Health Research Nonformula Grants - State Fiscal Year 2011-12

Translational Genomics Research Projects
Health research nonformula grants totaling $5,728,474 were awarded to two organizations in response to the Request for Application (RFA) # 67-4 for Collaborative Research on Translational Genomics. These research projects addressed the following translational research priority, which was established by the Department in conjunction with the Health Research Advisory Committee.

Research Priority: Translational Genomics
Research to evaluate the clinical utility of genomic information for improving patient outcomes and clinical decision making.

Advances in genomics have the potential to improve the delivery of health care by targeting interventions to individuals who, due to genetic factors, will receive the greatest benefit and experience the lowest risk of adverse events. The promise of personalized medicine for improving health outcomes has led to investment in research to sequence the human genome and identify genetic markers for disease and disease outcomes. The success of this investment depends on the ability to translate these discoveries into clinical practice. Although a number of associations linking genetic variants with disease susceptibility or drug metabolism profiling have been identified, there are few rigorous, prospective studies demonstrating the presence or absence of specific variants with specific outcomes, such as improved therapeutic response or reduction in adverse events. Clinical studies integrating genomic findings into clinical trials and population-based studies are necessary to justify the increased costs of testing.

While advances in genomics have the potential to improve clinical decision making by identifying who will and will not benefit from an intervention, comparative effectiveness has the potential to improve health care outcomes and reduce health care costs by determining the relative clinical and economic impact of alternative interventions. Comparative effectiveness research examines differences in outcomes across populations of patients, focusing on whether the "average" patient would benefit from a given intervention. However, even for interventions found to be effective, the benefit often accrues to only a minority of patients in the population. The ability to identify which patients will and will not benefit from an intervention based on genetic factors could greatly increase the impact of comparative effectiveness research and the utility of personalized medicine.

There is a critical need to generate the evidence necessary to ensure the effective translation of genomic tests into improved health and health care. This research falls into the gap between comparative effectiveness research and basic research to identify novel genetic factors that are associated with response to therapy or risk of disease. The focus of this research is on evaluating and maximizing the clinical utility of genomic information, including the impact of genomic information on clinical decision making and patient outcomes, the ability for genomic information to predict who will and will not benefit in a comparative effectiveness study, and the dissemination and utilization of evidence based strategies for the use of personalized medicine to improve health care value.

Research may include, but is not limited to, the following areas:

- Research to evaluate how therapies tailored to genomic information compare to standard therapies in prevention, screening and treatment in terms of health care cost and outcomes
- Research to evaluate the impact of genomic information compared to existing methods of individualizing health care services including methods which use family history of disease or individual behavioral risks to tailor prevention, screening and treatment.
- Research to determine how well genomic information can predict individual outcomes in comparative effectiveness studies, including clinical trials and prospective cohort studies
- Research to determine how the use of genomic information influences clinical decision making and patient outcomes
- Research to evaluate the effects of incorporating genomic risk prediction into electronic medical records
- Research to identify patient, provider and system barriers and interventions to overcome barriers to the implementation of personalized strategies for prevention, screening and treatment

Research in the following areas will not be considered:
- Identification of novel genomic markers for disease and disease outcomes
- Comparative effectiveness research that does not include the evaluation of genomics strategies for personalized medicine.
- Conduct of Genome Wide Association Studies (GWAS) or similar techniques to develop risk scores based on multiple single nucleotide polymorphisms (SNPs) alone. However, the results of prior GWAS and similar studies could be used to select high risk subjects for preventive or clinical therapeutic studies which are focused on evaluating the utility of genomics.
- Studies that include only investigation of somatic mutations.
- Gene therapy.

Funds must be used for clinical research and/or health services research, as defined in Act 2001-77. None of the funds can be used for biomedical research as defined as defined in Act 2001-77.

The research should hold the potential for addressing the health needs of underserved segments of the population, including rural, urban, racial/ethnic minorities, or older adults and other high risk Commonwealth populations. To foster cross-institutional collaborative research among organizations across the Commonwealth, an applicant must conduct research in collaboration with other research institutions and organizations. To the extent possible, organizations that are not academic medical centers, such as smaller colleges and universities, businesses, biotechnology and pharmaceutical companies, health care providers and local public health agencies should be included in addition to major research institutions. At least two of the collaborators must be major research institutions. Collaboration with a minority-serving academic institution or a minority-serving community-based organization in Pennsylvania is strongly encouraged, and should include the mentoring and training of students. All research collaborators must play a substantive and meaningful role in multiple aspects of the proposed research. Research proposals must be organized around specific focused topics or issues rather than a wide range of unrelated projects. Health services research must include objective evidence of outcomes. Research must test at least one hypothesis, not be merely descriptive or hypothesis-generating. No more than 50% of the funds may be used for research infrastructure as defined in the Act, as amended. Research

infrastructure is defined as including the following items: office equipment, office supplies, nonprofessional personnel, and laboratory or building construction or renovations, used to conduct research.

Cancer Diagnostics and Therapeutic Research Projects
Health research nonformula grants totaling $9,635,597 were awarded to 10 organizations in to the Request for Application (RFA) #10-07-03 Research on Cancer Diagnostics or Therapeutics with Commercialization Potential. These research projects addressed the following cancer research priority, which was established by the Department in conjunction with the Health Research Advisory Committee.

Research Priority: Commercialization of Research Related to Cancer Diagnostics and Therapeutics

The primary purpose of this priority is to support research activities that commercialize and bring to market new cancer diagnostics and therapeutics for which proof of concept has previously been demonstrated, that is, preliminary data confirm that the product, technology or approach is capable of solving or diminishing a specific problem related to the diagnosis or treatment of one or more malignant diseases. Research activities should lead to a better understanding of the biology and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability, ultimately leading to improvements in the health of all Pennsylvanians. A goal of this initiative is commercialization of innovations derived from prior research endeavors.

Research may include, but is not limited to, the following areas:
- Research to reduce health disparities through the development of medical technologies that are affordable, accessible and acceptable to the targeted populations
- Research to develop technologies, reagents, instrumentation, and methodologies to improve cancer diagnosis or treatment or to predict or assess response to therapy
- Research on new therapeutics and monitoring technologies for cancer
- Research on medical imaging systems for cancer screening and early cancer detection or image-guided cancer interventions
- Research aimed at the discovery or development of health-related nanoscale and nanostructured technologies, devices and systems for the diagnosis or treatment of cancer

Research in the following areas will not be considered:
- Research related to cancer vaccines
- Research on cancer diagnostics and therapeutics that are currently approved by the Food and Drug Administration for commercial use.

Funds shall be used for biomedical research and/or clinical research and/or health services research, as defined in Act 2001-77. Activities that are not biomedical, clinical or health services research as defined by Act 2001-77 will not be considered. Collaboration between business and academic institutions is encouraged. The research should hold the potential for addressing the health needs of underserved segments of the population, including rural, urban, racial/ethnic minorities, and other populations that are at high risk for the health condition addressed by the proposed research project. Research proposals should include a reasonable sustainability plan including but not limited to how the project will contribute to the growth or maintenance of a sustainable business entity; how the innovation will be produced

and marketed; how revenues will be generated to commercialize the innovation and other funding sources; and the organization's prior commercialization experience. No more than 50% of the funds may be used for research infrastructure as defined in the Act, as amended. Research infrastructure is defined as including the following items: office equipment, office supplies, nonprofessional personnel, and laboratory or building construction or renovations, used to conduct research.

Translational Genomics Research Projects

The following list of grant awards provides the lead institution and subcontractors, title of the research project, amount of the grant award, grant award period, contact principal investigator, other key researchers, project purpose, project overview and expected research benefits and outcomes.

- Geisinger Clinic, Temple University and the University of Pittsburgh - *Utility of Genomic Data in Population Screening for Abdominal Aortic Aneurysm*, $2,909,969 for a 36-month project (June 1, 2012 — May 31, 2015)

  Contact Principal Investigator:
  David J. Carey, PhD
  Director and Senior Scientist, Weis Center for Research
  Geisinger Clinic
  100 North Academy Avenue
  Danville, PA 17822-2602
  Telephone: (570) 271-6660
  Email: djcarey@geisinger.edu

  Other Key Research Personnel:
  Gerardus Tromp, PhD; S. Helena Kuivaniemi, PhD; Sanjay Udoshi, MD; W. Andrew Faucett, MS; Diane Smelser, PhD; Robert Garvin, MD; James Elmore, MD; H. Lester Kirchner, PhD – employed by the Geisinger Clinic
  Daniel E. Weeks, PhD; Elizabeth Gettig, MS – employed by the University of Pittsburgh
  Eric T. Choi, MD – employed by Temple University

  Type of Research: Clinical and Health Services Research

  Project Purpose: Abdominal aortic aneurysm (AAA) is the 13th leading cause of death in the U.S. AAAs are frequently undiagnosed due to the absence of symptoms and lack of a simple laboratory test. Elective surgical or endovascular repair is a safe and effective treatment for AAA. Population screening to detect undiagnosed AAAs has been proposed, but current guidelines result in the screening of a large segment of the population with a low risk of AAA and exclude a significant fraction of individuals who do have an AAA. The purpose of this project is to create a novel risk stratification tool for AAA screening that combines clinical and genetic risk factor data and to test the utility of the tool in a real-world clinical setting.

  Project Overview: The scientific goals of this project are to create a novel risk stratification tool for abdominal aortic aneurysm (AAA) screening that combines elements of clinical and genetic risk factor data (Aim 1) and to test the utility of the tool in a real-world clinical setting (Aim 2). Aim 1 builds on the considerable expertise in AAA pathobiology, genetics and statistics of the study team as well as an existing biorepository of DNA samples collected for genomics research that are linkable to patient electronic medical records (EMR). Retrospective clinical risk factor data obtained from the EMR and genomic risk factor data obtained by genotyping known or suspected AAA-

associated variants in AAA case and control DNA samples will be used to create a novel predictive model for AAA risk. In Aim 2 the impact of the novel genomically-informed risk model will be evaluated in Geisinger primary care clinics and compared to current screening guidelines with respect to uptake and efficiency of AAA screening. Aim 2 utilizes Geisinger Clinic's resources for developing, implementing, and testing novel mechanisms to deliver actionable information to clinicians using the health system's advanced health information technology infrastructure. Because the screening tool will be created and evaluated initially in a patient population that is predominantly of White-European ancestry, we will also validate the risk scoring tool in a more racially diverse population of patients who receive their medical care at Temple University School of Medicine in Philadelphia, PA (Aim 3). The project also includes the development of new research educational programs targeted at students from minority populations that are underrepresented in medicine and biomedical research. This will be done by enrolling minority students in an existing undergraduate summer research internship program, and by developing a two-week intensive course in translational genomics for minority students.

Expected Research Outcomes and Benefits: The research project will lead to the creation of a novel genomically-informed model for predicting risk of abdominal aortic aneurysm (AAA) and an evaluation of the impact of implementation of this novel risk model on AAA population screening in a primary care clinic setting. Improved detection of AAA will lead directly to a reduction in mortality from rupture of undiagnosed AAAs. A more highly predictive risk model that can identify patients for population screening will also have enormous public health benefits. A refined risk prediction model will focus screening resources on patients with the highest risk, increases the number of positive AAA diagnoses, and decreases the number of negative diagnoses. Early diagnosis of AAAs (prior to rupture) will allow elective repair of aneurysms, and will allow patients with small aneurysms to be treated medically, when such therapies become available. We will also learn from this study whether the inclusion of genetic information, even if it adds only a modest level of increased risk, is a more potent motivator of a positive health behavior, i.e., participation in an AAA screening referral, than non-genetic risk information.

- University of Pennsylvania and The Fox Chase Cancer Center - *Translation of Genomics into Improvements in Cancer Prevention and Treatment*, $2,818,505 for a 48-month project (June 1, 2012 — May 31, 2016)

Contact Principal Investigator:
Peter Groeneveld, MD
Associated Professor of Medicine
University of Pennsylvania
1229 Blockley Hall
423 Guardian Drive
Philadelphia, PA 19104
Telephone: (215) 898-2569
Email: petergto@mail.med.upenn.edu

Other Key Research Personnel:
Angela Bradbury, MD; Susan Domchek, MD; Andrew Epstein, PhD; Monica Ferguson, MD; Joanne Levy, MBA; Nandita Mitra, PhD; Anil Vachani, MD – employed by the University of Pennsylvania
Mary Daly, MD, PhD: Michael Hall, MD, MS; Eric Ross, PhD; Yu-Ning Wong, MD, MSCE – employed by The Fox Chase Cancer Center

Hendrik Vermeulen, MS; Aaron Smith-McLallen, PhD – employed by Independence Blue
     Cross
Jennifer Chambers, MD – employed by Capital Blue Cross
Nicole A. Thomas, MBA
Linda Patrick-Miller, PhD – employed by MacLean Center for Clinical Medical Ethics

Type of Research: Health Services Research

Project Purpose: The overarching goal of the project is to improve the translation of genomic testing into reductions in the clinical, economic and societal burden of the four most common cancers affecting Pennsylvanians: breast, colon, and lung cancer. The project uses a highly integrated series of studies to assess clinical utility and/or population utility for the testing scenarios, and integrates data from administrative claims, cancer registry, clinical records, patient surveys, and genetic studies. The proposed research focuses on the potential for use of genomic information to reduce racial cancer disparities. This initiative includes a training and community advisory core to ensure its relevance to the communities in question and to support the training and career development of underrepresented minorities within the Commonwealth of Pennsylvania.

Project Overview: We propose an innovative, transdisciplinary research initiative that generates critically needed evidence about the effects of currently available genomic markers on cancer-related outcomes and lays the foundation for an ongoing, comprehensive approach to the evaluation of future genomic tests. This initiative spans half the continuum of the translational research in genomics – moving from research assessing the population impact of the use of clinically available genomic tests in cancer treatment, to research assessing the optimal strategy for the dissemination of the genetic risk information from a family history pedigree. The proposed research will use a series of rigorous methods including observational study using propensity score and instrumental variable techniques, and a randomized controlled trial of communication strategies:

Aim 1 (Population utility): To determine the effect of clinically available genomic tests for cancer prognosis and treatment on treatment regimen, disease-free survival, direct medical costs and racial disparities in these outcomes among patients with breast, colon and lung cancer in the Commonwealth of Pennsylvania.

Aim 2 (Clinical utility): To evaluate the effects of two alternative strategies for conveying the genetic risk information from family history on risk reducing behaviors among 1st and 2nd degree relatives of newly diagnosed breast or colorectal cancer patients.

Aim 3: To develop and implement a successful minority training and community engagement core to advance the careers of minority scientists and ensure that the research is relevant to the communities in question.

The proposed initiative has five key characteristics that will greatly increase its impact including: (1) Focus on major cancer burden; (2) Focus on racial disparities; (3) Multidisciplinary science; (4) Partnerships with key stakeholders including community-based, minority-serving organizations and private insurers; and (5) Leveraging existing resources.

Expected Research Outcomes and Benefits: The proposed initiative will have two major outcomes and benefits. First, the research will provide critically needed evidence about

the effect of currently available cancer genetic tests on patient and population outcomes, including cancer treatment, treatment complications, cancer mortality, economic costs and cancer racial disparities. Information about the outcomes of these tests is critically needed to enable patients and providers to make informed decisions about if and when the tests should be used and for payers and policy makers to make decisions about coverage, recommendations and other strategies to guide the use of the tests. In addition, this research will also identify key determinants of appropriate and inappropriate testing use, thereby enabling interventions to improve the quality of care around cancer genomics.

Second, the research will develop and test a novel strategy for conveying the genomic risk information captured in a family history pedigree. Increasingly, pedigree information is recognized as a potentially effective clinical and public health tool for increasing risk reduction behaviors and for identifying appropriate individuals for genetic testing. The development of an effective communication strategy will facilitate the use of this information and reduce the burden of cancer among individuals at increased genetic risk. Together, these three highly integrated projects will improve the use of genomic information surrounding cancer prevention and treatment, thereby addressing one of the major clinical and public health problems facing Pennsylvania today.

Cancer Diagnostics and Therapeutic Research Projects with Commercialization Potential

The following list of grant awards provides the lead institution and subcontractors, title of the research project, amount of the grant award, grant award period, contact principal investigator, other key researchers, project purpose, project overview and expected research benefits and outcomes.

- Apogee Biotechnology Corporation, Premier Research Group and Ricerca Biosciences, LLC - *Development of ABC294640 for Combination Chemotherapy of Pancreatic Cancer*, $832,608 for a 24-month project (June 1, 2012 — May 31, 2014)

   Contact Principal Investigator:
   Lynn W. Maines, PhD, MBA
   Vice President, Research
   Apogee Biotechnology Corporation
   1214 Research Blvd, Suite 1016
   Hershey Center for Applied Research
   Hummelstown, PA 17036
   Telephone: (717) 531-4758
   Email: lwmaines@apogee-biotech.com

   Other Key Research Personnel:
   Charles D. Smith, PhD – employed by Apogee Biotechnology Corporation
   William Ridder, DVM – employed by Ricerca Biosciences, LLC
   Christina Rice, RN – employed by Premier Research Group

   Type of Research: Biomedical Research

   Project Purpose: This project will complete preclinical studies and regulatory activities to support an Investigation New Drug application to evaluate ABC294640 in combination with Gemzar and/or Abraxane for the treatment of pancreatic cancer. ABC294640 is currently in single-agent phase I testing, and has received Orphan Drug designation from the FDA for pancreatic cancer. To complete the preclinical studies, we will define

the therapeutic efficacy of ABC294640 *in vitro* and *in vivo* using an orthotopic model of pancreatic cancer, both as a single agent and in combination with gemcitabine or *Abraxane*. Concomitantly, we will complete preclinical regulatory tasks required to support an IND application and subsequent clinical testing of ABC294640 in combination with Gemzar and/or Abraxane in patients with advanced pancreatic cancer.

Project Overview: The research objectives of this project are to complete a preclinical efficacy and safety data package and all preclinical regulatory activities to support the approval of an IND application for a Phase I/IIa clinical trial evaluating ABC294640 in combination with Gemzar and/or Abraxane in pancreatic cancer patients.

The following Specific Aims will be completed:

1. To evaluate the effects of ABC294640, alone and in combination with gemcitabine or paclitaxel, on pancreatic cancer cells in vitro. Using a panel of human pancreatic cancer cell lines, we will determine the effects of ABC294640 on proliferation, apoptosis, migration (invasion) and cytokine production. The ability of ABC294640 to synergize with gemcitabine or paclitaxel in the proliferation and apoptosis assays will also be determined. Mechanism-based pharmacodynamic (PD) endpoints will be assessed in the treated cells to provide biomarkers for drug action.

2. To evaluate the effects of ABC294640, alone and in combination with gemcitabine or Abraxane, on pancreatic tumors in vivo. The antitumor, antiangiogenic and antimetastatic activities of ABC294640, alone and in combination with gemcitabine or Abraxane, will be determined in an orthotopic pancreatic tumor model in SCID mice using bioluminescent detection. Mechanism-based PD endpoints will be assessed in the tumors, and plasma sphingosine 1-phosphate levels will be determined as a potential clinical biomarker of drug action.

3. To complete all preclinical tasks necessary to initiate clinical testing of ABC294640 in combination with Gemzar and/or Abraxane, including limited additional toxicology studies; development of the clinical trial protocol; and submission of an IND application for the drug combination trial. It is important to note that these regulatory tasks will be highly leveraged by previous work completed by Apogee and utilized in the acquisition of the IND approval for testing ABC294640 as a single-agent, a clinical trial that is currently ongoing.

Expected Research Outcomes and Benefits: The expected outcome of this research project is the enablement of an innovative Phase I/IIa clinical trial of a new drug combination for the treatment of pancreatic cancer. There is a dire need for improvement of therapy for pancreatic cancer. The American Cancer Society estimates that the incidence of pancreatic cancer in the United States in 2010 was 43,140 cases. Approximately 20% of new pancreatic cancer patients present with localized disease, and for them, surgery alone provides a median survival of 12-14 months. However, there is a very high-incidence of locoregional and systemic recurrence in these patients. Additionally, poor response to systemic chemotherapy in patients with more advanced disease results in a dismal, overall 5-year survival rate of <5%. Systemic therapy for pancreatic cancer typically includes the antimetabolite gemcitabine, which provides palliation of symptoms, but has minimal impact on survival.

New and more effective therapies are needed for pancreatic cancer patients, and significant effort is being focused on the identification of appropriate new targets for pancreatic cancer drugs. Sphingolipid metabolism is being increasingly recognized as a

key pathway in cancer biology. Extensive research on sphingolipid metabolism demonstrates the roles of ceramide, sphingosine and sphingosine 1-phosphate (S1P) in regulating tumor cell apoptosis and proliferation, as well as angiogenesis, inflammation and tumor sensitivity to anticancer drugs. Apogee Biotechnology Corporation has developed the first non-lipid inhibitors of sphingosine kinases (SK1 and SK2), and conducted extensive studies of their therapeutic activities in multiple models of cancer and inflammatory diseases. Studies with pancreatic cancer cells and xenografts support the hypothesis that ABC294640 will be an effective therapeutic agent in pancreatic cancer. The significance of the proposed project is further enhanced by the fact that ABC294640 has entered clinical trials as a single agent. Furthermore, the FDA has granted Orphan Drug status to ABC294640 for the potential treatment of advanced pancreatic cancer.

The completion of this project will enable a promising clinical trial evaluating a new target and drug and its ability to extend life and improve the quality of life, providing new hope for pancreatic cancer patients and their families.

- Carnegie Mellon University, Omnyx, Inc., and the University of Pittsburgh - *Automated Biomarker Identification for Cancer Detection and Prognosis,* $983,783 for a 24-month project (June 1, 2012 — May 31, 2014)

  Contact Principal Investigator:
  Robert F. Murphy, PhD
  Lane Professor and Head of Computational Biology
  Carnegie Mellon University
  5000 Forbes Avenue
  Pittsburgh, PA 15213
  Telephone: (412) 268-3480
  Email: murphy@cmu.edu

  Other Key Research Personnel:
  Gustavo K. Rohde, PhD – employed by Carnegie Mellon University
  Anil Parwani, MD; John Ozolek, MD – employed by the University of Pittsburgh
  Rajiv Enand; Ronald Stone, PhD; Raghavan Venugopal, MS; Michael Meissner, PhD –
       employed by Omnyx, Inc.

  Type of Research: Biomedical Research

  Project Purpose: The purpose of this project is to dramatically expand the image analysis capabilities of the Omnyx digital pathology platform and to use this capacity to carry out translational research studies to further demonstrate the value of that technology for improving diagnostic and prognostic evaluation in two important patient populations. We propose to interface image analysis technology that is the intellectual property of Carnegie Mellon University with the Omnyx platform. Two research studies will be carried out, one for prostate lesions in adults and one for liver lesions in children and adults. The results of the image analysis will be compared with data on patient outcome and responsiveness to treatment.

  Project Overview: The goal of this project is to carry out translational research to further develop two related new cancer diagnostic methods for which proof-of-concept has been demonstrated. Carnegie Mellon University has intellectual property consisting of algorithms for (1) determining the subcellular location of marker proteins from immunohistochemistry images and identifying proteins that change subcellular location

between normal and tumor tissue, and (2) robustly identifying changes in nuclear morphology that can distinguish normal from cancerous tissues in several pathologies in the liver. The research seeks to build on these results to create commercially viable diagnostic products that can be marketed by Omnyx, a pioneering digital pathology company headquartered in Pittsburgh.

The first specific aim is to perform translational research studies to determine the value of automated image analysis technology developed at Carnegie Mellon University for providing enhanced diagnostic and prognostic information in adult prostate and pediatric/adult liver tumors. These studies will be done using paraffin-embedded tissue selected from tissue banks to cover a range of tumor grades, initial diagnoses and clinical outcome. The images will be analyzed to determine the prognostic value of the phenotypes measured by the two technologies. Additional image analysis methods will be developed as needed to improve upon the existing technologies. The second specific aim is to interface the automated technology with the Omnyx digital pathology platform and develop an appropriate and efficient clinician interface to the technology in order to facilitate the ability of the clinician to integrate its outputs into the diagnostic process.

Expected Research Outcomes and Benefits: In the case of liver lesions, the development of the nuclear analysis tool may give the pathologist an ancillary and perhaps at times diagnostic tool to aid in distinguishing between differential diagnoses in liver lesions. For example, nuclear morphological features are not typically used to distinguish between nodular regenerative hyperplasia, focal nodular hyperplasia, and hepatic adenoma because our visual system cannot process the subtle chromatin features present in one nucleus compared to another over a hundred or several hundred nuclei. While all three have differing pathogenic mechanisms, this may be reflected in the nuclear morphology (size, chromatin patterns, etc.) that reflect the transcriptional and gene silencing activity for each lesion. For a given lesion, comparing nuclear morphology can allow the pathologist to distinguish or narrow the list of possibilities. This is particularly important in biopsy specimens where larger microarchitectural context is lost. The subcellular location of particular biomarkers may also help the pathologist distinguish between different pathologies.

In the case of the prostate, the research outcome would be to go beyond the current standard of Gleason scoring and provide a tool to select those patients who may have a low Gleason score but are likely to go on to have aggressive disease. Both nuclear morphology and location biomarkers may contribute to this distinction. In the case of the prostate, identifying patients at high risk for aggressive disease is very relevant as this could prevent unnecessary and morbid therapy for the many men affected by prostate cancer.

The results of these translational studies are anticipated to improve patient outcomes through more appropriate choice of therapies and enhanced diagnostic capabilities. They will also set the stage for many additional studies for other tumor types using Omnyx' industry-leading digital pathology platform, enabling significant growth and job creation in Pennsylvania.

- Geisinger Clinic, Cernostics, Inc., University of Pennsylvania, and University of Pittsburgh - *Diagnostic-Prognostic Testing in Patients at High Risk for Esophageal Cancer*, $1,000,000 for a 24-month project (June 1, 2012 — May 31, 2014)

Contact Principal Investigator:
Jeffrey W. Prichard, DO

Director of Surgical Pathology
Geisinger Medical Laboratory
100 North Academy Avenue
Danville, PA 17822
Telephone: (570) 214-6795
Email: jwprichard@geisinger.edu

Other Key Research Personnel:
Jinhong Li, MD, PhD; David L. Diehl, MD – employed by Geisinger Clinic
Rebecca J. Critchley-Thorne, PhD; Bruce Campbell, MS – employed by Cernostics, Inc.
Gary W. Falk, MD, MSc; Anil K. Rustgi, MD; Antonia Sepulveda, MD, PhD – employed by
the University of Pennsylvania
Blair A. Jobe, MD; Jon M. Davison, MD; Ali H. Zaidi, MD; Roger S. Day, ScD – employed
by the University of Pittsburgh

Type of Research: Biomedical Research

Project Purpose: The purpose of this project is to clinically validate a diagnostic-prognostic test for esophageal cancer, which will accurately diagnose at a premalignant stage and predict which patients are at high risk for esophageal cancer to enable early, preventative therapy. A prototype test has been developed and proof-of-concept of the testing technology has been established in collaborative work by Geisinger and Cernostics. The project aims to perform clinical validation studies in a training cohort and two independent validation cohorts of esophageal biopsies with clinical outcome data from Geisinger, University of Pittsburgh and University of Pennsylvania to select diagnostic and prognostic classifiers and to establish the sensitivity, specificity and positive and negative predictive values of the diagnostic-prognostic test for patients at high risk for esophageal cancer.

Project Overview: The broad objective of the research is to clinically validate a diagnostic and prognostic test that accurately assigns diagnosis and predicts risk of developing esophageal cancer. The test is a spatial systems biology-based approach to anatomic pathologic testing. The test employs multiplexed fluorescence labeling of tumor system biomarkers, including malignant, immune and stromal processes in anatomic pathology specimens with digital imaging and image analysis to quantify biomarker expression and spatial relationships between biomarkers in the context of tissue morphology. This is coupled to classifier software to integrate biomarker data with morphology data and clinical data to produce diagnostic and prognostic scores. These scores will be used to accurately diagnose and predict the risk of developing esophageal cancer in individual patients to enable early treatment. A prototype test has been collaboratively developed by Geisinger (lead applicant) and Cernostics, Inc (small business collaborator) as a proof-of-concept. As a next step, a consortium of investigators will perform retrospective clinical validation studies of the test towards the long term goal of commercializing the test via a CLIA-certified laboratory. The test will be performed first in a training cohort of formalin-fixed paraffin-embedded esophageal biopsies with clinical data from Geisinger using Cernostics' spatial systems biology technology and diagnostic and prognostic classifiers will be developed. The test, including the classifiers, will then be performed in two independent validation patient cohorts from the University of Pittsburgh and the University of Pennsylvania to determine specificity, sensitivity and positive and negative predictive values of the diagnostic-prognostic test. The specific research aims are, 1) Determine the performance of the prototype test in stratifying patients according to diagnosis and predicting risk for esophageal cancer in a retrospective training patient cohort; and 2)

Validate the diagnostic and prognostic performance of the optimized diagnostic-prognostic test in two independent retrospective patient cohorts. The training and validation cohorts represent both urban and rural populations and are designed to reach the maximum number of the underserved and will ensure a significant statewide impact on the health of Pennsylvanians. Paralleling the proposed project, Cernostics and Geisinger will perform further analytical validation studies on the test. The test will be commercialized by Cernostics and will be offered as a service to pathologists and gastroenterologists to guide individualized patient management to help prevent the development of esophageal cancer.

Expected Research Outcomes and Benefits: The project employs a testing technology for which Geisinger Health System and Cernostics have demonstrated proof-of-concept. The investigators have selected a comprehensive panel of diagnostic and prognostic biomarkers, many of which have established significance in diagnosing the stages of Barrett's esophagus and in predicting risk for esophageal cancer. Therefore, the expected research outcomes of the project are classifiers based on optimal sets of biomarker, morphology and clinical data that can accurately assign diagnosis and predict whether a patient will develop high grade dysplasia or esophageal cancer and also estimate the sensitivity, specificity and overall accuracy of the diagnostic-prognostic test. It is expected that the test will have high sensitivity and specificity and high positive and negative predictive values based on the known diagnostic and prognostic significance of the panel of biomarkers and based on the high stringency of feature selection for the classifiers. It is also expected that the research will identify a key set of biomarkers and related molecular pathways involved in the progression of Barrett's esophagus to esophageal cancer, which will lead to a better understanding of the biology and behavior of esophageal cancer and aid in the design of new therapeutic agents to prevent and treat esophageal cancer.

The diagnostic utility of the test will improve health status by increasing the accuracy of pathological diagnosis, thus reducing the number of repeat endoscopies and biopsies that patients with Barrett's esophagus must currently undergo, particularly for patients who are initially diagnosed as "indefinite/indeterminate" for dysplasia. The prognostic utility of the test will improve health status by identifying patients at high risk for developing esophageal cancer early in the disease progression when treatments such as endoscopic mucosal resection and radiofrequency ablation can be applied to effectively prevent development of cancer. The prognostic utility will also identify low risk patients, who will not develop esophageal cancer, and who can be spared unnecessary endoscopies, biopsies and treatments.

The expected benefits of the project include; significant improvements in diagnostic and prognostic accuracy to prevent delays in treatment of patients at high risk for esophageal cancer, and a reduction in unnecessary and costly endoscopies and biopsies. This individualized approach will benefit patients by reducing the incidence and mortality associated with esophageal adenocarcinoma and will benefit health care systems by targeting treatments and screenings to the high-risk patients who need them.

- Institute for Hepatitis and Virus Research, Absorption Systems, LP – *A New Inhibitor of the Akt/mTOR Pathway with Remarkable Potency and Selective Anti-Hepatocellular Carcinoma Activity*, $909,170 for a 24-month project (June 1, 2012 — May 31, 2014)

Contact Principal Investigator:
Andrea Cuconati, PhD
Project Leader and Assistant Professor

Institute for Hepatitis and Virus Research
3805 Old Easton Road
Doylestown PA 18902-8400
Telephone: (215) 489-4918
Email: ACuconati.Research@hepb.org

Other Key Research Personnel:
Xiadong Xu, PhD; David L. Horn, MD, FACP, FIDSA; Nelson Carvalho, MBA; Patti
        McAloon, MBA – employed by the Institute for Hepatitis and Virus Research
Ju-Tao Guo, MD – employed by Drexel University College of Medicine
Tong Xiao, MS – employed by Enantigen Therapeutics, Inc.
Feng Zhou, MD; Joseph Rager; Lyle Miller – employed by Absorption Systems, LP

Type of Research: Biomedical Research

Project Purpose: This is a proposal for the development into a drug of a novel chemical
family with activity against primary liver cancer, known as hepatocellular carcinoma
(HCC). HCC is very resistant to chemotherapy, has few therapeutic options for most
patients, and is usually fatal. This new drug would be selective for liver cancer cells and
would function through a different mechanism than the currently approved anti-HCC
chemotherapies. Based on *in vivo* proof-of-concept studies with the parent compound,
we predict this series will lead to a drug with higher efficacy, lower toxicity and fewer
side effects. At the end of the proposed project, novel compounds will be ready for FDA-
sanctioned studies that would lead to an investigational new drug application.

Project Overview: Our proposal centers on the development of a novel compound for
chemotherapy of hepatocellular carcinoma (HCC) patients. HCC is a common
consequence of viral hepatitis and fatty liver disease, and its incidence is on the rise in
the United States. Globally, it the fourth most common cause of cancer deaths. Current
HCC therapies include surgery and liver transplantation, for which only a minority of
patients are candidates. Chemotherapy options are limited in both efficacy and
availability, as there is only one drug currently approved for use in advanced HCC cases.
Our proposal is to test the feasibility of developing a therapeutic compound to selectively
target HCC cells. Using cell lines derived from HCC and normal liver tissues, and our "in-
house" diverse compound library, we have identified a disubstituted aminothiazole,
called HBF-0079 that selectively inhibits growth and viability of HCC-derived cells, while
exhibiting minimal effects on normal liver-derived cells. Unlike currently used HCC
drugs, HBF-0079 does not exhibit indiscriminate cytotoxicity, indicating a distinct
mechanism of action, and suggesting that it may be useful in cases where resistance to
the current drugs has emerged, or where liver damage has rendered the patient
sensitive to therapy. We have determined that HBF-0079 inhibits anti-apoptotic and pro-
mitotic signaling through the Akt/mTOR axis, with ensuing cell cycle arrest and
apoptosis. In addition, the compound also inhibited tumor growth in an *in vivo* xenograft
model, constituting proof of concept. Finally, initial chemical optimization of HBF-0079
has already increased potency (CC_{50}) from 1.5 to 0.02 micromolar. The activity of the
compound on HCC cell lines with disparate genotypes and oncogenic lesions suggests
that it may have broad spectrum activity against HCC, a cancer known for great
variability in its response to therapy. This proposal is to perform critical chemical and
biological experiments to determine if this approach is practical and feasible. HBF-0079
has several chemical features that offer modification possibilities. Therefore, we will: 1)
explore the chemistry and formulation of HBF-0079 to develop an even better analogue;
2) test the active compounds against primary hepatocytes, and a variety of normal
hepatocyte, HCC and non-HCC derived cell lines to examine selectivity; 3) determine the

absorption, drug metabolism, extraction, and toxicity (ADMET) profiles of two active analogues in the rat; 4) confirm the efficacy of the new compounds in an in vivo model of human HCC; and 5) identify the molecular target of the these compounds to facilitate drug design.

Expected Research Outcomes and Benefits: Fulfillment of this proposal will test the feasibility of developing a novel drug-like compound series into a new anti-cancer drug. This project is specifically intended for the treatment of hepatocellular carcinoma, which is a growing problem in Pennsylvania and the US especially among Asian immigrant and disadvantaged urban populations. At completion, the compounds that emerge from this work will 1) be ready for formal FDA required studies to support an investigational new drug (IND)-application, 2) appear to be attractive candidates for further investment and licensing with an industry partner, and 3) open a new avenue toward fulfilling a significant medical need.

- Oncoceutics, Inc., The Pennsylvania State University, Provid Pharmaceuticals, Inc. and University of Pennsylvania – *Development and Commercialization of Novel Cancer Therapeutic TIC10*, $1,295,646 for a 24-month project (June 1, 2012 — May 31, 2014)

   Contact Principal Investigator:
   Lee Schalop, MD
   Chief Financial Officer, Secretary and Treasurer
   Oncoceutics, Inc.
   1214 Research Blvd.
   Hummelstown, PA 17037
   Telephone: (917) 327-6423
   Email: lee.schalop@oncoceutics.com

   Other Key Research Personnel:
   Bimalendu Dasmahapatra, PhD; Wolfgang Oster, MD, PhD – employed by Oncoceutics, Inc.
   Wafik S. El-Deiry, MD, PhD; Joshua E. Allen; Michael Glantz, MD; Zhaohai Yang, MD, PhD; Jiangang Liao, PhD; Thomas O'Leary, PhD – employed by The Pennsylvania State University
   Dorothy C. Brown, DVM, MSCE; Erika Krick, VMD, DACVIM; Michael DiGregorio, CVT – employed by the University of Pennsylvania
   Gary Olson, PhD – employed by Provid Pharmaceuticals, Inc.

   Type of Research: Biomedical, Clinical and Health Services Research

   Project Purpose: The overall purpose of the proposed research studies is to enable and complete phase I/II clinical trials with the novel antitumor agent TIC10 to improve treatment options and outcomes for cancer patients in Pennsylvania. While we have obtained a vast and comprehensive body of evidence regarding the preclinical efficacy, mechanism, and toxicity of TIC10, there are critical components of the Investigational New Drug (IND) application that must be completed prior to human studies. Completion of such studies will allow for IND and IRB clinical protocol approval, thereby potentiating a phase I/II clinical trial at Penn State Hershey Medical Center. This clinical study will determine the toxicity and pharmacokinetic profile of TIC10 in humans to directly assess the viability of TIC10 as novel treatment for human cancer.

   Project Overview: The goal of this research proposal is to enable and conduct a phase I/II clinical trial with the promising new small molecule TIC10 as a new and potent

treatment for therapy-resistant cancer. The objectives of this research proposal are to (i) complete remaining preclinical and administrative components of the Investigational New Drug (IND) application, (ii) obtain IND and IRB clinical protocol approval, and (iii) conduct a phase I/II trial with TIC10 to determine its safety, optimal dose, pharmacokinetics (PK), and efficacy in humans. To enable and complete a first-in-man phase I/II clinical trial with TIC10 as a novel antitumor agent, we aim to:

1. Complete remaining preclinical components of IND application.
      A. Development of correlative assays for the clinical protocol.
      B. Define the PK profile of TIC10 in mice.
      C. CMC and GMP-compliant synthesis of TIC10.
      D. Complete IND-enabling animal toxicity studies.

2. Conduct phase I/II clinical trial with TIC10.
      A. Development and submission of IRB clinical protocol and IND application.
      B. Enroll and conduct phase I/II clinical trial.
      C. Conduct pharmacokinetic and pharmacodynamic assays on TIC10 in humans.
      D. Interpretation of results to support further development and commercialization of TIC10.

Methods: Aim 1A-B will develop assays for markers of response to TIC10 based on its mechanism and for serum detection of TIC10 for pharmacokinetic profiling. Aim 1C will secure a GMP-compliant source of TIC10 for GLP toxicity studies and the phase I/II clinical trial. For Aim 1D, GLP-compliant toxicology studies will be conducted in rats and beagle dogs along with brain tumor efficacy/toxicity studies in dogs. Aim 2A will submit applications for IND and IRB clinical protocol for the phase I/II study in Aim 2B. Aims 2C-D will execute and interpret assays to define molecular marker of response/resistance, the PK/toxicity profile, any preliminary signs of tumor response, and cumulatively guide the future development of TIC10 in terms of future clinical trial design and strengths/limitations. A multi-faceted fund-raising approach and partnering will be implemented for commercialization of TIC10 in the world market.

Expected Research Outcomes and Benefits: The expected benefit from this research project is to gain a new cancer therapy, TIC10, for the treatment of therapy-resistant malignancies including triple-negative breast cancer, non-small cell lung cancer, and brain tumors. Brain tumors are an urgent priority in clinical oncology as survival time is generally 6 months and the standard of care treatments offer little improvement in outcome. Importantly, TIC10 doubles the survival of mice with brain tumors and triples the survival when combined with bevacizumab, which is used for the treatment of brain tumors as well as metastatic colorectal cancer. In lung cancer, TIC10 also synergizes with paclitaxel and docetaxel to yield cures. Lung cancer is the leading cause of cancer-related death in the US with tobacco use by far being the major culprit. The malignancies targeted in this study are considered unmet clinical needs and patients harboring such disease are left with few, if any, treatment options. Chemotherapy remains the predominant class of cancer medicines but causes dose-limiting toxicity due to its effects on normal cells. Several targeted anticancer agents have been approved over the past two decades such as bevacizumab, cetuximab, sorafenib, etc. These agents have possessed generally favorable toxicity profiles but clearly more treatment options are necessary as they do not offer cures and many are biological agents that are very expensive to produce. TIC10 is an inexpensive small molecule that possesses therapeutically desirable properties such as oral activity, thermal stability, temporally sustained activity, ability to cross the blood-brain barrier, and safety. TIC10 is expected to provide cancer patients an inexpensive and practical targeted antitumor agent in

clinical settings where other available therapies are ineffective. As a result, TIC10 is expected to improve the quality of life, decrease disease progression, and help alleviate practical issues that burden cancer patients.

In addition to the direct patient benefits, the proposed studies will provide critical academic benefits such as preliminary validations of efficacy, toxicity, and pharmacokinetic profiles in humans. While these profiles appear favorable in mice, they may be altered in human patients and the proposed phase I/II trial will identify any potential limitations or strengths of TIC10 as an anticancer agent for humans. Correlative assays will be conducted in trials to validate the mechanism of TIC10 and will directly assess the viability of this therapeutic mechanism as a new class of therapeutics in cancer management. If the novel mechanism of TIC10 is conserved in humans, it will pave the way for generating other therapeutics within its class. The toxicity and pharmacokinetic profiles will be particularly important for TIC10 as any limitations in these properties may be overcome by derivatives of the molecule in future development.

Outside of health-related benefits, the majority of these funds will go to Pennsylvania institutions and will serve to support and create jobs within the state. The construction of this proposal has been an efficient collaborative effort between Oncoceutics and the indicated subcontractors. The execution of this proposal will continue to foster collaboration between these Pennsylvania (PA)-based institutions that include Oncoceutics, Penn State Hershey Medical Center, and the University of Pennsylvania. The timeline, allocation of responsibilities, and communication routes have already been planned and are summarized in section VI. In summary, this research project is expected to translate the novel anticancer treatment TIC10 as a new practical and unparalleled treatment option for cancer, inform on its strengths and limitations in humans, enable the commercialization of TIC10, improve the health status and outcomes of cancer patients in PA, create and support jobs in PA, and foster collaborations among small business and academic institutions in PA.

- The Pennsylvania State University and Keystone Nano, Inc. – *Therapeutic Delivery of siRNA Using Calcium Phosphate NanoJackets for Improved Cancer Treatment*, $1,000,000 for a 24-month project (June 1, 2012 — May 31, 2014)

  Contact Principal Investigator:
  Mark Kester, PhD
  G. Passananti Professor
  The Pennsylvania State University
  500 University Drive
  P.O. Box 850, MC R130
  Hershey, PA 17033
  Telephone: (717) 531-8964
  Email: mkester@hmc.psu.edu

  Other Key Research Personnel:
  James Adair, PhD; Jiangang Liao, PhD – employed by The Pennsylvania State University
  Mylisa Parette, PhD – employed by Keystone Nano, Inc.

  Type of Research: Biomedical Research

  Project Purpose: Currently molecular-based therapeutic approaches, including siRNA, are limited by poor cellular uptake and cellular degradation. The design and engineering of delivery systems that protect and target molecular-based therapeutics is a critical

unmet need in the arsenal of cancer-fighting agents. Nanotechnology offers the promise of enhancing cancer cell uptake while protecting the siRNA cargo during systemic delivery. Penn State University has engineered a non toxic, biocompatible, uncharged calcium phosphate nanoparticle that has proven efficacious for delivering siRNA to cancer. In collaboration with Keystone Nano and Calvert Laboratories, the physical, chemical and biological properties of these nanocolloids will be evaluated. These commercialization studies will provide the data for a preclinical package that will support an IND application to the FDA.

Project Overview: The research objective is to commercially develop improved cancer treatments that utilize biocompatible, bioresorbable and bioneutral calcium phosphate nanoparticles, known as NanoJackets, for systemic therapeutic delivery of small interfering ribonucleic acid (siRNA) molecules. However, the ability to effectively deliver siRNAs for cancer treatments has proven challenging, particularly for systemic administration. The ability to concentrate siRNAs to achieve therapeutic threshold concentrations in tumors remains difficult. Non-toxic nanoscale delivery modalities may offer the best chance to achieve therapeutic dosing of siRNAs within tumors.

As proof of concept, we have developed and demonstrated the biological efficacy of siRNA NanoJacket prototypes targeting the 3140A>G point mutation in the human PI3K gene that is over-expressed in a cohort of breast cancer patients with poor outcomes. This approach is distinct from competitor technologies in two main ways. First, the use of calcium phosphate particles that can be produced at the 100nm scale alleviates the toxicity and limited biodistribution profiles observed with current nano-delivery technologies. Second, the strategy to design siRNA oligonucleotides for selected cancer-causing mutations provides an additional layer of specificity that will minimize off-target side effects.

To support initial product development of the 3140A>G PI3K siRNA NanoJackets, the overall goal of the proposed project is to enable an investigational new drug (IND) application to the FDA for regulatory review. In order to achieve the next stages of commercialization for the 3140A>G PI3K siRNA nanoproduct, the following specific aims are proposed:

1. Selection of optimal siRNA NanoJacket formulation based on in vivo efficacy
2. Optimization of manufacturing to produce material for chemistry, manufacturing and control (CMC) characterization and preclinical testing
3. Evaluation of dose-defining in vivo studies
4. Completion of pivotal GLP preclinical studies
5. Compilation of siRNA NanoJacket IND package for FDA review

Expected Research Outcomes and Benefits: Cancer is a disease that results from genetic mutations that cause aberrant cell survival and growth. The vast majority of current chemotherapeutic treatments utilize cytotoxic pharmacological or radioactive compounds to kill cancerous cells. However, virtually all of these treatments result in toxic side effects, mostly due to the nonselective mechanisms of pharmaceutical action and poor biodistribution profiles. In fact, severe side effects often limit the dosage that patients can receive. For many cancers, this leaves severely ill patients with little choice but to endure widespread toxicity for small gains in therapeutic efficacy.

The present grant focuses on another approach, the delivery of molecular-based therapeutics that target mutated oncogenic proteins, over-expressed preferentially in cancer cells. The overall expected outcome of this proposal is to complete the preclinical

evaluation of a nontoxic, biocompatible nanoscale delivery system for siRNA. Although the focus of the proposed project will center on NanoJackets delivering siRNA designed for the 3140A>G point mutation in the PI3K gene, a common breast cancer mutation, the encapsulation of siRNA within NanoJackets is sequence-independent. So while this project will provide for the commercialization of a defined RNAi-based breast cancer therapy, it will also serve as proof of concept for a platform siRNA delivery technology. Further, with the increasing use of pharmacogenetics to identify specific mutations in primary tumor biopsy samples, siRNA NanoJackets could provide a customized therapeutic product that targets each patient's specific cancer-causing mutations. Thus, the true benefit of the research program is the commercialization of a platform delivery system that allows for the realization of personalized medicine.

Since siRNA NanoJackets can be utilized as a platform technology, successful funding and completion of this project will likely lead to considerable revenue, growth and job creation within PA as well as improve the health status of Pennsylvanians. In addition, this will serve as an effective model by which to translate technologies developed in Universities to commercial nanomedical products, which could promote further commercialization of University technologies.

- Thomas Jefferson University, The Fox Chase Cancer Center, and the University of Pittsburgh – *Occult Tumor Burden as a Marker Stratifying Therapy to Eliminate Racial Disparities in Colon Cancer*, $744,156 for a 24-month project (June 1, 2012 — May 31, 2014)

  Contact Principal Investigator:
  Scott A. Waldman, MD, PhD
  Professor and Chairman
  Pharmacology and Experimental Therapeutics
  Thomas Jefferson University
  1025 Walnut Street, Room 901
  Philadelphia, PA 19107
  Telephone: (215) 955-6086
  Email: Scott.Waldman@jefferson.edu

  Other Key Research Personnel:
  Terry Hyslop, PhD; Ronald E. Myers, PhD – employed by Thomas Jefferson University
  David Weinberg, MD – employed by The Fox Chase Cancer Center
  Robert E. Schoen, MD – employed by the University of Pittsburgh

  Type of Research: Biomedical and Clinical Research

  Project Purpose: In Pennsylvania, colorectal cancer incidence and mortality are higher than in the nation with ~15,000 cases treated each year, associated with in-patient annual costs of >$200M. Moreover, there is a disparity in outcomes in African Americans, who exhibit 40% excess mortality compared to Caucasians. This project will develop the critical clinical trial evidence essential to commercialize a molecular test that identifies colon cancer patients at risk for developing recurrent disease who will benefit from adjuvant chemotherapy. This test will identify patients who have excess risk reflecting race who should receive treatment, to reduce racial disparities in outcomes in colon cancer mortality. Moreover, this project will identify barriers to physician adoption of this test that limit commercialization.

Project Overview: The *significance* of the project is highlighted by the populations at risk, which include 1.5 million patients worldwide with colorectal cancer and the associated racial disparities in outcomes. The *clinical impact* can be appreciated by considering that one of the greatest gaps in management of these patients is identifying who will respond to chemotherapy. The *commercial impact* is underscored by the market size for diagnostics predicting therapeutic response in colorectal cancer, which exceeds $1.2 billion annually worldwide. The *feasibility* of this project reflects the innovation of the team in creating this field, its history of >10 years of collaboration, and the advantage of an existing population of patients, specimens and analyses which this project will leverage. In that context, the broad research objectives include: (1) defining the utility of occult tumor burden analysis by GUCY2C RT-qPCR (quantitative reverse transcriptase-polymerase chain reaction) to identify African American (black) and Caucasian (white) patients with early stage (lymph node-negative; pN0) colon cancer at excess risk for developing recurrent disease who benefit from therapy; (2) defining barriers that restrict the adoption of molecular diagnostic tests by practicing physicians and limit commercialization success; and (3) advancing commercialization of this novel molecular paradigm. These objectives will be accomplished by executing specific aims, which include: (1) the *Clinical Development Aim*, in which a retrospective multicenter clinical trial central to the commercialization plan will be conducted that defines the utility of GUCY2C RT-qPCR as a predictive marker of therapeutic response in pN0 black and white patients; (2) the *Health Services Research Aim*, which will identify physician barriers to adopting molecular diagnostic tests that could restrict commercialization; and (3) the *Commercialization Aim*, which will advance commercial deployment of occult tumor burden as a molecular diagnostic test to identify pN0 colon cancer patients who benefit from adjuvant chemotherapy. Commercialization will occur through a well-established and successful public-private partnership between Thomas Jefferson University and Targeted Diagnostics & Therapeutics, Inc., a Pennsylvania-based biotechnology company with a track record of success in commercializing GUCY2C-based diagnostics for managing patients with colorectal cancer.

Expected Research Outcomes and Benefits:
(1) The *Clinical Development Aim* will define the utility of quantifying occult tumor burden, utilizing GUCY2C RT-qPCR, to identify pN0 black and white colon cancer patients at risk for recurrent disease who derive benefit from adjuvant chemotherapy. This study will be the first to employ a molecular diagnostic to effectively identify pN0 colon cancer patients who benefit from adjuvant chemotherapy, one major unmet clinical gap in colon cancer management. Also, this study will demonstrate that pN0 patients with excess risk related to race can be identified and treated, to reduce racial disparities in outcomes in colon cancer. Moreover, this study is absolutely required to advance the commercialization of this molecular diagnostic platform for the therapeutic management of patients with pN0 colon cancer.
(2) The *Health Services Research Aim* will identify factors that influence the adoption of molecular diagnostic tests by practicing physicians. There is a substantial time lag between development and adoption of new medical technologies, including molecular diagnostics, for use in routine clinical care. Delay in translating innovations into practice is one primary hurdle to commercial success for molecular diagnostic products. Although these issues have been explored for other diagnostic products, there are no data on the uptake of molecular diagnostics to stage and treat pN0 colon cancer patients. We will complete structured interviews with practicing physicians, using established decision analysis methods, to assess barriers to physician adoption of molecular diagnostics for staging pN0 colon cancer patients. Interview data will be used to identify specific issues underlying resistance to adoption, and to develop outreach strategies which inform the commercialization plan for GUCY2C RT-qPCR.

(3) The *Commercialization Aim* will leverage the studies described herein as an essential element in the strategy to commercialize occult tumor burden quantified by GUCY2C RT-qPCR to stratify therapeutic responsiveness in pN0 colon cancer. One of the greatest barriers to adoption of molecular tests by practicing physicians is the absence of clinical trials that are adequately powered and robust in statistical analysis that conclusively demonstrate clinical utility. The central component of the present project, the retrospective analysis of the predictive utility of GUCY2C RT-qPCR in black and white pN0 colon cancer patients (Aim 1), will provide the analytical and clinical validation of the utility of this diagnostic platform in patient management. Beyond the impact of this project on physician adoption, the present study is significant because it will demonstrate the utility of GUCY2C RT-qPCR in providing clinically actionable data defining management of pN0 colon cancer patients. The present project will provide the base of evidence for the use of GUCY2C RT-qPCR in clinical management decisions that are essential to promote physician adoption and reimbursement by third party payers, including Medicare, that are key to commercial success.

- UE LifeSciences, Inc., Drexel University, M Squared Electronics, and NextFab Studios – *Commercial Prototype Development and Clinical Validation of Low-Cost Hand-Held Breast Scanner*, $878,244 for a 24-month project (June 1, 2012 — May 31, 2014)

    Contact Principal Investigator:
    Mihir B Shah
    Chief Executive Officer
    UE LifeSciences, Inc.
    4435 Lobella Ct.
    Chester Springs, PA 19425
    Telephone: (267) 342-3303
    Email: Mihir@NoTouchBreastScan.com

    Other Key Research Personnel:
    Matthew S. Campisi, MS – employed by UE LifeSciences, Inc.
    Ari Brooks, MD; Jean Kirk, MD; Cynthia Gifford-Hollingsworth, CRNP; Wan Young Shih, PhD; Wei-Heng Shih, PhD; Xin Xu – employed by Drexel University
    Mark Robinson – employed by M Squared Electronics
    Evan Malone, PhD – employed by NextFab Studios
    Younsoo Chung, PhD – self-employed

    Type of Research: Clinical Research

    Project Purpose: The purpose of this project is to further develop and clinically validate a low-cost, easy-to-use mobile medical technology that can noninvasively (from the surface of the breasts) detect and classify breast tumor by measuring its mechanical properties in-vivo. For women with dense breasts, women at higher than normal risk due to genetic and family history and women younger than 40 years of age, conventional tools and methods (Mammogram, Clinical Breast Exam) are less effective. For these women, patented Piezoelectric Finger Sensor (PEFS) technology may offer suitable adjunctive screening solution. Pilot clinical study results for breast cancer/abnormality detection and classification are promising; 71 cases ex-vivo with 94% sensitivity, and 40 cases in-vivo with 86% positive predictive value. PEFS detected 9 out of 11 clinician non-palpable tumors and 1 invasive cancer missed on mammogram.

    Project Overview: Clinical Research Objective: To further develop and clinically validate Piezoelectric Finger Sensor (PEFS) based mobile breast scanner.

Aim 1: To develop a low-cost, accurate and easy-to-use hand-held breast scanner for commercial application:
Sub-Aim 1a: To develop software and signal processing algorithms.
Sub-Aim 1b: To reduce the overall procedure duration.
Sub-Aim 1c: To integrate low-power electronics within the PEFS sensor.
Sub-Aim 1d: To develop connectivity with various mobile operating system environments.

Specific Aim 2: To clinically validate the effectiveness of PEFS breast scanner:
Sub-Aim 2a: To correlate PEFS findings with conventional exams for tumor identification, in-vivo.
Sub-Aim 2b: To correlate PEFS findings with conventional exams for tumor classification, in-vivo.
Sub-Aim 2c: To compare the efficacy of PEFS against hand-palpation using gelatin breast phantoms.

Methods for achieving the above objectives and aims:
Sub Aim 1a: Apply image processing and frequency analysis techniques to earlier raw PEF data to extract physical features, use MatLab and Simulink to implement filters and digital signal processing algorithms. The tuning of the analysis will be based on a 'metaheuristic' optimization approach.
Sub Aim 1b: Build multiple array (4x4) PEFS sensor, positioning by optical sensor or gyroscope integration
Sub Aim 1c: Redesign the controller board circuitry for miniaturization to 3"x3".
Sub Aim 1d: Application Programming Interface (API) enables building native mobile application.
Sub Aim 2a, 2b: Under an IRB approved clinical study; consenting women meeting the study criteria will be enrolled in the study. Asymptomatic women, presenting to the clinic for routine breast exam and symptomatic women scheduled to undergo pathological exam will be examined by a trained technician using PEFS but blinded to mammogram/pathology results. Results will be documented and analyzed for efficacy metrics.
Sub Aim 2c: General population women will be requested to palpate a mechanical gelatin breast phantom to detect embedded 'tumor-like' lumps first by using the PEFS device and then by using bare hands. The same test will be repeated by clinicians/technicians skilled in performing Clinical Breast Exam (CBE). Results will be compared.

Expected Research Outcomes and Benefits: Expected research outcome is a commercially built, accurate, easy-to-use, low-cost and portable medical device that can be used by physicians at the clinic and potentially even by general population at home, to routinely monitor breasts for small abnormal structures. The research project will validate the device's efficacy in comparison with conventional modalities in being able to identify and classify various breast abnormalities.

The resulting outcome will be a mobile medical device ready for FDA 510(k) and other regulatory submissions.

As per Census.gov, 25% (1.6m) of women in Pennsylvania and 40m women in the USA are currently expected to be between the ages of 20 and 40 years. For these women, PEFS will make it easier to accurately detect nonpalpable lumps, which are otherwise

difficult to locate at an early stage by the current standard of care, i.e., Clinical Breast Exam (CBE) or Breast Self Exam (BSE); hence addressing a sizeable health disparity.

PEFS will allow accurate documentation of each test, making it possible to compare past exams with new and track changes in breast anatomy over time. This type of trending feature is not possible with manual palpation. Although challenging from the regulatory perspective, PEFS may also help reduce the number of unnecessary biopsies every year that do not identify any malignancy.

PEFS will offer similar benefits to women in various high-risk or vulnerable segments including women with dense breasts, women at high risk due to genetics or family history, women with inadequate or no insurance and women deterred from breast screening due to pain during the exam.

In summary, the research project will facilitate the overall commercialization of the PEFS technology leading to regulatory submissions and in building clinical confidence within the medical fraternity.

- University of Pennsylvania – *New PET Imaging Agents for Cancer Diagnosis*, $1,000,000 for a 24-month project (June 1, 2012 — May 31, 2014)

  Contact Principal Investigator:
  Hank F. Kung, PhD
  Professor
  University of Pennsylvania
  Rm. 305, 3700 Market Street
  Philadelphia, PA 19104
  Telephone: (215) 662-3096
  Email: kunghf@gmail.com

  Other Key Research Personnel:
  Mitchell Schnall, MD, PhD; Karl Ploessl, PhD; Daniel A. Pryma, MD – employed by the University of Pennsylvania

  Type of Research: Biomedical Research

  Project Purpose: The purpose of this project is to find new fluorine-18 (F-18) radioactive labeled glutamine derivatives as imaging agents to diagnose cancer. Current diagnosis methods often miss a significant portion of tumor in cancer patients. There is an urgent need to improve cancer diagnosis by introducing new imaging agents for detecting those tumors, which use a different nutrient to thrive. The proposed new F-18 glutamine derivatives will be patent-protected and serve as drug candidates for commercialization. The new drugs will have potential for a wide spread application for cancer diagnosis.

  Project Overview: The objective of this project is to develop specific tumor-targeting imaging agents for cancer diagnosis. The specific aims focus on the preparation and testing of novel fluorine-18 (F-18) labeled glutamine derivatives as candidates for commercial drug development. Currently, positron emission tomography (PET) imaging, which uses the glucose derivative F-18 labeled 2-fluoro-2-deoxy-glucose (FDG), is the method of choice in tumor diagnosis. A growing tumor consumes a higher amount of glucose than normal tissue, so excessive FDG uptake is mapped by FDG-PET imaging. Recently, it was discovered that some rapidly growing tumors do not take up glucose. In

order to grow continuously, many tumors use glutamine, an amino acid with a high concentration in blood, as their source nutrient. These tumors therefore cannot be detected by FDG-PET imaging. The inability to detect these tumors has a critical impact in real life: increased cancer mortality. To improve cancer diagnosis, we will design and evaluate novel glutamine derivatives which mimic glutamine. The new glutamine-based drug candidates will be patentable new chemical entities. They will receive worldwide patent protection and thus will attract additional private venture funding for commercial development. The Office of Technology Transfer at the University of Pennsylvania will file the US patents and serve as the holder of intellectual properties. A newly established Philadelphia-based company will license the technology for further commercial development. The project will not only discover new drug candidates but also will facilitate the establishment of a new company to develop and market the new drugs. This is an excellent opportunity to create a more effective means of cancer diagnosis; it will also provide economic benefits for the region. It is worth noting that in 2004 the PI cofounded Avid Radiopharmaceuticals, Inc. in the University City Science Center, Philadelphia to develop PET imaging agents for diagnosis of neurodegenerative diseases. Avid Radiopharmaceuticals, Inc. has completed a phase III clinical trial for a new F-18 PET imaging agent, florbetapir f 18, for imaging amyloid plaques in patients at risk of developing Alzheimer's disease. Eli Lilly and Company acquired Avid Radiopharmaceuticals, Inc. in 2010. The PI's previous success in bringing new imaging drugs from the laboratory to the market will serve this project well.

Expected Research Outcomes and Benefits: The proposed project will synthesize and test a series of fluorine-18 labeled glutamine derivatives as imaging agents for detecting tumor growth. We expect that this project will produce two new drug candidates suitable for commercial development. The potential outcome will be to improve cancer diagnosis, thereby providing a widespread benefit to current and future cancer patients. A newly established Philadelphia-based company will license the technology for further commercial development. The expected outcome of this commercialization will be both the manufacture and distribution of novel cancer imaging agents, as well as potential economic benefits to the Philadelphia region in the form of new jobs.

- Wistar Institute of Anatomy and Biology, Helen F. Graham Cancer Center at Christiana Care, Temple University, and the University of Pennsylvania – *Diagnostic Markers for Early-stage Lung Cancer in PAXgene Blood Samples*, $991,900 for a 24-month project (June 1, 2012 — May 31, 2014)

Contact Principal Investigator:
Louise C. Showe, PhD
Professor
The Wistar Institute of Anatomy and Biology
3601 Spruce Street
Philadelphia, PA 19104
Telephone: (215) 898-3791
Email: lshowe@wistar.org

Other Key Research Personnel:
Michael K. Showe, PhD; Andrei V. Kossenkov, PhD; Qin Lui, MD, PhD; George D. Hobbs, JD–employed by The Wistar Institute of Anatomy and Biology
Steven M. Albelda, MD – employed by the University of Pennsylvania School of Medicine
Gerard J. Criner, MD – employed by Temple University
Thomas L. Bauer, MD – employed by the Helen F. Graham Cancer Center at Christiana Care, Newark, DE

Type of Research: Biomedical Research

Project Purpose: This proposal will verify the hypothesis based on preliminary results (published and unpublished) that tumor-specific signatures induced by a cancer in the lung are present in the peripheral blood and can be identified by global gene expression analyses. The commercialization of this technology requires that the samples be collected in a manner that stabilizes the nucleic acids in the samples at the time of the blood draw. A commercially available blood collection system, the PAXgene tube developed by PreAnalytX, meets this requirement. The purpose of the present study is to confirm the presence of the tumor-specific signatures in blood samples collected using PAXgene samples. This simplification of the blood collection will facilitate commercialization of our blood-based diagnostic platforms.

Project Overview: Our novel finding is that mononuclear white blood cells (PBMC) from lung cancer patients contain a tumor-relevant gene signature that accurately predicts early-stage lung cancer. Using microarray data from 267 individuals, we developed: 1) a 29-gene signature that predicts the presence of lung cancer with 86% accuracy when compared to a wide variety of controls with non-malignant, smoking-related lung disease, and 2) a 24-gene signature that distinguishes control nodules from cancers with an apparent specificity of 80% using a subset of the controls (41 controls) that included only those with various types of lung nodules.

The product we propose to develop is a gene-expression-based signature derived from an easily obtained peripheral blood sample. In the first application, this blood test would be used to provide additional information as to whether a suspicious lung nodule identified by a spiral computerized tomography (CT) scan is malignant. Because CT scans cannot identify whether a nodule is malignant or benign, the genomic information provided by this test would help to reduce unnecessary surgery or biopsies and their associated expense and risks. We have already demonstrated that our diagnostic system works accurately using RNA from PBMC collected under research conditions under peer review.

The next step, the development of a clinically useful test, requires the simplification of the sample collection to one that is appropriate to a variety of clinical settings including clinicians' offices and more remote clinical settings. The commercially available blood collection tubes (PAXgene) from PreAnalytiX perfectly meet this requirement. These tubes provide rapid stabilization of RNA in whole blood at the moment of the blood draw so that a reproducible and highly standardized blood collection system can be established. Samples are stable for several days at room temperature and for more than a year at -20 to -80°C. Our preliminary results from microarray studies on 48 cancer and control samples in PAXgene support the viability of this approach.

These results support the feasibility of moving our PBMC results to a commercially viable platform. The validation of our preliminary studies using the PAXgene collection system is the object of this proposal. We have proposed to analyze 600 PAXgene samples to test and validate a blood-based approach to develop an accurate lung cancer diagnostic.

Expected Research Outcomes and Benefits: Lung cancer remains the primary cause of cancer-related deaths. In part, this is due to the lack of viable early detection protocols and the fact that common early symptoms are easily ignored by the individual. We know that a very large (>95%) percentage of lung cancers are the result of smoking, with additional risk factors that include exposure to asbestos, radon, and second-hand

smoke. Thus, there is a large and identifiable population at risk for developing lung cancer. Deaths from lung cancer are higher for minorities, higher in men than women, and higher in underserved populations. In a ranking of lung cancer incidence by state into four classes, with the fourth class being the highest incidence class, Pennsylvania's lung cancer rate is in the third class (70 cases/100,000, with a range from 22-98/100,000). Neighboring Delaware, where many Pennsylvania workers live, is in the fourth or highest incidence class. In the rankings for lung cancer deaths, Pennsylvania is in the second class and Delaware is in the fourth. These numbers are striking given that fact that both of these states are located in a corridor of prestigious academic, medical, and biotech organizations.

Although the use of CT scans is projected to increase significantly for lung cancer detection, access to this technology will be much less available in rural settings and less likely to be available, and also perhaps less desirable, to underserved and ethnically diverse communities. Blood tests, by contrast, are routine and well-accepted occurrences associated with a visit to a doctor's office. The collection system we propose could also be easily used in community settings where, for example, flu shots are given or blood donations are taken. Such a test can be an early warning for imaging tests that would not otherwise be warranted; or it can be used in combination with imaging results that are inconclusive, essentially providing a second opinion based on an independent assessment.

It is clear from years of lung cancer statistics that early detection of lung cancer is the most viable way to prevent lung-cancer-related deaths and to minimize the costs of treatment, the costs to employers, and the tolls on families of the affected individuals. Recent advances in sample collection and storage and more sensitive and reliable platforms for testing multi-gene diagnostic panels suggest that the development of such platforms is now feasible.

July 2, 2012