Health Research Nonformula Grants - State Fiscal Year 2008-09

Health research nonformula grants totaling $17,926,819 were awarded to four organizations in response to the Request for Application (RFA) # 07-07-09 for Collaborative Research on Autism Spectrum Disorders or Antibiotic Resistance. 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:
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> Autism Spectrum Disorders
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> Research to identify underlying causes of, determine the nature of the brain alterations in, better understand the genetic, metabolic, immunologic or environmental influences on, or improve early diagnosis and treatment of autism spectrum disorders. Research shall be limited to those disorders classified as pervasive developmental disorders (PDD) in the "Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)": Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified; research on other diagnoses will not be considered. Research may include, but is not limited to, the following areas:
> - Studies of genetic and environmental epidemiology to determine risk and protective processes in the etiology of autism spectrum disorders.
> - Studies of brain mechanisms underlying the development and regulation of behaviors characterizing autism spectrum disorders.
> - Studies of brain maturation during vulnerable developmental periods for the appearance or worsening of specific signs or symptoms of autism spectrum disorders.
> - Studies that unravel the complex circuitry of the central nervous system to understand the changes in neural structure and network connections associated with the disorder.
> - Studies into the pathogenesis of autism spectrum disorders including research to identify specific autism susceptibility genes, studies that combine imaging and genetic techniques, and studies that examine behavioral and cognitive-genetic variability in autism.
> - Studies of the pathology of autism spectrum disorders to identify novel molecular targets for drug development.
> - Studies of the pathophysiology of specific components of the clinical syndrome of autism in order to develop novel biomarkers that can be used to monitor new treatment interventions.
> - Studies of the correlation between key developmental factors and the valid diagnosis of autism spectrum disorders, including genetic, environmental and epi-genetic studies of families in which more than one child has been diagnosed with an autism spectrum disorder. Such studies should incorporate expertise in genetics, environmental measures and brain neurobiology and imaging.
> - Studies to develop new treatments or compare and validate treatment of autism spectrum disorders.

- Studies aimed at developing and testing the efficacy and safety of pharmacologic agents to target the most common and impairing features of autism spectrum disorders.
- Studies to improve practices of healthcare providers and the quality, coordination or delivery of diagnostic and treatment services.
- Studies to establish methods for validated, population based registries of autism that can be utilized for public health research and service evaluation, especially in underserved regions of the Commonwealth.

The research should hold the potential for addressing the health needs of underserved segments of the population, including rural, urban, 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, biotechnology companies, health care providers and public agencies should be included in addition to 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, fellows and junior faculty. All research collaborators must play a substantive and meaningful role in multiple aspects of the proposed research. Research in health services 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.

Antibiotic Resistance

Research to better understand and test approaches to reduce the prevalence of infections caused by antibiotic resistant bacteria in health care settings and in the community and to reduce associated morbidity and mortality of these infections. Research must be focused on bacteria that are resistant to all or most of the commonly-prescribed antibiotics. Research must include one or more of the following approaches: (1) studying the transmission of antibiotic-resistant organisms within community and/or healthcare settings, (2) studying the overuse of antibiotics within community and/or healthcare settings as a risk factor for emerging resistance, (3) evaluating novel approaches to reduce the transmission of antibiotic resistant organisms within community and/or healthcare settings and (4) applied research and clinical trials for products for which proof-of-concept has been demonstrated.

Research may include, but is not limited to, studies in the following areas:
- Development and/or evaluation of rapid, inexpensive, diagnostic tests capable of accurately guiding directed antimicrobial drug therapy, limiting broad spectrum use when unnecessary. Tests may be directed at single or multiple pathogens or biochemical pathways distinguishing infectious etiologies.
- New computational tools in systems biology and metabolomics to identify complex biochemical pathways that can uncover novel mechanism of action compounds.

- New approaches to antibacterial resistance using in vivo analysis of bacterial and host transciptomes and metabolomes.
- Development of new therapeutic antibiotic drugs and bactericidal biomaterials.
- Clinical trials to determine the safety and efficacy of new drugs and biologics that can be used to treat and control drug-resistant bacterial infections.
- Evaluation of existing and/or novel surveillance systems for usefulness in detecting transmission of antibiotic resistance in the community and health care settings, including determinants of differences in prevalence and type of antibiotic resistance among regions of the Commonwealth, racial and ethnic groups, children and the elderly.
- Development and testing of novel control policies and interventions with healthcare professionals and the public to improve the use of antibacterial agents in humans and preserve the effectiveness of existing antibiotics.

Research in the following areas will not be considered:
- Research related to antimicrobial resistance other than bacterial drug-resistance
- Research to improve the use of antibacterial agents in veterinary medicine
- Research related to the prevention of healthcare infections associated with transplants
- Research related to tuberculosis

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 diseases caused by antibiotic resistant agents. 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. 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, fellows and junior faculty. Research should collaborate with the Bureau of Epidemiology in the Department of Health and focus on the identification of areas and subregions of the state with an unusually high prevalence of antibiotic resistant organisms and clinical disease so as to identify the causal pathways and potential remedial actions. All research collaborators must play a substantive and meaningful role in multiple aspects of the proposed research. Research in health services 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 person and a description of the project.

Autism Spectrum Disorders Research Projects

- The Children's Hospital of Philadelphia (CHOP), Lincoln University and University of Pennsylvania - *CHOP/Penn Center of Excellence for Autism Research*, $4,708,555 for a 48-month project (June 1, 2009 — May 31, 2013)

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  This funding will support a Center of Excellence for Autism Research located at Children's Hospital of Philadelphia (CHOP), with partnerships at Lincoln and Temple Universities, the University of Pennsylvania, and the Philadelphia Public School System. This project's central theme is understanding the relationship between genetic risk factors, brain and behavior (including treatment response) in persons with an autism spectrum disorder (ASD). We will conduct a series of integrated subprojects that follow upon several recent breakthroughs in the genetics of ASD. We have identified the first common genetic variant for ASD. Our data also suggest that rare sequence and structural variants serve as significant risk factors for ASD. The genes appear to have a common biological function related to synaptic connectivity. We aim to study 400 children with ASD, and to investigate the relationship between genetic risk factors and clinical presentation, brain function, and response to treatment. Individual subprojects in the Center will focus on our common variant finding (Project I), rare genetic variant findings (Project II), animal knockout models of risk variants replete with social behavioral and brain assays (Project III), comprehensive assessment ("deep phenotyping") of the ASD sample to assess the clinical impact of genetic risk factors, including treatment responsiveness (Project IV), and measures of the "social brain" using magnetic resonance imaging and magnetoencephalography (Project V). Neuroimaging will include several measures of connectivity (including diffusion tensor imaging, functional MRI connectivity, and coherence analysis with magnetoencephalography), as we aim to relate connectivity to genetic risk factors. Participants with an ASD from Project IV will be enrolled in projects I, II, and V, so as to provide a set of tightly inter-related experiments. Our animal models will knock out the rare and common genetic risk factors, and perform behavioral and imaging studies that parallel the human studies.

  In addition, we will create undergraduate and graduate level training programs for underrepresented minorities in collaboration with the University of Pennsylvania, Temple University and Lincoln University (Project VI). Students will work within the labs of researchers on this grant, and will receive additional group and individual teaching and mentorship to prepare them for professional work in the area of autism.

- University of Pittsburgh and Carnegie Mellon University - *Deciphering Altered Brain Connectivity in ASD to Improve Intervention*, $2,978,656 for a 48-month project (June 1, 2009 — May 31, 2013)

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Recent scientific research has led to the understanding of autism spectrum disorder (ASD) as resulting from altered information processing by the brain and mind. Research has demonstrated alterations in social understanding, language comprehension, reasoning, emotion, motor movements, sensory processing, and learning related to alterations in brain connections. The goals of this research project are to: 1) develop a new intervention for ASD that enhances thinking capacity or meaningful integration of information and brain circuitry; 2) define the brain connections for thinking and emotion that underlie emotion dysregulation, the basis for meltdowns, aggression, and withdrawal in ASD, so that more effective and individualized treatment can be developed; and 3) identify genetic and brain development mechanisms underlying the abnormal development of brain circuitry.

The objectives of this research are to translate recent scientific advances in ASD into a novel intervention, identify the cognitive, neural and genetic neural mechanisms underlying major behavioral issues in childhood and adulthood that will directly support improvements in everyday treatment, and expand knowledge about the fundamental developmental neurobiologic and genetic mechanisms of autism that will lead to the next generation of discoveries. In the study "Inducing Plasticity in Cortical Connectivity via a Novel Intervention in ASD," a novel-learning paradigm will be used to enhance multi-dimensional information integration and promote development of the supporting neural circuitry with the aim of secondary improvement in related cognitive and affective skills. Phenotypic markers of responders and non-responders will be identified so that the intervention can be refined to address individual variability in initial skill level and rate of response. Pre- and post- functional Magnetic Resonance Imaging (fMRI) will assess intervention effects on neural circuitry. In "Neuropathology and Genetics of Connectivity: Altered Axonal Pathfinding in ASD," developmental neurobiological studies of gene expression will be conducted in postmortem tissue to ascertain the pattern of temporal and anatomic involvement of brain structures to inform the search for genes in ASD. The selection of these axonal pathfinding genes is based on findings from a genome wide association study in ASD families. Health status and access will be addressed through a web-based, archived and audiotaped Continuing Medical Education (CME)-accredited lecture program on ASD and related medical and behavioral issues created for a large established practice-based pediatric research network (Pediatric PittNet) that serves 115,000 families in 5 counties representing all racial and geographic segments of Western Pennsylvania. Collaboration with Programs for Living, Education and Advocacy (PLEA), a community organization serving minority and low income children and adults with ASD, will result in translation of research results to this community to improve intervention. PLEA staff will be trained in the national Autism Treatment Network medical guidelines, research administration of the Autism Diagnostic Observation Schedule (ADOS), and Cognitive Enhancement Treatment (CET) program for adults with ASD. CET is new comprehensive intervention that targets cognitive, social, and complex adaptive skills.

Antibiotic Resistance Research Projects

- University of Pennsylvania, The Children's Hospital of Philadelphia, Lincoln University and Penn State Hershey Medical Center - *Epidemiology and Prevention of MRSA Transmission in the Community*, $5,531,053 for a 48-month project (June 1, 2009 — May 31, 2013)

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  The purpose of this study is to understand the reasons for recent dramatic increases in infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) in the community. Through a broad collaboration with partners in Eastern and Central Pennsylvania, we will study why patients with MRSA infections frequently have recurrent infections despite appropriate treatment. We will also study how often and why household members of such patients develop new MRSA infections. We will determine how often MRSA spreads between household members and how long individuals harbor MRSA over time. We will also test whether treatment to eliminate MRSA colonization prevents MRSA infections in the household. Finally, we will establish a program to develop a pipeline of new scientists and clinicians among underrepresented minorities in the Commonwealth.

  This study will elucidate the longitudinal dynamics of MRSA colonization and infection and test an intervention to prevent MRSA transmission. To achieve this objective, we propose <u>three scientific objectives</u>:

  1) to identify host, microbiological and environmental risk factors for prolonged MRSA colonization, MRSA transmission, and MRSA infection among patients with MRSA skin or soft tissue infections (SSTIs) and their household contacts and to use stochastic agent-based modeling methods to quantify secondary spread of CO-MRSA in households.
  2) to evaluate the impact of a decolonization intervention on MRSA infections in the household.
  3) to identify immunological mechanisms underlying the ability of *S. pneumoniae* colonization to inhibit MRSA colonization, transmission and infection.

  In conjunction with these scientific goals, we also propose <u>two educational and organizational objectives</u>:

  1) to foster multi-disciplinary and cross-institutional collaborations and develop the infrastructure for a Center of Excellence focused on antimicrobial drug resistance research.
  2) to enhance opportunities for basic and clinical research training for undergraduate and graduate students, particularly from underrepresented minorities, to increase the pipeline of future scientists.

  To achieve the study aims, we propose a multicenter prospective cohort study of outpatients with newly diagnosed MRSA SSTIs. The source population for this study will be all adults and children receiving care in the emergency departments (EDs) of the Hospital of the University of Pennsylvania (HUP), Penn Presbyterian Medical Center (PPMC), the Children's Hospital of Philadelphia (CHOP), and Hershey Medical Center

(HMC). These subjects and their household members will undergo regular sampling for MRSA colonization over time. Subsequently, we will conduct a randomized controlled trial to assess the impact of two decolonization interventions on MRSA infections in the household. The proposed novel approach to sampling of cases and their household contacts over time represents a unique opportunity to elucidate the longitudinal transmission dynamics of MRSA in the community. The inclusion of adults and children from a geographically, racially, and ethnically diverse population will greatly strengthen the generalizability of the results and maximize the public health impact for all Pennsylvanians.

- University of Pittsburgh and Carnegie Mellon University - *Center of Excellence in Prevention and Control of Antibiotic Resistant Bacterial Infections*, $4,708,555 for a 48-month project (June 1, 2009 — May 31, 2013)

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  The primary goals of this project are to employ novel strategies to reduce the morbidity and mortality caused by *Acinetobacter baumannii*, *Clostridium difficile*, and methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitalized patients and to develop a research training program for racial minorities that are underrepresented in biomedical, health services, and clinical research. We plan to develop and test new tools that will lead to substantial reductions in disease caused by these organisms. As we disseminate the results of our studies through published manuscripts and presentations at scientific meetings, the results of this project will improve the control of these pathogens well beyond the Commonwealth.

  Antibiotic resistance is increasing at an alarming rate and new tools are needed for prevention and control. The specific aims of the Center of Excellence in Prevention and Control of Antibiotic Resistant Bacterial Infections are to:

  1. Develop, validate, and employ novel molecular detection of asymptomatic *C. difficile* carriage and assess an intervention to control this substantial source of *C. difficile* disease;
  2. Understand the implications of the introduction of community-associated MRSA strains into the hospital and employ rapid, PCR-based diagnosis of MRSA infection to reduce use of broad spectrum antibiotics;
  3. Develop a new, multilocus variable number tandem repeat analysis-based molecular subtyping tool for tracking transmission, validate improved methods for detecting *A. baumannii* colonization, and assess an intervention to control the spread of this organism in intensive care units;
  4. Employ infectious diseases modeling techniques to understand the health and economic impacts of these novel strategies on the prevention and control of serious infections caused by these bacterial pathogens; and
  5. Establish a research training program for racial minorities that are underrepresented in biomedical, health services, and clinical research.