution at the level of single nucleotide and has the potential to greatly improve the ability to detect allele-specific methylation and provide deeper insight into the pathogeneses of PC[3,12]. Second, blood-based test is a noninvasive test. It is performed in the absence of symptoms. Detection of epigenetic alterations will reveal the earliest of signs of PC[13]. Therefore, cell free, circulating epigenetic biomarkers are ideal for PC early detection. Third, integrated analysis of methylation and miRNA has the potential to identify a set of composite biomarkers consisting of DNA methylation and miRNA which will either enhance the tumor signals or provide complementary information. A panel of DNA methylation and miRNA integrated biomarker will substantially improve accuracy and reliability for early diagnosis of PC. Fourth, using large cohort of PC studies allows developing reliable and robust biomarkers for PC early detection. PC is highly heterogeneous. Only large cohort of PC studies can reveal wide-range of epigenetic variation in the PC population and provide sufficient information for developing valid and reliable epigenetic biomarkers for PC early detection.

3.1.2. The developed matrix approximation theory, supervised and unsupervised feature selection algorithms for large-scale machine learning will offer a powerful tool for developing a general framework for efficiently extracting genomic and epigenomic variants of clinical utility and shift paradigm for cancer early detection.

Discovering biomarkers from miRNA-seq and methylation-seq profiles is a high-dimensional small sample size problem in machine learning. Due to the high cost of sequencing and imaging techniques and limited access to samples, the number of features included in genomic, epigenomic and image data may reach millions, but the biggest number of samples available in the experiments cannot exceed thousands. A fundamental question is how to efficiently extract epigenomic variants of clinical utility and to develop novel unified approach to classification analysis of genomic, epigenomic, and image data. Discovery of epigenetic biomarkers is usually formulated as a feature selection problem that aims at selecting a small subset of features (epigenetic variants) with high precision for PC early detection from whole genome circulating methylation and miRNA profiles. Feature selection is a critical step before developing a panel of epigenetic biomarkers for PC early detection. The traditional paradigm for identifying biologically significant markers is based on their ranking, which usually evaluates variants on an individual basis, for example, tests for differential expression or methylation of individual variant between cases and controls[14]. However, ranking-based feature selection methods overlook correlation information between features. Therefore, those individually weak, but jointly important markers will be rarely selected. Alternatively, efficient methods for finding epigenetic variants of diagnostic utility is to systematically search variants that contain sufficient information for

phenotype prediction across the genome. To systematically search the variants of clinical utility should address several critical issues. The first issue is data reduction where the huge redundancy in the datasets may compensate for the possible errors of technology and sampling[15]. The popular approach to data reduction is unsupervised data reduction. However, unsupervised dimension reduction selects dimensions without taking information on class labels or disease status of the individuals into account. The reduced data will then lose important class information. The second issue is overfitting. Due to small sample size and large number of features, the selected features and classifier often tend to overfit training data and show poor generalization performance on testing data[14]. The third issue is lack of search algorithms that are able to deal with large number of features. Selection of variants of clinical utility from huge number of features raises a substantial computational challenge. The fourth issue is overwhelming problem. The number of samples in different classes is often unbalanced. The number of samples in one class may be much smaller than that in other classes. Majority class dominates the minority class, which will further damage feature selection process and lead to worsen the already overfitting problem in minority class. To overcome these limitations, we first propose a supervised dimension reduction method in which both epigenetic variant information and disease information will be used. The proposed method for supervised dimension reduction is sufficient dimension reduction (SDR) which projects the original high dimensional data to very low dimensional space while preserving all information on clinical outcomes and phenotypes, and formulate feature selection problem as a subset selection problem for matrices[16-19]. Many popular dimension reduction methods such as principal component analysis (PCA), multidimensional scaling and singular value decomposition produce results that are hardly interpret and comprehend. To overcome these drawbacks, we develop matrix approximation theories as powerful tools for optimally identifying low-dimensional features from big datasets. Both deterministic and randomized algorithms which include low rank matrix approximation and matrix sunset selection are designed to select epigenomic variants with ensured high accuracy and help scale machine learning algorithms to large-scale datasets[20-30]. Specifically, the CUR matrix decomposition simultaneously selects both columns (features) and rows (samples) for classification. Therefore, the CUR matrix decomposition methods can be used to overcome overfitting and overwhelming problems in PC early detection[15,30,31]. The developed matrix approximation theory, supervised and unsupervised feature selection algorithms for large-scale machine learning will offer a powerful tool for developing a general framework for efficiently extracting genomic and epigenomic variants of clinical utility and shift paradigm for cancer early detection. We can expect that the proposed research not only will identify a set of accurate methylation and miRNA markers for PC early detection, but also will provide bioinformatics tools and guidance for developing biomarkers for other cancer diagnosis.

3.1.3. Using functional data analysis as a powerful tool to develop a general framework for multiscale integration of miRNA, methylation and imaging data and using matrix subset selection and linear combiners to develop novel algorithms for integrative analysis of imaging, miRNA-seq and methylation-seq data will substantially improve our ability to accurately detect PC at its early stage while control its overdiagnosis.

Currently popular imaging techniques for the diagnosis of PC include abdominal ultrasound (US)[32], contrast-enhanced computer tomography (CT)[33], Magnetic Resonance Imaging (MRI)[34], MR Cholangiopancreatography (MRCP)[35], Endoscopic Retrograde CholangioPancreatography (ERCP)[36], and Endoscopic Ultrasound (EUS)[37]. Contrast-enhanced CT is one of the most popular imaging techniques for the detection and preoperative staging of PC[38-40]. Although biomedical imaging is playing an ever more important role in diagnosis of cancer, it does not take into account the key biologic processes that are involved in cancer development[41]. There is increasing recognition that the ability to detect disease before symptoms arise by integrating imaging data and molecular profiles[42]. Data sets from biomedical imaging, genomics and epigenomics are extremely high dimensional and high heterogeneous and are from multiple

sources and multiple scales[43]. Integrative analysis of high dimensional CT, miRNA-seq and methylation-seq datasets poses great challenges. To meet these challenges, we plan first to adapt or develop functional principal component analysis (FPCA) methods for unifying representation of biomedical imaging, miRNA-seq and methylation-seq data and reducing their dimensions. Raw imaging data are often quantified as intensity of pixels in the image. Data for miRNA-seq are represented as the number of reads at a genomic position. Methylation-seq data are measured as number of methylated reads at a CpG site. The forms and scales of three types of data are different. A more serious problem is the high dimensions of the data. Typical multislice CT image data of a sample may include approximately 1 million of pixels. Methylation sequencing data of a sample contain 450,000 CpG sites. Even miRNA-seq data may include 88,000 genomic positions. Traditional statistical methods for image cluster and classification analysis often fail to obtain accurate results because of high dimensional nature of image data[44]. Noisy and irrelevant features result in overfitting. A key issue for integration of imaging, miRNA-seq and methylation-seq data is how to develop an unified representation of these three types of data, which makes intensity of imaging, the number of methylated reads and number of reads comparable, and to reduce the dimensions of the data. A popular method for extracting informal features from imaging data is principal component analysis (PCA). However, PCA does not explore spatial information. It takes the set of spectral images as an unordered set of high dimensional pixels[45]. Spatial information is very important for image cluster and classification analysis. To overcome limitation of PCA and utilize spatial information of image signal, the functional expansion of images based on Fourier and wavelet transform are proposed as a useful tool for image feature extraction and data denoising[46]. Recently, Wavelet PCA in which we compute principal components for a set of wavelet coefficients is proposed[45] to explore both spatial and spectral information. The wavelet PCA improves efficiency to extract image features, but not explicitly consider smoothing image signals over space. To overcome this limitation and fully utilize both spatial and spectral information, we extend one dimensional functional principal component analysis (FPCA) to two or three dimensional FPCA. Similarly, we model the number of methylated reads in methylation-seq data or the number of reads in miRNA-seq data as a random function of genomic position and expand the random functions in terms of orthogonal functional principal components (FPC) through Karhunen-Loeve expansion decomposition to capture methylation variation or miRNA variation at the genomic positional level. FPC scores of the imaging, methylation-seq and miRNA-seq data will be used as their representation and provide basis for their integration. In addition, FPCA compresses the original high dimensional imaging and sequencing data into a small number of FPC and hence substantially reduce their dimensions. Therefore, we can propose a general framework for integrating imaging, methylation-seq and miRNA-seq data by taking their FPC scores as features. Although FPCA will reduce the dimensions of imaging, miRNA-seq and methylation-seq data, their reduced dimensions after RPCA are still high. The SDR and matrix subset selection methods that are described in Section 3.1.2 can be applied to FPC scores of imaging, miRNA and methylation data. We can expect that the proposed novel multiscale integrative analysis of imaging, miRNA-seq and methylation-seq data for early detection of PC not only substantially increase accuracy of PC diagnosis, but also allow developing completely automatic and intelligent clinical decision making system for early detection of PC where its operation is simple, does not need much human intervention and requires minimum training for local healthcare staff.

3.2. Innovation.

The major innovations of the proposed research are as follows. **First,** this would be the first large genome-wide circulating miRNAs and methylations profiling from plasma using NGS and a comprehensive cell free circulating miRNA and methylation biomarker discovery study for the PC early detection. **Second**, a key issue for the successful discovery of miRNA and methylation-based biomarkers for the PC early detection is how to unbiasedly identify and evaluate biomarkers from searching a huge volume of genome-wide miRNA-seq and

methylation-seq profiles. Developing sparse SDR and matrix subset selection algorithms as a general framework for efficiently identifying epigenomic variants of clinical diagnostic utility with NGS data while correcting for misdiagnosis and sequencing errors is a challenging task, but highly innovative. **Third,** we propose the novel idea of modeling the imaging intensity of a pixel as a two or three variate function of its location, the number of methylated reads at the CpG site as a function of genomic position and the position-level number of reads of miRNA as a function of genomic position, and offer creative mathematical formulation of multiscale integration of imaging, miRNA-seq and methylation-seq data as a FPC score feature selection problem, which open a new way to combine imaging and biomarkers for early detection of cancer. **Fourth**, developing multiplex assay for rapid and accurate detection and quantification of circulating miRNA and methylation in plasma is novel. **Fifth,** this is the first attempt, to the best of our knowledge, to develop automatic PC detection system on integration of imaging, circulating miRNA sequencing and methylation sequencing data.

3.3. Approach.

3.3.1. Overall Strategy. The goal of this application is to develop a low cost, convenient, readily available informational and assay system for early detection of PC. The overall approach to accomplishing this goal is shown in Figure 1. To increase accuracy rates of early detection of PC, but control its overdiagnosis, the study participants are divided into three groups: early PC, pre-invasive PC and control. Early PC group includes ductal adenocarcinoma at the stage 1. Pre-invasive PC group includes intraductal papillary mucinous neoplasm (IMPN) and mucinous neoplasm (MCN). Control group consists of healthy individuals, acute pancreatitis, chronic pancreatitis, pancreatic cysts (not IPMN), and patients with non-abdominal cancer. We assembled a team with background, expertise, and resources from several disciplines in oncology, genomics, epigenomics, miRNA and methylation sequencing profiling, image, engineering and assay development, bioinformatics and statistics from the University of Texas School of Public Health, MD Anderson Cancer Center, and Virginia Commonwealth University. With this team we plan to perform genome-wide miRNA and methylation sequencing,

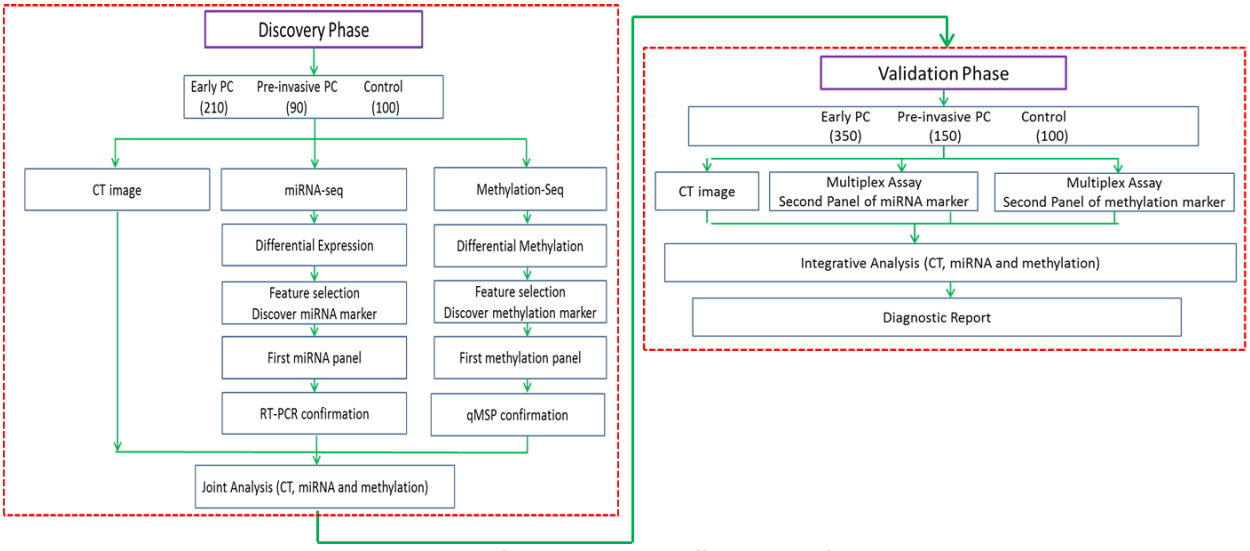

Figure 1. Overall Approach.

and miRNA and methylation marker discovery in a cohort of 400 participants collected from the University of Texas Anderson Cancer Center (Aim 1). Novel two or three dimensional FPCA method, sparse SDR and matrix subset selection algorithm for efficiently identifying biomarkers from high volume of imaging and whole genome miRNA-seq and methylation-seq profiles for PC early detection will be developed (Ami 2). A multiplex assay derived from a panel of discovered miRNA and methylation markers in Aim 2 will be validated and integrative analysis

of CT image, miRNA and methylation markers will be conducted in a cohort of 600 participants newly recruited by The University of Texas MD Anderson Cancer Center (Aim 3). Abdominal CT images will be available for all participants. Together this will allow us to develop a blood test consisting of CT image and the panel of miRNA and methylation biomarkers for PC early detection with high accuracy and less overdiagnosis.

3.3.2. Aim 1. To use NGS to perform whole genome cell free circulating miRNA and methylation profiling and comprehensively characterize their alternations among early PC, pre-invasive PC and controls in a large cohort of 400 participants.

3.3.2.1. Methods

3.3.2.1.1. Genome-wide cell free circulating miRNA and methylation profiling by NGS.

Rationale and Strategy. The current most widely used biomarkers such as CA19-9 have offered inadequate specificity and unreliable sensitivity to diagnosis of PC[8]. Numerous studies indicate that miRNAs are involved in tumorigenesis, cancer development and metastasis. Particularly, miRNAs are stable and can be easily extracted, detected and quantified in very low amounts of material and in highly degraded plasma samples[47,48]. Similarly, detection of DNA methylation also has several advantages over genetic and serum markers[49]. Both circulating miRNA and DNA methylation can be easily measured in blood. Methylation and miRNA profiling in plasma is noninvasive and simple. These very nice features of miRNA and methylation support their possible use as emerging biomarkers for early detection of PC at the clinical level. Due to its increased sensitivity, specificity, unprecedented dynamic ranges, single base resolution, detection of novel miRNA sequences or DNA methylation, ability to identify isoform miRNA, and genome-wide coverage, NGS is emerging as a powerful tool for miRNA and methylation profiling[50-53]. NGS is the technology of choice for miRNA and methylation profiling.

Cell-free DNA and RNA preparation. Blood samples from MD Anderson were collected in a case-control study of PC during 2000 to present. Cases were patients with pathologically confirmed pancreatic ductal adenocarcinoma and controls were from patient companions. During the recruitment, patients with undiagnosed pancreatic mass were consented and later excluded from the study if the pathological results are negative for cancer or positive for pancreatic lesions other than ductal adenocarcinoma. These excluded patients from the case-control study will serve as either the control group or the pre-invasive cancer group as described above. Plasma samples have been stored at -80^{0}C without thawing. Since the amount of DNA and RNA in the plasma is low, and RNA is sensitive to degradation, special cares are needed to ensure the consistency and reliability of sample preparation[54]. We will isolate the exosomes from the plasma first and then extract the RNA from exosomes because the exosomal RNA is protected by RNaseA treatment and exosomes provide a consistent source of miRNA for disease biomarker detection[84]. Dr. Li's lab has previous experience working with plasma miRNA and gene methylation profiling[85, 86]. The RNA concentration will be measured using Nano Drop 1000 and the quality of the RNA will be assessed using a small RNA chip and Agilent 2100 Bioanalyzer. Specifically, we will standardize our sample collection and preparation protocols, document the duration of blood sample collection and DNA/RNA isolation, catalogue chemical lot numbers and monitor hemolysis for each sample. Data recorded in sample collection and preparation can be used as covariates in our data analyses.

Genome-wide miRNA sequencing profiling. Genome-wide miRNA sequencing will be supported by BGI America (See supporter letter). Briefly, total RNA is first extracted from the samples, then gel electrophoresis will be used to select small RNAs (18~30nt) for sequencing. The RNAs are then reverse-transcribed to cDNA, followed by library construction. The libraries are ready for sequencing by Illumina HiSeqTM 2000 platform. Low quality reads and contaminated reads from rRNA, tRNA, mRNA, snRNA, and snoRNA will be removed. Clean reads are then mapped back to reference genome by SOAP2[55], and expression level of each miRNA will be analyzed.

Genome-wide methylation sequencing profiling. Whole genome bisulphite sequencing is still expensive, we use less expensive reduced representation bisulphite sequencing (RRBS) for methylation profiling. After passing the sample quality assessment, the DNA samples will undergo the following procedures for methylation profiling: (1) Genomic DNA fragmentation by restriction enzyme, (2) Size selection of 40-220bp fragments, (3) bisulfite treatment by ZYMO EZ DNA Methylation-Gold kit, (4) PCR amplification, and (5) library construction and sequencing. Sequencing data will be mapped to reference genome. We trim the raw sequencing reads and remove the low quality bases on read ends[56]. The processed data are then aligned to the in silico converted reference genome. We will use only those uniquely mapped reads defined by the expected restriction enzyme cutting sites to get methylation information of the cytosines. After that, we will check sequencing quality of the data and calculate the methylation level for the cytosine sites and report genome-wide methylation profiles.

Statistical analysis. Analyzing miRNA-seq and methylation-seq data is challenging. The pipeline for miRNA-seq and methylation-seq profiling data analysis includes read-processing, alignment, normalization and differential expression or methylation analysis. To compare miRNA levels across the datasets, we will incorporate proper methods for normalization of the sequencing read count for each miRNA, including simple RPKM method and model-based methods[57-60]. Intersample normalization, such as quantile Normalization will also be used to ensure the quality of methylation data[61]. Flexible differential expression or methylation is an essential component for miRNA-seq and methylation-seq data analysis. The most commonly used methods for differential expression analysis are implemented in the packages: Cuffdiff[62], edgeR[63], DESeq[64], PoissonSeq[65], baySeq[66], and limma[67]. These analysis either summarize the number of reads aligned to specific regions into quantitative measurements (overall expression level) or use one or two parameters in the model of miRNA-seq data for each gene. The methods for testing differentially methylated CpG sites (DMCs) or regions (DMRs) include Fisher's exact test, logistic regression and χ^2 test[68,69]. These methods for DMR analysis ignore dependence among methylated CpG sites. To overcome these limitations, we propose to use to model base-level read counts as a random function of genomic position and expand the random functions in terms of orthogonal functional principal components through Karhunen-Loeve decomposition. We will develop a formal functional principal component analysis (FPCA)-based statistic for testing differential expressions between two conditions by comparing the difference in FPC scores[70].

A unified FPC representation of miRNA-seq and methylation-seq profiles. Both miRNA expression and methylation level measured by NGS at single base resolution can be represented by a random function. We take a genomic region as a unit of analysis. Let t be a genomic position within a genomic region and T be the length of the genomic region being considered. Let $x_i(t)$ denote the number of measured reads, covering the genomic position t, from the *i*-th sample. Let ϕ_1, ϕ_2,… be orthonormal eigenfunctions. By the Karhunen–Loève theorem, one can express the centered random function in the eigenbasis[70], $x_i(t) = \sum_j \xi_{ij}\phi_j(t)$, where $\xi_{ij} = \int_T x_i(t)\phi_j(t)dt$ is the principal component score associated with the k-th eigenfunction ϕ_k

FPCA for testing differential miRNA expression or methylation. Consider n_A cases and n_G controls. Similar to comparing differences in expression or methylation level between cases and controls in the standard χ^2 association test, we propose to compare differences in functional principal component scores $\bar{\xi}_k$ and $\bar{\eta}_k$ between cases and controls as follows:

$T_{FPC} = \sum_k (\bar{\xi}_k - \bar{\eta}_k)^{2)} / [(1/n_A + 1/n_G)\lambda_k]$. Under the null hypothesis of no differential expression or methylation, the statistic asymptotically follows a central $\chi^2_{(k)}$ distribution, where k is the number of functional principal components.

Power to test for differential methylation. We use real DNA methylation-seq dataset that was downloaded from the GEO database (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSM955161) to simulate populations where 7,250 genes/regions were selected from a total of 28,227 genes/regions in the dataset. We perform 1,000 simulations. In each simulation we sampled 210 cases and 192 controls. The methylation profile in each CpG island was expanded in terms of FPC. Figure 1 plots power of FPCA test for DMR as a function of change of differential methylation. Similar power calculation can be calculated for testing differential miRNA expressions with miRNA-seq data.

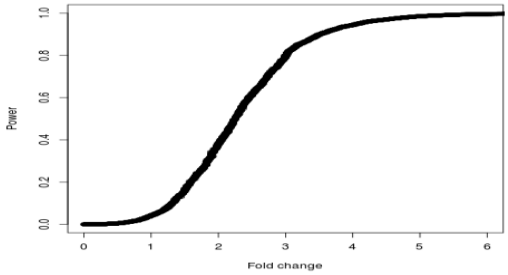

Figure 1. Power for methylation-seq

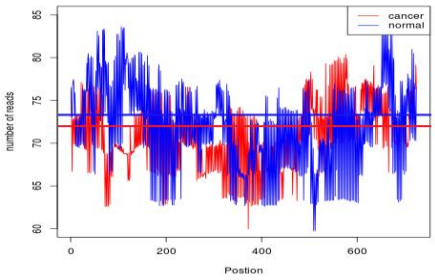

Figure 2. Methylation-seq profile of gene ABCG2

3.3.2.2. Preliminary Studies. To evaluate the feasibility of the proposed FPCA for testing DMR, the proposed statistic was applied to a methylation-seq dataset where methylation levels of 28,227 genes/regions were measured by bisulfite sequencing. We observed that although mean methylation levels of gene/region were not significantly different between cancer and normal samples, the methylation profiles were significantly different as Figure 2 shown. Figure 2 demonstrated that the FPCA-based methods can capture base-level read counts variation, extract the more information content of methylation-seq data and have higher power than many other existing methods.

3.3.2.3. Potential problems and solutions. A potential problem for miRNA-seq and methylation-seq data analysis is read quality assessment and data normalization. Due to sequencing technique variation, read counts are often skewed. Therefore, a number of parametric and nonparametric normalization methods will be explored to reduce read count variation due to sequencing technique.

3.3.3. Aim2: To discover miRNA and methylation biomarkers for PC early detection by integrative analysis of imaging and whole genome miRNA-seq and methylation-seq data.

3.3.3.1. Method

Computed tomography (CT) as a major imaging tool for diagnosis of pancreatic cancer. CT is routinely used as the most important imaging tool for diagnosis of PC. It provides very thin slice cuts with high resolution and fast image acquisition[71]. Multi-detector CT (MDCT) employs a thin section and multi-phase techniques. It starts with pre-contrast images and early arterial phase images of the aorta and the superior mesenteric artery, 17-25 s after contrast injection. Then, pancreatic phase (35-50 s after contrast injection) and portal venous phase imaging (55-70 s after contrast injection). The arterial-phase images show the underlying pancreatic lesions and enable the detection of subtle perivascular infiltration of the underlying cancer. Pancreatic phase images display the peak pancreatic parenchymal enhancement and offer the best lesion on pancreas contrast. Portal venous phase images assess the extent of venous involvement

and are useful for identifying liver metastasis. Each participant in the study has CT images with PC diagnosis which is confirmed by pathology.

RT-qPCR for validation of circulating miRNA. Potential miRNA biomarker discovered through initial miRNA-seq profiling in Aim 1 need to be validate by RT-qPCA. We will validate upto 20 promising miRNA biomarkers. Protocol for RT-qPCR validation of circulating miRNA is described as follows[8]. Briefly, QIAamp circulating Nucleic Acid Kit and QIAvac Connecting System, will be used to extract miRNA from 2.0 to 4.0 mL of plasma. The concentration of extracted miRNA would be in the range of 10 to 100 ng. miRNAs are quantified by RT-qPCR analyses with TaqMan miRNA assays. RNA (1 to 10 ng) isolated from plasma is diluted and used in 5 μ L of RT reaction. The converted cDNA is diluted 1:3 in water. A total of 5 μ L is used in white PCR plate wells for qPCR measurements with miRNA-specific TaqMan PCR primer. The qPCR will be performed on 7500 real-time PCR system. Data will be normalized against an RNU6B target used as internal control[72]. The Minimum information for publication of Quantitative Real-Time PCR experiments is used to provide a detailed framework for the analysis and measurement of miRNA[54]. To control intra- and inter-assay variation from multiple sources, a set of selected parameters such as limit of detection, linear dynamic range, PCR-efficiency and precision should be included in each assay.

Quantitative Methylation-Specific PCR (qMSP) for validation of circulating methylation. qMSP[73] is used to validate potential methylation biomarkers discovered in Aim 1. Briefly[73], to perform bisulfite conversion,30 μ l of extracted plasma DNA was digested in a 40 (μL) reaction volume with 30 U of methylation-sensitive restriction enzyme. To ensure complete bisulfite conversion, 30 ng of completely methylated or unmethylated control DNA will be used as controls. Then, QuantiTect SYBR Green PCR Kit in ABI 7900 HT system is used to perform qPCR on same amount of digested or undigested plasma DNA along with control digestion for quantitative detection of methylation. 500 nM each primer and 16 SYBR Green PCR Master mix is used to perform each reaction in a final volume of 20 μ l containing digested (1.3 μ l) or undigested (1 μ l) plasma DNA. The PCR product is confirmed by melting curve analysis at the end of PCR cycles. Finally, data are normalized.

FPCA for integration of imaging, miRNA-seq and methylation-seq data. We use FPC to unify representation of imaging, miRNA-seq and methylation-seq data and reducing their dimensions. The current FPCA has been developed for one dimensional data. However, our imaging data are two or three dimensional. We extend FPCA from one dimensional to two or three dimensional. Let $x(s,t)$ be an intensity function of image signal of the pixel located in the position (x,y). Consider a linear combination of functional values: $f = \int_S \int_T \beta(s,t)x(s,t)dsdt$, where $\beta(s,t)$ is a weight function. To capture the variations in the random functions, we chose weight function $\beta(s,t)$ to maximize the variance of f,

$\max \quad \mathrm{var}(f) = \int_S \int_T \int_S \int_T \beta(s_1,t_1)R(s_1,t_1,s_2,t_2)\beta(s_2.t_2)ds_1dt_1ds_2t_2$ which leads to the following integral equation[74,75] $\int_S \int_T R(s_1,t_1,s_2,t_2)\beta(s_2.t_2)ds_2dt_2 = \lambda\beta(s_1,t_1)$. Then, the intensity function of image can be expanded in terms of FPC: $x_i(t,s) = \sum_j \xi_{ij}\beta_j(s,t), i = 1,...,N$, where FPC score is $\xi_{ij} = \int_S \int_T x_i(t,s)\beta_j(s,t)dsdt$. Similarly, we can obtain three dimensional expansion of the image intensity function: $x_i(t,s,u) = \sum_j \xi_{ij}\beta_j(s,t,u), i = 1,...,N$.

Sparse sufficient dimension reduction (SDR) as a tool for biomarker discovery. To identify potential biomarkers from miRNA-seq and methylation-seq profiles, we first calculate the FPC scores for each miRNA or CpG island. Taking FPC score as features, marker discovery problem can be formulated as a SDR problem[76,77]. Let Y be a class label and X be a p dimensional vector of features. SDR aims to find a linear subspace S such that the variable Y depends on X only through vectors in the subspace S. In other words, all information of X about Y is contained in the space S. The intersection of all space S it is referred to as central space (CS) and denoted by $S_{Y|X}$. Let $B=[\beta_1,...,\beta_d]$ be the matrix of basis forming $S_{Y|X}$. A classification can be modeled by $y=f(\beta_1^T X,...,\beta_d^T X,\varepsilon)$[78]. To calculate bases for forming $S_{Y|X}$, we need to solve the following eigenequation[79]: $\mathrm{cov}(E(X-E(X)|Y))\beta=\lambda_x\Sigma_x\beta$, where Σ_x is a covariance matrix of the random vector X. Since the number of features is extremely large, eigenequation is difficult to solve. To overcome this barrier, we explore faster subset selection algorithms for matrices to select a small set of features in solving eigenequation[80]. Let $A=\Sigma_x^{-1}\mathrm{cov}(E(X-E(X)|Y))$. Our goal is to compress matrix A via selecting a subset of its columns (features) to form a new matrix $C=AS$, where S is a column selection matrix, such that $\|A-\Pi_{C,k}(A)\|_F\le\varepsilon$, where $\Pi_{C,k}(A)$ denotes the best approximation to A within the column space that has rank at most k .Then, the eigenequation with respect to C can be easily solved.

3.3.3.2. Preliminary Studies. A key step for integrative analysis is FPCA analysis of imaging data. To evaluate the feasibility of FPC expansion of the imaging intensity for classification, the proposed FPCA and feature selection algorithms were applied to 113 Pancreatic Cancer Histology Images (77 PC and 36 controls). Fivefold cross validation was used to evaluate the performance. The results were summarized in Table 2 where the results of sparse logistic regression and traditional SVM were included. Table 2 shows that FPCA for image analysis works very well.

Table 2. Accuracy of four methods for classifying PC using imaging data.

	Training			Test		
Method	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Deterministic	0.9026	0.4113	0.7499	0.8952	0.4533	0.7613
Randomized	0.9835	0.8311	0.9313	0.7297	0.7433	0.7427
Logistic Regression	0.9938	0.0000	0.6768	0.9857	0.0222	0.6814
SVM	0.9967	0.0067	0.6813	1.0000	0.0000	0.6814

3.3.3.3. Potential problems and solutions. A potential limitation for circulating miRNA and methylation as biomarkers for PC early detection is the lack of standard protocols for their measurements. Solution for this is to introduce controls for assessing the consistency of the results and develop proper normalization methods. Another potential problem is how to ensure the numerical stability of the large inverse matrix calculation. Solution is to introduce numerically stable and fast single value decomposition methods for the calculation of the inverse matrix.

3.3.4. Aim 3. To develop multiplex assay for rapid and accurate detection and quantification of circulating miRNA and methylation in plasma. To develop automatic PC detection system on integration of imaging and the multiplex miRNA and methylation assay, and validate its performance for PC early detection in an independent cohort of 600 (350 early PC, 150 pre-invasive PC and 100 controls) participants.

3.3.4.1. Methods

Overall Strategy. After discovery and confirmation of miRNA and methylation biomarkers, an essential task is to first develop multiplex assay for assessing the potential use of miRNA and methylation markers as a diagnostic panel for PC early detection. Then, the developed multiplex

assay with 10~15 miRNA markers and 10~15 methylation markers will be developed and tested in an independent cohorts of 600 participants collected from the University of Texas MD Anderson Cancer Center. Integrative analysis of Imaging data and the results of multiplex assay will be performed to evaluate the performance of abdominal CT imaging and the panel of miRNA and methylation markers for the PC early detection. Finally, the panel of miRNA and methylation markers for PC early detection will be selected and reported.

Multiplex assay of circulating microRNA for PC early diagnosis. Based on our sequencing and analyses of the discovery samples, we will select 10~15 most promising microRNA and validate their presence and the amount in plasma in an independent cohorts of 600 participants. We will use TaqMan microRNA detection method which is one of the most sensitive and reliable methods[81,82]. For each mature microRNA, we will work with scientists at Applied BioSystems to design TaqMan microRNA probes, and use real time PCR to detect the presence and quantity of this microRNA. Technically, we will isolate total RNAs from plasma, and reverse transcribe the RNAs into cDNA. TaqMan real-time PCR assays will be performed on the cDNA in triplicates, and $\Delta\Delta C_T$ method will be used to calculate the amount of the target microRNA compared to RNU6B used as control.

Validation of methylation sites and methylation levels in circulating DNA. Similar to microRNA, we will validate up to 15 promising methylation sites in circulating DNA isolated from independent samples of patients and controls. There are many methods to assess methylation as well. For sensitivity and reliability, we plan to use bisulfate treatment followed quantitative PCR as described before[83].

Integrative analysis of imaging, miRNA and methylation.

There are two approaches to combining information from imaging, miRNA and methylation to detect PC at the early stage. One approach is to develop a classifier that directly integrates imaging, miRNA and methylation data for classification as we discussed in Aim 2. Another approach to combining three individual classifiers for imaging, miRNA and methylation into a final classifier for PC early diagnosis. We will use three combining schemes[84]: voting-based combining, Bayesian network based combining and information-theoretic combining.

Voting-based combining. Let a binary random variable x_i denote the output of the i-th classifier. Let $S = x_1 + x_2 + x_3$. Final decision is made as follows: $f(S) = 1$ if $S \geq d$ **or** 0 **otherwise**. single instance: $d = 1$, majority vote: $d = 2$ and all instance voting: $d = 3$.

Bayesian Network based combining. Let P_i be the sensitivity of the i-th classifier that classifies the new individual being tested as PC and k be the number of classifiers that classify the new individual as PC. Define a decision function: $A = (\sum_1^k P_i)/k$. If $A \geq \tau_d$ then the individual being tested is classified as PC, where τ_d is a threshold.

Information-theoretic combining method. Define $S = w_1x_1 + w_2x_2 + w_3x_3$, where the weights are defined by entropy: $w_i = [1 + p_i \log_2 p_i + (1-p_i)\log_2(1-p_i)]/\sigma_i$, where σ_i is the classifier's standard deviation in sensitivity. Decision function is defined as $f(S) = 1$ if $S \geq d$ **or** 0 **otherwise**.

3.3.4.2. Preliminary Studies. To examine the roles of combined imaging, miRNA and methylation markers for the diagnosis of PC, we performed the integrative analysis of imaging, miRNA and methylation data for classifying stages of PC by voting. The data were downloaded from TCGA dataset. Since TCGA dataset includes few normal samples, we used stages of PC to test the proposed algorithms. Samples from stage 1 and 2A were classified into controls (13 samples) and samples from stages 2B, stages III and IV were classified into cases (56 samples). We constructed three independent classifiers for imaging, miRNA and methylation data, separately. We used three-fold cross validation to evaluate the performance of the classifiers. The results were shown in Table 3. Figure 3 showed the Venn Diagrams for sensitivity,

specificity and accuracy in the test dataset. We observe that individual imaging, miRNA and methylation do not have high accuracy for diagnosis of PC, but jointly, they can reach as high as 99% accuracy. We also observe that methylation plays an important role in discriminating early stages from later stages of PC.

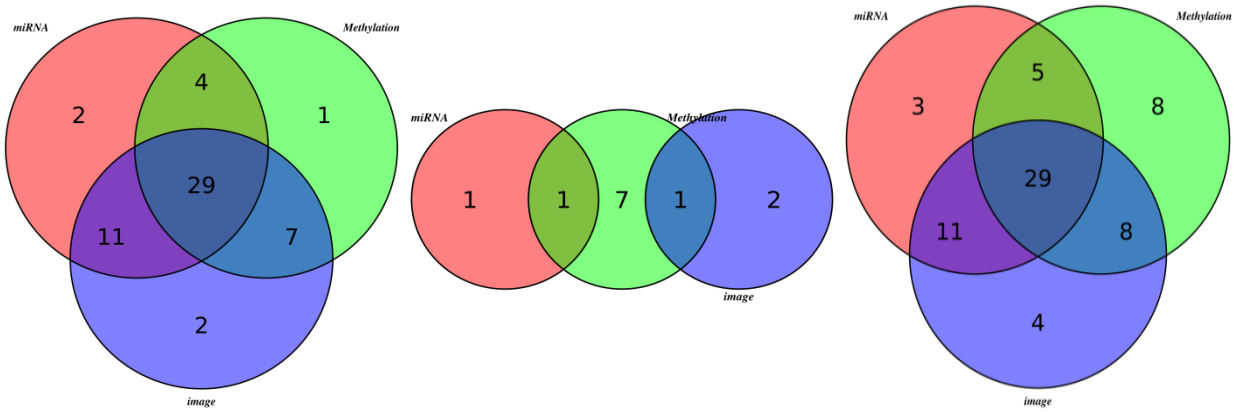

Figure 3. Venn diagram for (A) sensitivity, (B) specificity and (C) accuracy.

Table 3. Accuracy for PC diagnosis.

	Sensitivity	Specificity	Accuracy
image	0.8750	0.2308	0.7536
miRNA	0.8234	0.2222	0.7448
methylation	0.7183	0.9048	0.7422
miRNA+image	0.9821	0.3846	0.8696
methylation+image	0.9643	0.8462	0.9420
miRNA+methylation	0.9643	0.9215	0.9565
miRNA+methylation+image	1.0000	0.9231	0.9855

3.3.4.3. Potential problems and solutions. A potential problem for combining classifiers is how to determine threshold for classification decision. A solution is to divide the samples into three groups: training, verification and test. We select threshold to reach the highest accuracy in the verification set.

3.4. Tentative timeline. The project will take five years to complete. Tentatively, we will collect samples, develop statistical methods for miRNA and methylation differential analysis and for miRNA and methylation biomarker identification, perform genome-wide miRNA and methylation sequencing profiling in the first cohort of 400 participants (210 early PC, 90 pre-invasive PC and 100 controls), and discover miRNA and methylation biomarker from the sequenced miRNA and methylation data (Aim 1) in grant years 1 and 2. In grant year 3, we will verify the miRNA and methylation alternations detected by sequencing using RT-PCR and develop a panel of miRNA and methylation biomarkers for multiplex assay. We will also develop software for imaging data analysis (Aim 2). In grant year 4, we will continuously develop multiplex assay for rapid and accurate detection and quantification of circulating miRNA and methylation in plasma. We will also develop statistical methods and software for the interactive analysis of imaging, miRNA-seq and methylation-seq data, and classifier for PC early detection. In grant year 5, the developed multiplex assay with 10~15 miRNA markers and 10~15 methylation markers will be validated in the second independent cohorts of 600 participants (350 early PC, 150 pre-invasive PC and 100 controls) newly recruited by the MD Anderson Cancer Center. Finally, the panel of miRNA and methylation markers for PC early detection will be selected and reported.

6. Protection of Human Subjects

6A. Risk to Subjects

1. Human Subject Involvement and Characteristics.

This proposal is to develop assay that consists of CT, miRNA and methylation biomarkers for pancreatic cancer early detection. The participants will be recruited from the MD Anderson Cancer Center. Information for all participants includes image, plasma samples. Some patients will have tissue samples for biopsy. All scientists will take part in the scientific aspects of the study, but only physicians and healthcare workers in the hospitals will have direct access to patients' data. Other investigators only access de-identified data. Data obtained for this project will be encrypted.

2. Source of Material

Detailed information will be obtained from the participants during the diagnosis. All research specimens (image and plasma) will be identified by a code for data analysis. Results will be correlated with coded clinical information files, such that individual data will not be identifiable without these files. Clinical data will be maintained by physicians in the hospitals with limited access to ensure confidentiality.

3. Potential Risks.

This study involves collection of plasma. Circulating microRNA and methylation will be measured by next-generation sequencing. Approximately, 15 ml of plasma will be drawn. The procedure is quite safe. Abdomen CT image will also not harm the patients.

6B.ADEQUACY of PROTECTION AGRAINST RISK

1. Recruitment and Information Consent.

Patients will be recruited from hospitals. Consent will be sought at the time of entry into the study and documented on a currently approved consent form. Participants will be told that the following are required for participation: abdomen CT image test results, a plasma sample from the subject, miRNA and methylation sequencing and test results, biopsy results, and signed consents.

2. Protection against risk.

Confidentiality will be assured. All participants will be assigned a unique random laboratory number and all records will be identified only by this number and will be stored in a file cabinet in a locked office in the hospitals. Plasma drawn has minimal risk. National regulations and policies have been developed to protect the rights, safety, and well-being of people who take part in screening and diagnosis of cancer and to ensure that diagnosis tests are conducted according to strict scientific and ethical principles. All these regulations and policies will be strictly enforced. The confirmed pancreatic cancer (PC) patients should be treated in the hospitals.

6C. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS.

The potential benefit to the individuals in the study is to provide information that may be helpful for their medical care and management in the future. The potential PC will be identified and treated at the early stage of PC in the hospital.

6D. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED.

The knowledge to be gained from this study is to provide information on developing guidelines on the early diagnosis of PC. This will have potential to reduce the death rate of PC and save life of many people. This study will have important social impact.

6E. DATA AND SAFETY MONITORING PLAN.

All data will be encrypted in the computer.

7. Inclusion of Women and Minorities

Men and women are equally included in the proposed research. For the detailed description, please see Section 6: Protection of Human Subjects.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Combined Image and Biomarker Approach to Early Detection of Pancreatic Cancer

Domestic/Foreign: Domestic

Comments:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	0	0	0	0	**0**
White	500	500	0	0	**1000**
More than One Race	0	0	0	0	**0**
Total	**500**	**500**	**0**	**0**	**1000**

Study 1 of 1

Funding Opportunity Number: PAR-13-189. Received Date: 2014-07-10T13:14:47.000-04:00

9. Inclusion of Children

No children were recruited as part of this study; therefore this inclusion is not applicable to this application.

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26 June 2014

From: Noel Chen, Ph. D.
Director of Scientific Collaboration
BGI Americas
1 Broadway – 3rd Floor
Cambridge, MA 02142
Phone: 301-412-1588
Fax: 202-640-4391

To: Momiao Xiong
Professor
Human Genetics Center
Division of Biostatistics
University of Texas School of Public Health

Dear Dr. Xiong:

BGI is pleased to support your proposal “Combined Image and Biomarker Approach to Early Detection of the Pancreatic Cancer”. Your proposal that attempts to develop a low cost, convenient, readily available informational and assay system that integrates raw imaging data and blood-based biomarker data derived from miRNA-seq and methylation-seq for screening and early detection of pancreatic cancer (PC) is highly relevant and important. The accomplishment of the project will facilitate the joint use of biomarkers derived from circulating miRNA-seq and methylation-seq and image for early detection of PC while controlling overdiagnosis.

BGI, the largest genome center in the world, is the leader in using next-generation sequencing techniques to measure miRNA and methylation levels. BGI will provide reliable and cost-effective sequencing techniques for miRNA and methylation studies. The produced miRNA-seq and methylation-seq data with high quality will help you to identify biomarkers to accurately and detect PC at its very early stage. We support this proposal and are prepared to negotiate the necessary agreement should an award be made.

I am extremely enthusiastic about this project. I think that this proposal could represent a major breakthrough in developing a new generation of clinical diagnosis system integrating image, miRNA and methylation for PC early detection. I am really looking forward to this collaboration and wish you success on your grant application!

Best regards,

Respectfully Yours,

Noel Chen, Ph.D.
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THE UNIVERSITY OF TEXAS
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July 1, 2014

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RE: Combined Image and Biomarker Approach to Early Detection of Pancreatic Cancer

Dear Dr. Xiong,

I am happy to serve as the Co-Principal Investigator on your NIH R01 grant application. As you know, I am professor in and Chair of the Department of Surgical Oncology, Division of Surgery, The University of Texas MD Anderson Cancer Center. A major area of clinical expertise is the evaluation and surgical management of patients with pancreatic tumors and pancreatic cancer. My major research interest involves investigation of the role of genetic polymorphisms and other blood biomarkers in the progression of melanoma and other cancers. As Co-PI, I will provide expertise in the clinical staging of pancreatic cancer and interpretation of imaging data. I will also provide samples, laboratory space, and experimental equipment for data storage and analysis. I will advise the data analyst on the extraction of imaging and clinical data. I will be responsible for overseeing the study design, monitoring study progress, and reviewing the research findings, grant proposals and manuscripts. I will meet with you each month during the award period.

Best wishes for a successful R01 application for this R01 project.

Sincerely yours,

Jeffrey E. Lee, M.D.
Professor & Chair, Department of Surgical Oncology
Irving and Nadine Mansfield and Robert David Levitt Cancer Research Chair

JEL:dh

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RE: Combined Image and Biomarker Approach to Early Detection of Pancreatic Cancer

Dear Dr. Xiong,

I am happy to serve as the co-investigator in your NIH R01 grant application. I am an assistant professor at the Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center. My major interest focuses on statistical genetics and cancer epidemiology, and my projects have included the impact of health service on cancer patients, the genetic epidemiology of familial childhood cancer syndromes, the identification of novel susceptible loci for lung cancer using linkage analysis, and genome-wide association analysis of common genetic variants associated with melanoma development. I will help study design and data collection of pancreatic cancer image and blood samples at MD Anderson Cancer Center. I will seek and maintain approvals for use of human samples including pancreatic cancer, pre-invasive, and pancreatitis blood samples. I will also advise research investigator and help him/her implement the proposed research activities. I will also attend lab meeting and help interpret the results during the award period of this project.

I wish you a successful application for this R01 project. I fully support your grant submission and will actively monitor all investigations as outlined in the application.

Best wishes,

Shenying Fang, MD, PhD
Assistant Professor
Dept. of Surgical Oncology
UT MD Anderson Cancer Center

15. Resource Sharing Plan

Data Sharing

In this project, we will generate CT image, genome-wide miRNA-seq and methylation-seq data and develop novel methods for integrative analysis of image, miRNA-seq and methylation-seq data. All partners will strictly comply with the instructions for the Resource Sharing Plans and the policies of immediate data release developed for the project by the NCI. These results will be made available to the scientific community through the mechanisms of public use data and ancillary study collaborations, according to guidelines formulated by the NIH. A full description of these results, including manuals of operations, data forms, variable definitions, data dictionaries and result interpretation will be posted on website. We will also distribute multiple assay for pancreatic cancer early detection.

Software Sharing

We plan to develop software package to implement the proposed methods and algorithms for biomarker discovery from genome-wide miRNA and methylation sequencing profiles, intelligent clinical decision making and automatic image, miRNA and methylation diagnosis system. It is our intention to make all the developed software and bioinformatics tools publicly available. The software will be well documented and easily transferable, so that other individuals and organizations can continuously maintain and modify the source code.