Health Research Nonformula Grants - State Fiscal Year 2006-07

Health research nonformula grants totaling $16,824,386 were awarded to four organizations in response to the Request for Application (RFA) # 05-07-11 for Collaborative Research on Vaccine Development or Gene-Environment Interactions. All research projects addressed one of the following research priorities established by the Department in conjunction with the Health Research Advisory Committee:

Vaccine Development

Research into the development and/or evaluation of vaccines for viruses, bacteria, and other infectious agents, including cancer vaccines for cancers that are caused by infectious agents, with an emphasis on those vaccines that pose a serious health risk to a significant proportion of the population, including children. All such research must be focused on, and preparatory to, the development of one or more specific vaccines. Research may include, but is not limited to, studies in the following areas:

- Population-based studies of vaccine preventable diseases; predictive modeling of the spread of infections; identification and evaluation of strategies to contain and control the spread of infection.
- Prevention-related health services research aimed at improving the use of newly developed vaccines of proven efficacy among the populations at greatest risk; research to test the delivery and efficacy of relatively new vaccines such as the human papillomavirus (HPV) or new uses of vaccines such as pneumococcal and influenza vaccines for children; practical approaches for the implementation of effective vaccination strategies with applications to underserved populations; community participatory research and studies that test and evaluate the cost-effectiveness of vaccine-based interventions conducted in community, neighborhood, and nontraditional settings; and evaluation of the effectiveness of various outreach methods for improving immunization rates among populations such as Hispanics, rural and urban residents and immigrants.
- Investigations into the basic biology of viral, bacterial, and other infectious agents and how these agents cause disease, including their interactions within the host organism and mechanisms of transmission; studies of how the agent under study relates to other human and animal infectious agents; research on basic human immunology, with an emphasis on the contribution and role of various components of the immune response against the agent being studied; basic research to establish mechanisms of inducing long-lasting protective immunity against viral and other pathogens; the development of platform vaccine technologies that can be applied to a broad spectrum of disease targets; the conception, design, and preparation of candidate vaccines, ideally agents that are stable, require only one dose, and remain at least partially effective despite mutation in the agent's genome. Relate this to the immunization coverage rate necessary to provide herd immunity for a vaccine.
- Translational research, including clinical trials of candidate vaccines; research on vaccine delivery systems, including DNA vaccines; proof of concept of new platform vaccine technologies; development and testing of adjuvants that would improve vaccine efficacy; development of new methods for large-scale vaccine production.
- Phased clinical trials to test the safety and efficacy of candidate vaccines in human subjects, once appropriate studies have been completed.

Research in the following areas will not be considered:

- Research related to the human immunodeficiency virus (HIV);
- Research addressing tropical diseases, like malaria, that are not highly prevalent in Pennsylvania and are not spread by aerosol transmission;
- Research related to the development of antibiotics; and

- Research related to animal vaccines to prevent zoonotic transmission to humans.

Research should emphasize populations that are at high risk for and/or disproportionately affected by the vaccine-related issue under study. The proposed research should hold the potential for population-based applications that address disparities among underserved segments of the population, including rural and urban residents, racial/ethnic minorities or 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, health care providers and public agencies should be included in addition to major research institutions. To increase research capacity in Pennsylvania, the proposed research must include collaboration with a predominantly minority-serving academic institution in Pennsylvania and should encourage the mentoring and training of students, fellows and junior faculty. Research in health services must include objective evidence of outcomes, including the use of vaccines in a defined community or clinical setting.

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

Gene-Environment Interactions

Research on gene-environment interactions related to etiology and outcomes of chronic disease including, but not limited to, cardiovascular disease, asthma, serious mental disorders and cancer. Research shall focus on potentially modifiable environmental exposures, or behaviors including nutrition, which are hypothesized to affect disease etiology or outcomes in humans and genes that modify these associations. Research shall include, but not be limited to:
Several integrated research studies around a common theme to identify: 1) genetic and environmental determinants of disease etiology or outcomes; and 2) biological mechanisms that underlie associations of genes and/or the environment with disease.
Studies that use a statewide or regional cohort for research on gene-environment interactions in chronic disease etiology and outcomes and health disparities.
Research involving haplotype and SNP analysis, as well as family studies with major gene effects and candidate genes.

Health services research that will improve the identification of "high risk families" that are disproportionately affected by the interaction of genetics and lifestyles, i.e., environmental agents, and will benefit from specific interventions to reduce risk can be supported by this proposal.

Research should emphasize populations that are at high risk for and/or disproportionately affected by the chronic disease under study. Because of the very large sample sizes required for identifying relatively small, relative risk <2, gene-environment effects, collaborations across institutions in Pennsylvania are strongly encouraged as well as collaborations with the Pennsylvania Cancer Registry or other appropriate state health resources. The proposed research should hold the potential for population-based applications that address disparities among underserved segments of the population, including rural and urban residents, racial/ethnic minorities or 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, health care providers and public agencies should be included in addition to major research institutions. To increase research capacity in Pennsylvania, the proposed research must include collaboration with a predominantly minority-serving academic institution in Pennsylvania and should encourage the mentoring and training for students, fellows, and/or junior faculty. Additionally, resources to identify genetic and environmental contributions to chronic disease etiology and outcomes should be developed for use in future grants and contracts.

Research in the following areas will not be considered:
Genetic screening without inclusion of specific defined environmental and lifestyle interactions; and
Gene therapy.

At least 50% of each grant's funds must be spent on health services and/or clinical research as defined in Act 2001-77 (Act 77); no more than 50% of each grant's funds may be spent on biomedical research, as defined in Act 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 person and a description of the project.

Gene-Environment Interactions Research Projects

- Pennsylvania State University, Lehigh Valley Hospital, Lincoln University and the Northeast Regional Cancer Institute - Gene-Environment Interactions for Colorectal Cancer in Northeast PA, $4,206,097 for a 48-month project (June 1, 2007 — May 31, 2011)

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  The overall goal of the present study is to determine the relationship between haplotypes of relevant Phase I and Phase II metabolizing enzymes that are responsible for the activation or detoxification of polycyclic aromatic hydrocarbons (PAHs), heterocyclic amines (Has) and nitrosamines and the risk of CRC. In particular, we will examine whether there is an interactive effect between exposure to specific environmental factors and haplotype tagging SNPs (htSNPs) in linkage disequilibrium with metabolizing gene variants. This approach will enable us to determine the risks associated with known SNPs, and also will allow us to identify new potentially functional SNPs that are in linkage disequilibrium with htSNPs that capture the full haplotype information. Another important aspect of our approach is that we are conducting a population-based study in a contiguous 9-county high risk area of northeastern PA. Thus, our results will be directly generalizable to the residents of this area, but the scientific findings should be pertinent to all PA and U.S. residents. We will enroll newly diagnosed incident cases identified directly from the participating tumor registries that serve in this region of PA within ~6-9 months since cancer diagnosis. Controls will be frequency-matched to cases by sex, age (within 5 years) and race and will be identified by random-digit dialing (RDD). Our pilot studies have demonstrated the feasibility of this approach, and interestingly have shown increased risks associated with meat consumption and cigarette smoking. The specific aims of this study are:

(1) Determine the association between haplotypes of genes that are involved in the metabolism of PAH, HA and nitrosamine, and colorectal cancer risk in northeastern PA.
(2) Determine the association between red meat consumption, meat cooking methods, dietary carcinogens, and cigarette smoking with the risk for colorectal cancer in northeastern PA.
(3) Measure the interaction between these haplotypes and diet and smoking on the risk of colorectal cancer.
(4) Sequence those haplotypes associated with colorectal cancer risk from aim 3, in order to identify novel functional SNPs.
(5) Confirm the functional capacity of newly identified high-risk genotypes identified in aim 4.

- University of Pennsylvania, Lincoln University and Pennsylvania State University College of Medicine - Center for the Study of Gene-Environment Interactions in Lung Cancer, $4,206,096 for a 48-month project (June 1, 2007 — May 31, 2011)

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  This program will define gene-environment interactions that increase risk of lung cancer in African American and Caucasian smokers and non-smokers. Six hundred smokers with lung cancer and 600 disease-free control smokers will be recruited from each of two medical centers: the University of Pennsylvania Health System (UPHS) in Philadelphia serving a population living in an urban, industrial environment with poor air quality; and the Penn State Milton S Hershey Medical Center (PSHMC) serving a rural population living in a less polluted region. At USPHS equal numbers of African Americans and Caucasians will be enrolled. Philadelphia County has almost 1.5 times the incidence of lung cancer as Dauphin County, in which PSHMC is located.

  A candidate gene approach will be taken. The major carcinogens in tobacco smoke are nitrosaminoketones (NNK) and polycyclic aromatic hydrocarbons (PAH). Polluted air also contains high levels of PAH, together with carcinogenic particulates derived from fossil fuel combustion. Variants of genes involved in the metabolic activation and subsequent detoxification of NNK and PAH, as well as DNA adduct repair, are excellent genetic candidates for lung cancer susceptibility. As methylation is important for maintaining a normal cell phenotype, and for the efficient function of the above activating and detoxifying enzymes, variants of genes involved in folate metabolism may act as risk modifiers. DNA from all 2400 subjects will be subjected to high throughput single nucleotide polymorphism (SNP) genotyping of the above classes of genes using the Illumina Golden Gate platform. Biomarkers of NNK, PAH and folate will be tested in the urine and blood of the same subjects.

  Sophisticated biostatistical tests that account confounders such as population stratification will be applied to the genetic, biomarker, clinical and environmental exposure data to establish the relationship between key genes and/or biomarkers and lung cancer susceptibility in African Americans, Caucasians, smokers living in relatively polluted locations, smokers living in relatively unpolluted locations, and non-smokers who have the disease.

Vaccine Development Research Projects

- University of Pennsylvania, Albert Einstein Medical Center, Cheyney University, Children's Hospital of Philadelphia, Family Planning Council and Geisinger Health System- HPV Vaccination of Underserved Adolescent and Young Women in Pennsylvania, $4,206,097 for a 48-month project (June 1, 2007 — May 31, 2011)

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  The two primary objectives of this project are to: 1) evaluate whether HPV vaccination rates among adolescent girls/young women ages 9 – 18 in Philadelphia and NE Pennsylvania can be increased by interventions targeting barriers to immunization; and 2) evaluate the proportion of adolescents and young women who are sexually experienced that are already infected with the HPV types in the vaccine; and analyze how HPV vaccination influences acquisition of HPV types not included in the vaccine.

  Initially, we will assess knowledge of and attitudes towards HPV vaccination among consumers and health care providers. From our findings educational materials designed to overcome barriers to vaccination will be developed. The project will continue with an interventional phase. Research communities will be mapped using census data; five communities of similar size, demographics, and income will be constructed in Philadelphia and three in NE Pennsylvania. Two tiers of interventions will be introduced sequentially into these communities using a stepped wedge study design. The first intervention will consist of community education targeting adolescents and their parents designed to improve knowledge and overcome barriers to vaccination. Twelve months after the first intervention was introduced in Philadelphia and 18 months after the first intervention was introduced into NE Pennsylvania, a second tiered intervention will be introduced into the communities, again using a stepped wedge strategy. The second tier intervention will consist of Recruitment, Reminder, Recall Outreach consisting of patient identification and outreach through health care providers' offices. Vaccination rates will be compared across the communities.

  At selected sites, adolescents who are sexually active and seeking family planning services will be tested for previous HPV infection using HPV DNA hybridization techniques. The HPV types detected in women entering the study at earlier versus later time points will be compared to test how the epidemiology of HPV infection changes over time as a result of HPV vaccination in the community. Serologic assays will be used to evaluate the immunogenicity of the vaccine administered under real world conditions.

- Wistar Institute of Anatomy and Biology, Cheyney University, Children's Hospital of Philadelphia, Lincoln University, Temple University and University of Pennsylvania Medical School and School of Veterinary Medicine, - Development of a Universal Influenza A Virus Vaccine, $4,206,096 for a 48-month project (June 1, 2007 — May 31, 2011)

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Influenza virus vaccines protect through induction of subtype specific antibodies against surface antigens of the virus. These antigens constantly mutate and vaccines thus have to be redesigned and reapplied annually. Vaccines against a new pandemic strain cannot be produced in advance, as the molecular composition of this strain cannot be predicted. The goal of this proposal is to generate a novel universal influenza virus vaccine that induces broad protection against all strains of the virus. We will test 5 hypotheses: 1) CD8+ T cells to conserved internal proteins, such as the nucleoprotein (NP) and the matrix (M) protein, and antibodies to the ectodomain of the matrix 2 protein (M2e) of influenza A virus protect against diverse strains of the virus. 2) CD8+ T cells and M2e-specific antibodies act synergistically and vaccines that induce both responses provide superior protection than vaccines that induce only one type of response. (3) Inactivated vaccines and infections with influenza A virus do not induce sufficiently potent cross-reactive immune responses to protect against a heterotypic infection. 4) Novel subunit vaccines based on adenovirus vectors can induce protective cross-reactive T cell responses; and 5) adenovirus vectors expressing M2e can induce protective antibodies to M2e; such responses may be enhanced by a prime-boost regimen with M2e peptides. The proposal has 4 specific aims. We will develop vaccines based on replication-defective chimpanzee adenovirus vectors expressing NP, M or M2e and M2e peptides. Viral vector and peptide vaccines will be tested individually and then in combination for their ability to induce cross-reactive immune responses in aim 1 and for protection against challenge with different strains of influenza A virus in mice and ferrets in aim 2. We will test human subjects for cross-reactive immunity to influenza A virus strains in aim 3 to provide baseline data for future clinical trials with a universal influenza A virus vaccine. Cohorts will include subjects that are highly susceptible to influenza virus, that have been exposed to avian strains, and that are acutely infected or convalescent. Sera from volunteers will be tested for neutralizing antibodies and for antibodies to M2e. Peripheral blood mononuclear cells will be tested for T cells to NP and M. The analyses will show to what degree the magnitude and diversity of neutralizing antibodies to different strains of influenza A virus correlate with titers of antibodies to M2e and T cells to NP and M. Analyzing antibody titers to H5 and H7 will show if cohorts with reported exposure to birds have an increased prevalence of such antibodies. We will develop a cocktail of human monoclonal antibodies to M2e for treatment of acute influenza A virus infections in aim 4.