

Health Research Nonformula Grants - State Fiscal Year 2009-10

Health research nonformula grants totaling \$20,088,283 were awarded to four organizations in response to the Request for Application (RFA) # 08-07-07 for Collaborative Research on Cancer Vaccines or Blindness and Visual Impairment. All research projects addressed one of the following research priorities established by the Department in conjunction with the Health Research Advisory Committee:

For the purpose of priority setting and funding, the Health Research Advisory Committee recommends combining the two nonformula funding categories of clinical and health services research and other research. The research priorities shall involve collaborative Center of Excellence efforts integrating research efforts from several disciplines. The research priorities for nonformula-funded research are:

Blindness and Visual Impairment

Research to understand the underlying etiology of blindness and visual impairment and to evaluate promising new medical, surgical and genetic therapies to prevent and/or treat blindness and visual impairment as well as interventions to reduce disparities in access to care. Priority will be given to projects that emphasize the population aged 40 or older, given Pennsylvania's disproportionate share of older individuals as well as the over-representation of blinding eye diseases in older individuals.

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

- Studies of the molecular and genetic bases of common blinding eye diseases, such as macular degeneration, glaucoma, diabetic retinopathy, and cataract.
- Studies to develop new therapies, including molecular, genetic, cellular, or nanotechnologies for retinal regeneration or transplant; optic nerve regeneration; prevention or reversal of cataract; and definitive therapy for diabetes and diabetic retinopathy.
- Studies to determine the extent and degree of cortical plasticity in the adult visual system.
- Studies to improve the quality, coordination or delivery of early detection and treatment services to the aging population.
- Studies of methods to restore vision by leveraging the non-visual senses.
- Studies of novel interventions for reducing barriers to vision care.
- Studies to determine the most efficient and effective approaches to providing vision care to underserved populations.

Research must include, as one component, a demonstration project in a defined population. The demonstration project must include one or more of the following studies: (1) studies to improve the quality, coordination or delivery of early detection and treatment services to the aging population, (2) studies of methods to restore vision by leveraging the non-visual senses, (3) studies of novel interventions for reducing barriers to vision care, (4) studies to determine the most efficient and effective approaches to providing vision care to underserved populations, and/or (5) another demonstration project closely aligned with the proposed research program.

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 populations that are at high risk for eye

diseases. 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.

At least 50 percent of each grant's funds must be spent on clinical and/or health services research as defined in Act 2001-77; no more than 50 percent of each grant's funds may be spent on biomedical research, as defined in Act 2001-77.

Cancer Vaccines

Research on the development, use and evaluation of vaccines for cancer prevention and treatment. Research in protective or therapeutic cancer vaccines may include, but is not limited to, the following areas:

- Studies to identify novel tumor antigens, particularly those on premalignant lesions, precursors to cancer, and/or cancer stem cells, and to develop vaccines against such antigens.
- Research on strategies to effectively co-deliver antigens and adjuvants to generate tumor-specific cellular immunity.
- Studies to identify novel viral antigens associated with or causatively linked to cancer.
- Studies to identify tumor microenvironment antigens that can be targeted to inhibit angiogenesis or tumor invasion.
- Research on novel adjuvants with potent and specific immunostimulatory function and reduced systemic toxicity such as defensins, cathelicidins, and neurokinins.
- Research on vaccine technologies designed to target dendritic cells and enhance dendritic cell-mediated tumor antigen presentation.
- Studies on epigenetic modulation of known cancer antigens.
- Research on the blockade of immunoinhibitory pathways through receptor antagonists.
- Studies to enhance viral and cancer vaccine effectiveness through immun augmentation adjuvant therapies.
- Studies to stimulate immunity to tumor antigens released by dead or dying tumor cells as an adjunct to traditional cancer therapies, including those based on chemotherapy or antibody-dependent cellular toxicity.
- Prevention-related health services research aimed at improving the use of the human papillomavirus (HPV) or hepatitis B vaccine among the populations at greatest risk.
- Analysis of the antigens of tumors in patients treated with immunomodulators that demonstrate antitumor efficacy, such as IL-2, IFN, and anti-CTLA4 blocking antibodies.

Research in the following areas will not be considered:

- Biomedical and clinical research to develop or improve prophylactic vaccines against hepatitis B and HPV.
- Clinical trials on the direct effects of therapeutic cancer antibodies currently approved and on the market (including but not limited to Rituxan, Herceptin, Erbitux, and Avastin).
- Research on cancer vaccines in veterinary medicine.

Research should hold the potential to address the health needs of underserved segments of the population including rural, urban, racial/ethnic minorities or older patients and other populations that are at high risk for cancer. 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 traditional academic medical centers such as smaller colleges and universities as well as businesses, biotechnology and pharmaceutical companies, healthcare 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 minority serving academic institutions or minority serving community-based organizations in Pennsylvania are strongly encouraged and should include the mentoring and training of students. All research collaborators must play a substantial 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. In addition to the clinical and basic science projects proposed, the research must either include an active clinical trial or result in a proposal for an approvable clinical trial at the completion of this body of research. Health services research may include research on any aspect of the selected cancer vaccine including studies of dissemination, patient adherence, behavioral science focused on cancer vaccines, and cost effectiveness research related to hepatitis B and HPV. Health services research must include objective evidence of outcomes. Research must test at least one hypothesis, not be merely descriptive or hypothesis-generating.

At least 50 percent of each grant's funds must be spent on clinical and/or health services research as defined in Act 2001-77; no more than 50 percent of each grant's funds may be spent on biomedical research, as defined in Act 2001-77.

The following list of grant awards provides the lead and collaborating institutions, title of the research project, amount of the grant award, grant award period, contact principal investigator, co-principal investigators, project purpose, project overview and expected research benefits and outcomes.

Blindness and Visual Impairment Research Projects

- The University of Pennsylvania, Lincoln University, Salus University, Temple University and the University of Pittsburgh - *Improving Vision and Preventing Visual Impairment in Rural Amish and Urban African Americans*, \$4,600,000 for a 48-month project (June 1, 2010 — May 31, 2014)

Contact Principal Investigator:
Dwight E. Stambolian, MD, PhD
Associate Professor of Ophthalmology
University of Pennsylvania

Room 313 Stellar-Chance
422 Curie Boulevard
Philadelphia, PA 19104
Telephone: (215) 898-0305
Email: stamboli@mail.med.upenn.edu

Co-Principal Investigators: Judith Thomas, EdD, Lincoln University; Elise Ciner, OD, Salus University; Jeffrey Henderer, MD, Temple University Health System; Geoffrey Aguirre, MD, PhD, University of Pennsylvania; Samuel Jacobson, MD, University of Pennsylvania; Daniel Weeks, PhD, University of Pittsburgh

Type of Research: Clinical and Health Services

Project Purpose: We propose to assess methods for improving treatment of visual impairment for Age-Related Macular Degeneration; determine the genes associated with Age-Related Macular Degeneration in African Americans; phenotype Amish and African American subjects with Age-Related Macular Degeneration to determine characteristic retinal signs associated with genetic risk variants; determine the extent of cortical plasticity in advanced Age-Related Macular Degeneration; and identify disparities in vision care within the African American community.

Project Overview: The overall goal of this project is to investigate the genetic and environmental determinants of Visual Impairment, to develop new methods of treatment to delay its progression, and enhance the use of remaining residual vision. In particular, this project will focus on Age-related Macular Degeneration (AMD), which is the leading cause of Visual Impairment in Pennsylvania. The research aims are to (1) enhance vision rehabilitation for African Americans with central visual impairment, (2) determine the genetic and environmental modifiers in AMD, (3) determine visual cortex function in response to the central visual deficit seen in AMD, and (4) identify the barriers for minorities that prevent access to vision care.

To address the need for enhancing vision rehabilitation, a clinical trial will be performed comparing home vs. office-based rehabilitation in 60 African American subjects with visual impairment to determine if there is an advantage of one method over another. To assess the genetic and environmental modifiers in AMD, African American and Amish case/controls will be genotyped for risk variants and phenotyped for retinal changes with advanced imaging technology. To address the need to understand visual cortex function in AMD subjects with central visual deficits, 40 subjects will undergo extensive testing with functional MRI to determine if there has been any remapping and shift of visual cortical responsiveness. To identify the reasons for minorities having poor access to vision care, faculty at Lincoln University in collaboration with other faculty participating on this project, will develop and test a study protocol to identify the hurdles that impede access to vision care in African Americans.

Expected Research Outcomes and Benefits: (1) Of the 50 states, Pennsylvania has the 4th highest prevalence of visual impairment and blindness. Age-related Macular Degeneration is the leading cause of Visual Impairment in Pennsylvania. The outcome of our project will be improved methods to treat and diagnose Age-related Macular Degeneration resulting in earlier therapeutic intervention to prevent and slow progression of this blinding disease. Slowing progression will lead to less advanced disease which will impact the overall prevalence of Visual Impairment in Pennsylvania.

(2) Ethnic, cultural and socio-economic factors contribute to the poor access of African Americans (AAs) to essential visual rehabilitative services and must be addressed to ensure that individual needs, rather than these modifiable factors, determine the potential for AAs to achieve successful outcomes. We expect that an understanding of these factors will lead to increased access to essential vision rehabilitative services and improved vision.

(3) There is a need to empower the African American community in Philadelphia to perform vision screening and refer subjects to appropriate facilities for continued vision care if needed. We will train lay screeners from the community to educate their communities so services can be continued beyond the grant period. This will result in less visual impairment long-term due to better education and access for community members.

(4) The future of stopping visual impairment will depend on preventing progression from early disease to later blindness. This project will identify modifiable risk factors in Age-related Macular Degeneration, such as diet and smoking behavior, and target subjects with these risks with interventions to reduce these risk factors. This reduction in risk factors will result in a decrease in prevalence of Visual Impairment.

- Wills Eye Health System, Thomas Jefferson University and Temple University School of Medicine - *Confronting Unequal Eye Care in Pennsylvania*, \$3,598,366 for a 48-month project (June 1, 2010 — May 31, 2014)

Contact Principal Investigator:

Julia A. Haller, MD
Ophthalmologist-in-Chief
Wills Eye Health System
840 Walnut Street, 15th Floor
Philadelphia, PA 19107
Telephone: (215) 928-3036
Email: jhaller@willseye.org

Co-Principal Investigators: Barry Rovner, MD, Thomas Jefferson University; Jeffrey Henderer, MD, Temple University

Type of Research: Clinical

Project Purpose: The purpose of the research project is to increase access to eye care for older African Americans with diabetes and to provide research training and mentoring for minority students. We will conduct a randomized, placebo-controlled clinical trial to test the efficacy of Behavior Activation, which is a culturally relevant intervention to increase rates of dilated fundus examinations in this population. We have also developed a research training and mentoring program to increase minority nursing and biomedical students' research skills.

Project Overview: The project's overarching goals are to increase older African Americans' access to eye care and to promote minority students' interest in pursuing research careers. Older African Americans with diabetes are more likely than Whites to develop and go blind from diabetic retinopathy (DR), which is a major complication of diabetes. To prevent and treat DR, dilated fundus examinations (DFE) are necessary. However, African Americans are less likely to have DFEs than Whites. To reduce this health disparity, we propose the following Specific Aims:

1. To conduct a randomized, placebo-controlled clinical trial to test the efficacy of Behavior Activation (BA), which is a culturally relevant intervention that is designed to increase rates of DFEs in older African Americans with diabetes. The control treatment is Supportive Therapy, which is a placebo therapy that controls for attention. Both interventions will be delivered to subjects in their homes. We will enroll 206 older African Americans with diabetes who have not had a DFE in the past year and randomize 50% to each treatment group in this 6 month clinical trial. We hypothesize that 60% of subjects who receive Behavior Activation compared to 35% of subjects who receive Supportive Therapy will receive a DFE by 6 months. Secondary outcomes include knowledge of the risk of diabetes complications, adherence to diabetes self-care recommendations, and depressive symptoms. We will also examine the long term efficacy of BA to increase annual DFE rates.

2. To develop a Minority Research Training and Mentoring Program at the Wills Eye Health System for undergraduate and graduate minority nursing and biomedical students to increase their research skills and promote their interest in pursuing research careers. To accomplish Aim 2, we will create a minority training program and summer research internship for up to four minority students per year.

Expected Research Outcomes and Benefits: This research project will have both immediate and long-term outcomes. The immediate outcome is 2-fold. First, we will determine the efficacy of an innovative, culturally relevant intervention to increase rates of diabetic eye screening in older African Americans. We know that many patients in this population do not fully understand diabetic eye disease or how to access care to prevent it. Our research will demonstrate ways to increase their access, thereby reducing their risk for vision loss and blindness and a pervasive health disparity. The research project's second immediate impact is that we will increase the research skills of a cadre of undergraduate and graduate minority nursing and biomedical students through direct participation in our research projects and research training programs. We will accomplish this via a research training program that consists of a summer research internship and individual student mentoring. The ultimate goal is to promote minority nursing and biomedical students' interest in pursuing research careers as another step towards reducing health disparities.

The long-term impact of our work will be to prevent unnecessary suffering and disability in an underserved population at high risk for vision loss. If our efforts are successful, they will reduce costs associated with vision-related depression, falls, hip fractures, and nursing home placement. Ultimately, the intervention that we are testing can serve as a broad-based, community health model for other medical conditions that disproportionately affect African-Americans such as asthma, hypertension, and prostate cancer, where treatment adherence is similarly low. In this way, our translational research project's impact extends well beyond the treatment of disorders of the eye. It will provide important new information to patients, clinicians, and policy makers about effective interventions that have the potential to save money using low cost, culturally relevant, community-based interventions.

Cancer Vaccine Research Projects

- Drexel University, Cheyney University, Inovio Biomedical Corporation and the University of Pennsylvania - *Therapeutic DNA vaccine for the Prevention of Hepatitis C Virus-associated Cancer*, \$2,769,497 for a 48-month project (June 1, 2010 — May 31, 2014)

Contact Principal Investigator:

Jeffrey M. Jacobson, MD

Professor and Chief, Division of Infectious Diseases and HIV Medicine

Drexel College of Medicine

Department of Medicine

245 N 15th St Ms 1011 2F

Philadelphia PA, 19102

Telephone: (215) 762-6555

Email: jeffrey.jacobson@sdrexelmed.edu

Co- Investigators: Sakkar A. Eva, PhD, Abdel A. Bior, PhD, Cheyney University; Michele A. Kutzler, PhD, Drexel University; Niranjana Y. Sardesai, PhD, Inovio Biomedical Corporation; David B. Weiner, PhD, University of Pennsylvania

Type of Research: Biomedical

Project Purpose: The main object of this project is to test a next generation DNA vaccine strategy for the prevention of hepatitis C virus-associated cancer using preclinical testing to demonstrate immunogenicity and toxicology/safety studies leading to development of a strong platform for clinical testing. In addition, this research consortium will provide a structured mentoring program with students from a collaborating minority institution for the development of future research scientists in highly translational bench research.

Project Overview: Specific Aim #1 will test the hypothesis that consensus antigenic plasmids NS3/4A, NS4B, NS5A, and NS5B from diverse genotype 1a and 1b sequences will exhibit immunogenicity *in vivo* using small animal models (C57Bl6 and HLA transgenic mice). In addition, experiments will be carried out to optimize immunological assay conditions for HCV responses, including ELISpot, polyfunctional flow and CFSE T cell proliferation. Secondly, we will utilize a NHP model to test immunogenicity of the constructs in a larger animal model. The cross-reactivity of this approach will be explored. Finally, our collaborative group will work to determine toxicity, biodistribution and integration studies for HCV antigens using rabbits.

Specific Aim #2 consists of the *Education and Training Component* that will serve as a mechanism for providing education and training through hands-on research experiences and lecture workshops for faculty, undergraduate and graduate students at Cheyney and Drexel Universities. Throughout the course of the work and critical to the research will be the development and application of data generated throughout the project. There are two primary goals of the application with regard to education and training: (1) to encourage undergraduate and graduate students to pursue careers in biomedical research and (2) to provide a framework for faculty and students to collaborate on research related to the development, engineering, immunogenicity, and protective effects of the DNA vaccine platform.

To achieve this goal, the *Education and Training Component* will offer a 10-week summer internship program at Drexel University for Cheyney University students. By

working closely with the faculty in the different components of the project, the students will be provided with valuable research experiences. Students will gain knowledge and skills on how to formulate research questions, develop a scientific methodology, analyze data and present research findings at a conference or through publications. As part of the summer internship program, students will conduct research projects under the supervision and mentorship of program faculty.

Expected Research Outcomes and Benefits: With more than 170 million individuals currently infected, hepatitis C virus (HCV) infection is a global pandemic, effecting approximately 3% of the entire world's population. In the United States chronic hepatitis C infection accounts for approximately one-third of all cases of hepatocellular carcinoma. While many important advances have been made in regard to immunotherapies for HCV, the field continues to be hindered by a general paucity of knowledge concerning how the virus not only interacts with the host immune system but more specifically what type of immune responses are critical for control and clearance of the virus. Understanding the immune correlates of protection against the virus is critical for designing vaccine strategies to combat infection. The role of antibodies in HCV infection is still not completely understood, with research being further compromised due to a lack of a widely accessible method of culturing HCV in vitro. Additionally, without a small animal model of HCV infection, elucidation of the specific cellular immune responses responsible for control of the virus has been slow, with the majority of what is known about the immune correlates of protection being gathered from chronically infected individuals. While chimpanzee models of infection have been instrumental in understanding the immune responses early in infection, unlike humans, these animals develop only mild clinical sequelae. Further complicating the situation is the mounting evidence supporting the idea that HCV viral proteins are able to modulate immune responses, which may in part explain the propensity of the virus to persist. Therefore, success in the development of novel immunotherapies to combat HCV is of the utmost importance. Ultimately, by improving the treatment of HCV infection, we would also have an impact on reducing the incidence of HCV-related hepatocellular carcinoma, a difficult-to-treat cancer with a poor prognosis.

- Thomas Jefferson University, Cheyney University, Fox Chase Cancer Center, Lincoln University, St. Joseph's University and the University of Pittsburgh - *Therapeutic Vaccine Bridging the Gap in Racial Disparities in Colorectal Cancer*, \$4,500,000 for a 48-month project (June 1, 2010 – 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

Co-Principal Investigators: Steven G. Hughes, PhD, Cheyney University; David Weinberg, MD, Fox Chase Cancer Center; Judith A. W. Thomas, EdD, Lincoln University; David S. Zuzga, PhD, St. Joseph's University

Type of Research: Biomedical, Clinical and Health Services

Project Purpose: This Center of Excellence for Cancer Immunotherapy will focus on therapeutic vaccines bridging the gap in racial disparities in outcomes in colorectal cancer. The purpose of this Center is to develop new vaccine strategies specifically targeted to patients at excess risk associated with race in colorectal cancer. Center goals include (1) advancing a novel vaccine paradigm for secondary prevention of recurrent colorectal cancer into phase I clinical trials in African American and Caucasian patients, (2) defining barriers and race-sensitive solutions to improve patient participation in cancer vaccine trials, (3) mechanism-based optimization of this novel colorectal cancer vaccine to maximize immunotherapeutic efficacy, and (4) developing the next generation of investigators from under-represented minorities for careers in biomedicine.

Project Overview: The Center of Excellence in Cancer Immunotherapy will develop a new vaccine paradigm that prevents disease recurrence and reduces stage-specific racial disparities in colorectal cancer. There is an unmet need for improved therapeutics in colorectal cancer, the third leading cause of cancer and second leading cause of cancer mortality worldwide. In Pennsylvania, colorectal cancer incidence and mortality rates are higher than those expected in the nation with ~15,000 cases treated each year associated with a total in-patient annual cost of >\$200M. Mortality reflects metastatic disease: ~50% of patients present with clinically apparent metastases, while ~30% present with occult metastases. Moreover, there is a disparity in outcomes in stage I and II African American patients, who exhibit ~40% excess mortality compared to Caucasians, reflecting occult metastases. This project advances an emerging paradigm in colorectal cancer detection and eradication, employing guanylyl cyclase C (GCC) as a prognostic marker and immunological target. GCC is a protein whose expression normally is restricted to intestinal epithelial cells, but universally over-expressed by metastatic colorectal tumors. GCC is a marker of occult metastases in lymph nodes, which disproportionately burdens African American patients. Also, GCC is the index example of a new class of vaccine targets, cancer mucosa antigens, whose expression normally is restricted to mucosae, but extends to the immunologically naive systemic compartment upon metastasis of mucosal tumors. Advantages of these antigens include systemic immunoreactivity profiles supporting durable antitumor immunity, with limited immune cross talk between compartments restricting autoimmunity. This Center will translate these advances in molecular diagnostics and immunotherapy into new vaccines that bridge racial disparities in colorectal cancer. Center objectives will be accomplished through: (1) the Translational Research Program, which will define the safety and immunological efficacy of a GCC-based vaccine in stage I and II African American and Caucasian colon cancer patients variably burdened by occult metastases identified by GCC; (2) the Health Services Research Program, which will identify barriers that prevent African Americans and Caucasians from participating in vaccine trials, and strategies to increase informed participation; (3) the Biomedical Research Program, which will define mechanisms shaping responses to cancer mucosa antigens that inform clinical strategies to maximize antitumor efficacy; and (4) the Training Program, a collaboration of regional universities to recruit new scholars from under-represented minorities for careers in biomedicine.

Expected Research Outcomes and Benefits: Outcomes from this program will: (1) Define the safety and immunological efficacy of adenoviral (AV)-GCC in Caucasian and African American stage I and II colon cancer patients with defined occult tumor burden in a phase I clinical trial. It is anticipated that AV-GCC will induce immune responses in African American and Caucasian patients variably burdened by occult metastases, without autoimmunity. This study will provide the first critical step in developing an immunotherapeutic approach to secondary colorectal cancer prevention that can bridge

racial disparities in disease outcome. (2) Identify barriers underlying racial disparities in participation in cancer vaccine trials. Processes underlying decision-making, racial differences in those processes, and methods to facilitate informed decisions with respect to participation in cancer vaccine trials have not been defined. Here, we will design patient education materials, adapt decision counseling materials, and revise survey data collection instruments to define barriers to participation in cancer vaccine trials through decision counseling, producing culturally-sensitive strategies to assist patients in making informed decisions about trial participation. (3) Define mechanisms shaping responses to cancer mucosa antigens that inform clinical strategies. The utility of cancer vaccines ultimately will reflect an understanding of mechanisms modulating immune responses that can be exploited to maximize efficacy. Studies here will identify tolerance landscapes that oppose vaccine therapy, define strategies to overcome that immunoinhibition, and identify receptor-dependent approaches to maximize immunotherapeutic efficacy, to optimize future clinical trials of AV-GCC. (4) Prepare trainees from under-represented minorities for careers in biomedicine. Here, we will provide training opportunities for students from under-represented minorities interested in careers in biomedicine through a summer internship program at Thomas Jefferson University that will include didactic and experiential research components.

- University of Pennsylvania, Fox Chase Cancer Center and Lincoln University - *Novel Adjuvants for Cancer Vaccine Immunotherapy*, \$4,620,420 for a 48-month project (June 1, 2010 — May 31, 2014)

Contact Principal Investigator:

Carl H. June, MD

Professor

University of Pennsylvania

Room 554, BRB II/III

421 Curie Blvd

Philadelphia, PA 19104-6160

Telephone: (215) 746-5133

Email: cjune@exchange.upenn.edu

Co-Principal Investigators: Robert H. Vonderheide, MD, DPhil, George Coukos, MD, PhD, Richard G. Carroll, PhD, University of Pennsylvania; Gregory P. Adams, PhD, Fox Chase Cancer Center; John O. Chikwem, PhD, Lincoln University

Type of Research: Biomedical and Clinical

Project Purpose: The purpose is to conduct a series of thematically related projects to test new cancer vaccine approaches. The projects will include a clinical trial in patients with lung and ovarian cancer, and basic, translational and pre-clinical investigation at three institutions to encourage collaboration. A programmatic effort to promote technology transfer in cancer vaccine research in Pennsylvania is included. Finally, there will be an innovative program to develop a pipeline of new scientists and clinicians trained in cancer research in the Commonwealth which will involve outreach in Philadelphia and Lincoln University.

Project Overview: The overall research objectives of this program are:

1. To prolong survival and reduce mortality of patients with ovarian and lung cancer by enhancing T cell activation in the tumor microenvironment.
2. To support cancer vaccine research and training throughout eastern Pennsylvania.

3. To provide a training and mentoring program in translational cancer research for underrepresented minorities.
4. To promote technology transfer and the potential for job growth within the Commonwealth in the biotechnology of cancer vaccines.

We propose the following specific research aims to accomplish the general objectives of this program:

1. Establish the safety, antitumor activity and optimum biologic dose of a bispecific antibody that targets CD326 (epithelial cell adhesion molecule (EpCAM)) with the first arm and anti-CD3 (MT110) with the second arm in a phase I/II clinical trial.
2. Determine whether or not the inclusion of specificities for costimulatory molecules or antagonists of inhibitory receptors will enhance the activity of the bispecific T cell engager platform.
3. Explore the role of tumor endothelial marker-1 (TEM1) vaccination targeting the tumor microvasculature with combination therapies that antagonize vascular endothelial growth factor (VEGF).
4. Determine whether or not the inclusion of adjuvants that augment the Th17 arm of the cellular immune system enhances antitumor effects.
5. Establish an educational program for undergraduate and graduate level training in translational cancer research.

Expected Research Outcomes and Benefits: This program in cancer vaccines will produce both short term and long term benefits. In the near term, the program will enable the conduct of a promising clinical trial for patients with lung and ovarian cancer, thereby providing scientific information on the ability of CD326 to serve as a vaccine target using bispecific T cell engager antibody technology. As a result of the inter-institutional collaborative research efforts, long term benefits will continue to accrue for patients in eastern Pennsylvania who will benefit by improved access to state of the art trials in cancer vaccine research. At the same time, the development of new approaches to harness the power of the immune system to attack tumor cells and the tumor microenvironment will be pursued in the laboratory. A world-class group of clinicians and scientists has been assembled to address this vital problem and will synergize to develop new cancer therapies. In summary, this Program will allow outstanding scientists, educators and clinicians to leverage the power and potential of the immune system to develop new cancer vaccines with improved efficacy and reduced toxicity.

In addition to research outcomes for cancer therapy, this project contains a significant focus on teaching and education in order to produce a durable result for years to come. We will reach out to the City of Philadelphia, and to college students at Lincoln University to enhance the pipeline of new investigators trained in this promising scientific field, while providing role models and unparalleled opportunities for aspiring under-represented minority students.