Health Research Nonformula Grants - State Fiscal Year 2007-08

Health research nonformula grants totaling $17,785,551 were awarded to five organizations in response to the Request for Application (RFA) # 06-07-15 for Collaborative Research on Violence Prevention or Regenerative Medicine and Post-Natal Stem Cell Biology. All research projects addressed one of the following research priorities established by the Department in conjunction with the Health Research Advisory Committee:

Regenerative Medicine and Post-Natal Stem Cell Biology

Research on regenerative medicine including tissue maintenance and repair via repopulation from adult stem cells, with the goal of better understanding health and disease including, but not limited to, cancer, diabetes, stroke, heart disease, vascular disease and age-related disabilities.

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

- Basic, translational and clinical research into regenerative medicine and its applications.
- Interdisciplinary, collaborative research projects that would support multiple investigators working in diverse research fields. Such fields may include, but are not limited to, cell and developmental biology, engineering (including bioengineering, tissue engineering and nanotechnology), cancer biology and cancer stem cells, veterinary medicine, and dental medicine.
- Development of core research technologies that would be of use to multiple research investigators and teams, such as xenogeneic stem cell transplantation, post-natal stem cell preparation, the development of assays, e.g., identification of stem cell markers, and transduction of genes that modify stem cell behavior, and in vivo imaging.
- Preclinical research projects proposed by individual investigators and groups of investigators.
- Phased clinical trials to test the safety and efficacy of adult stem cells in human subjects, once appropriate studies have been completed.
- New investigator awards to support young physician scientists and basic research investigators to build careers in regenerative medicine, including studies of cancer stem cells, tissue engineering, nanotechnology, and stem cell developmental biology, stem cells in veterinary medicine, and translational medicine.

Applications to establish a regional Center of Excellence for Research on Regenerative Medicine that will integrate core technology resources, multidisciplinary basic, translational and clinical research projects, and career development awards are encouraged.

Research involving studies of or using human embryonic stem cells will not be considered.

The research should hold the potential for addressing the health needs of underserved segments of the population, including rural, urban, racial and 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. The proposed research must include collaboration with a minority-serving academic institution or a minority-serving community-based organization 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.

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.

Violence Prevention

Research on violence prevention that addresses both of the following goals: (1) research to improve the identification of specific high-risk individuals likely to engage in violent behavior in order to further understand the interrelationship between genetic, i.e., host susceptibility, and specific environmental (both social and physical) risk factors, biochemical parameters and both structural and functional brain measurements and (2) research to evaluate, through clinical trials with these high-risk individuals, the efficacy of interventions that have initially been demonstrated in other studies to reduce violence.

Goal (1): The first goal is to identify very high-risk individuals likely to express violent behavior years before these events. Research may include, but is not limited to, studies that would address the research question of whether or not such behavior is strictly a function of their social and physical environmental exposures early in life, or also a function of exposure to neurotoxic agents among genetically susceptible individuals, or both. Newer brain imaging techniques, including both structural and functional MRI and PET, as well as better measures of identifying neuroendocrine metabolic parameters and prior environmental exposures, offer a unique opportunity to greatly improve the identification of very high-risk genotypes and phenotypes that would make it possible to focus on more intensive primary and secondary prevention approaches.

These studies should include multidisciplinary expertise in psychiatry, psychology, genetics, neuroimaging, biochemistry, epidemiology, social work and community studies.

Goal (2): The second goal is to conduct clinical trials with these high-risk individuals in order to evaluate the efficacy of interventions that have initially been shown in other studies to reduce violence, or interventions that are novel and innovative for which there are preliminary data of potential efficacy. Because it is unlikely that a definitive reduction in violence can be measured in the four-year grant period, these trials should focus on intermediate outcomes that can be evaluated within the four-year period. The intermediate outcomes should be clearly defined, and evidence should be presented to support the outcomes. It is important to note that these trials do not require a placebo control group; researchers may compare alternate therapies or even current intervention programs within the community.

In developing these clinical trials, collaboration with community groups, schools, legal authorities, social service agencies is strongly encouraged. It is also important

that these trials clearly define the sample size, the estimated benefits expected and the power of the trial. It is expected that such studies should include heterogeneous populations at high risk, such as minorities, urban, low socioeconomic status, rural populations as well as both males and females.

Research in the following areas will not be considered:

- Research that is limited only to the identification of high-risk communities.
- Research that is limited to the identification of high-risk individuals only by age, race, ethnicity, geography or socioeconomic characteristics.
- Research that does not address both goals (1) and (2).
- Ecological studies that compare rates of violent behavior across communities, i.e., an intervention versus control community only.
- Suicide and intentional self-harm.

The research should hold the potential for addressing the health needs of underserved segments of the population, including rural, urban, racial and 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. The proposed research must include collaboration with a minority-serving academic institution or a minority-serving community-based organization 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.

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.

<u>Violence Prevention Research Projects</u>

- Pennsylvania State University, Harrisburg Area School District and Hempfield Behavioral Health - *Understanding Violence and Its Prevention in Grades K-3*, $3,912,217 for a 48-month project (June 1, 2008 — May 31, 2012)

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  The violence prevention project's focus is children aged 6–8 in the Harrisburg School District. There are two primary goals: (1) to understand the physiological and neural markers that differentiate young children who do and do not show early violent/physically aggressive behavior, via examination of both the sympathetic and

para-sympathetic nervous system, brain organization and reaction (using EEG), using neuropsychological tests to assess specific areas of brain function (executive functioning and the executive attention system) and measures that focus on underlying temperamental vulnerabilities related to difficulties in self-regulatory capacity; and (2) to develop a multi-domain intervention model that will target parenting and parent-child relations, and the child's social and self-regulatory skills related to emotion regulation and cognition.

Using two cohorts of kindergarten children in Harrisburg City Schools, a well-validated screening model will identify approximately 15% of children with the highest rates of aggressive and violent behavior. With parental consent, these children and their caregivers will be visited to assess baseline family and child status. Using a within-classroom design, these high-risk children then will be randomly assigned to intervention or control status. Prior to intervention, all high-risk children (intervention and control) will be assessed for neurobiological status and executive functioning. The sample size will be 100 high-risk intervention and 100 high-risk control children. To understand how aggressive/violent children differ (behavior, neurobiological markers, etc.), they will be contrasted with a sample of 100 children who received low scores on the violence screen.

The project has four aims. The *first aim* is to understand factors related to early violent/aggressive behavior. Identifying children screened for high aggression and comparing them to a low-aggression sample, the study will examine differences at multiple levels (behavioral, family processes, stress exposure and environment), focusing specifically on neurobiological factors that characterize young children with high rates of violent/aggressive behavior. The *second aim* is to implement and evaluate a multi-domain intervention designed to prevent severe and chronic violence/aggression in a sample of children at high-risk upon first entering school. The intervention is guided by a developmental theory positing the interaction of multiple influences on antisocial behavioral development. Five areas of development and functioning will be targeted: parenting and healthy socialization in the home; peer relations; child coping and problem-solving skills; classroom atmosphere and curriculum; and home-school relations. The *third aim* is to understand factors in successful preventive interventions with these high-risk children. Within the intervention group, individual differences in outcomes will be predicted from pretreatment factors at the family level (e.g., demographics and family stressors) and at the child level (gender, baseline problem behaviors, measurement of how neurobiological factors moderate intervention effects, e.g., HPA axis functioning, heart rate, neuro-cognitive/executive functions). The *fourth aim* is to understand how the intervention's short-term effects may mediate its longer-term effects.

- University of Pennsylvania, Achieve Ability, Children's Hospital of Philadelphia, Institute for the Development of African-American Youth, Inc., Pennsylvania State University and University of Pittsburgh - *Biosocial Prediction and Intervention on Childhood Aggression*, $3,941,025 for a 48-month project (June 1, 2008 — May 31, 2012)

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The purpose of this project is fivefold. First, it aims to identify the environmental, social, psychological, and neurobiological factors that raise the risk that a child will become seriously aggressive later in life. Second, it aims to test the effectiveness of two interventions for the treatment of childhood aggression both alone and in conjunction: cognitive-behavior therapy and nutritional supplements. Third, it aims to identify factors that protect some children who are predisposed to aggression from developing this outcome. Fourth, it uses animals exposed to environmental toxins (lead) to assess the effectiveness of nutritional interventions in reducing aggression. Fifth, it attempts to understand how environmental factors interact with biological factors in giving rise to child aggression, and how these risk factors may affect treatment outcome.

Understanding the joint neurobiological and social bases of aggression is critical to future attempts to tackle this major public health problem. The overarching goals are: (a) to conduct perhaps the most systematic integration of biosocial risk factors for childhood aggression in order to predict later aggression, (b) to conduct one of the very few biosocial interventions on childhood aggression, (c) to predict and treat two fundamentally different manifestations of aggression – proactive and reactive aggression – which likely have different etiologies and responsiveness to treatment. The specific aims are: (1) to assess biological (genetic, neurocognitive, brain imaging, neuroendocrinological, neurotoxin, psychophysiological, nutritional), psychosocial (neighborhood, family, school, peer, psychological) and psychiatric (ADHD, CD, ODD, depression, anxiety, PTSD, schizophrenia-spectrum) risk factors for male and female aggression in order to better predict later aggression, (2) to improve prediction by identifying the genetic, neurocognitive, psychophysiological, and neuroendocrinological factors that *protect* children socially at risk from violence outcome, (3) to develop a genetic mouse model of aggression to test the effectiveness of nutritional interventions in reducing aggression, (4) to begin to develop a new biosocial approach to the treatment and prevention of aggression, based on both cognitive-behavioral and nutrition treatments, (5) to assess the differential prediction and treatment of two fundamental variants of aggression in children: proactive and reactive aggression. The human sample will consist of 500 male and female 11-year-old children drawn from high-risk communities in Philadelphia. Participants will engage in a baseline assessment for risk factors of aggression, and then be randomly assigned to one of three three-month treatment programs: nutrition supplementation, cognitive-behavior therapy + nutrition, and no-treatment controls. Aggression outcome will be assessed throughout treatment and post-treatment. The animal component experimentally tests risk factors (genotype, stress, lead exposure) and nutritional interventions (omega-3 fatty acids, calcium, multivitamins) on the development of aggression. It is believed that this biosocial interdisciplinary study offers a truly unique opportunity to identify the mechanisms and processes associated with two fundamental forms of childhood aggression that are the precursors to a major public health problem: serious adult violence.

- University of Pittsburgh, Auberle, Holy Family Social Services and Kingsley Association - *Consortium on the Causes and Prevention of Violence*, $3,932,889 for a 48-month project (June 1, 2008 — May 31, 2012)

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In this project we will link biological and environmental factors to violence, and will examine the effect of a treatment model on behavioral outcomes and on brain function as well. Violent behavior is associated with certain neurotransmitters, and certain genes are linked to the function of these neurotransmitters. We will examine the links between these genes and violent behavior by examining the chain of connections between these genes, the function of regions of the brain believed to underlie aggression, and the course of violent behavior in a sample of adults whose history of violent behavior is well-described. We will test the effect of a treatment program on at-risk children for changes in aggression and changes in associated brain regions.

Primary Components of this Project**.** This project focuses on: (a) biological factors (genetic predictors and brain function) for aggression/violence in the context of environmental factors and (b) a promising treatment of boys at risk for violence on behavioral change and brain function as identified in (a). A strength of this proposal is the extensive data on aggression/violence and environmental causes from childhood to early adulthood in the Pittsburgh Youth Study (PYS) (N=1,009). Another strength is the involvement of the Stop Now And Plan (SNAP) Oversight Committee to provide the SNAP program for boys age 12 and under at risk for violence. Finally, this project brings together experts on biological factors (genes and brain function), on environmental factors, and on treatment for children at risk for violence.

Genetic Predictors: Aims**:** 1) Among PYS adults, genotype 8 genes linked to neurotransmitters that are associated with aggressive and violent behavior. 2) Evaluate the main effects of genetic variation, environment variation, and genetic-by-environmental interaction on risk for aggression/violence.

Brain Function: Aims. 1) Examine links between brain regions underlying inhibition, emotion processing, and reinforcement responsivity in PYS men with chronic (N = 45) or transient violence (N = 45), and non-violent controls (N = 45). 2) Use results of Genetic Aim 2 and Brain Function Aim 1 as a basis to test the mediation via brain function of genetic variation, environmental factors, and their interaction on aggression/violence. 3) For 10-12 year-old SNAP boys/controls (n = 70), describe the pre-treatment association between aggression or violence and brain regions underlying inhibitory control, emotion processing, and reinforcement responsivity. 4) For 10-12 year-old SNAP/control boys (n = 70), document treatment-specific changes in brain function that occur following the SNAP treatment program (N = 35) in comparison to the alternative treatment (N = 35).

Treatment Aims**:** 1) Evaluate the effectiveness of SNAP versus a control treatment on measures of aggression. 2) Examine moderation of treatment effects via brain function, child, family, demographic, and neighborhood risk factors. 3) Examine whether any changes in aggressive behavior result from changes in specific hypothetical mechanisms of change within the child (problem solving skills, emotional regulation skills, and socialization skills) or in terms of parenting behaviors.

Regenerative Medicine and Post-Natal Stem Cell Biology Research Projects

- Children's Hospital of Philadelphia, Cheyney University of Pennsylvania and Philadelphia/Delaware Valley Chapter of the Sickle Cell Disease Association of America -

Prenatal Stem Cell Therapy for Sickle Cell Disease, $2,110,362 for a 48-month project (June 1, 2008 — May 31, 2012)

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We are proposing a new and novel approach to cure Sickle Cell Disease. In utero hematopoietic stem cell transplantation is the transplantation of blood forming stem cells into the fetus. Because of unique aspects of fetal biology, these cells can engraft and produce a fraction of the blood cells in the recipient. While this fraction is too small to treat Sickle Cell Disease, it results in permanent immunologic tolerance for the specific donor. This tolerance allows a non-toxic bone marrow transplant from the same donor to be performed after birth, resulting in high enough levels of donor cells to cure Sickle Cell Disease. If the aims of this proposal are achieved, it will lead to clinical trials that may change the way Sickle Cell Disease is currently treated, and will provide a non-toxic therapy that will prevent children from ever experiencing the manifestations of this disease.

In utero hematopoietic stem cell transplantation (IUHCT) is a method of achieving allogeneic mixed hematopoietic chimerism with associated donor specific tolerance without myeloablation or immunosuppression. Individuals made tolerant by IUHCT can undergo a minimal conditioning postnatal hematopoietic stem cell transplant (HSCT) from the same donor without toxicity and improvement of donor cell chimerism to levels that are potentially therapeutic for Sickle Cell Disease (SCD). The broad objective of this proposal is to develop the strategy of IUHCT combined with minimal conditioning postnatal HSCT to cure patients that are prenatally diagnosed with Sickle Cell Disease. The Specific Aims of this proposal are:
Specific Aim #1. To perform pre-clinical studies in the canine model designed to optimize the safety of the IUHCT followed by postnatal minimal conditioning HSCT strategy. Further studies will be performed in the established pre-clinical canine model to confirm the optimal T-cell dose for facilitation of engraftment with minimal risk of GVHD. These studies are a priority and will be completed prior to initiation of the Phase I clinical trial.
Specific Aim #2. To experimentally test novel strategies to enhance engraftment and donor specific tolerance after IUHCT. We have developed a protocol in the canine model that can achieve levels of donor cell chimerism that would be anticipated to be curative for SCD patients. However, additional strategies designed to improve the consistency of tolerance induction that are translatable to clinical application will be evaluated.
Specific Aim #3. To establish a model of community based participatory research inclusive of the SCD and African American community and to lay the groundwork for a future clinical trial of IUHCT for treatment of SCD. This aim will be coordinated through the Sickle Cell Center at the Children's Hospital of Philadelphia, Cheyney University, and the Philadelphia/Delaware Valley Chapter of the Sickle Cell Disease Association of America. It will include: 1) a social awareness program designed for education of African American couples and others at risk for an affected child with SCD for assessment of their views and opinions regarding a trial of this therapy and 2) research training of undergraduate students and mentoring of junior faculty from Cheyney University through direct involvement in the scientific and social components of this proposal.

- University of Pennsylvania, Children's Hospital of Philadelphia, Fox Chase Cancer Center, Haverford College, Lincoln University and Thomas Jefferson University - *Penn Center of Excellence for Regenerative Medicine*, $3,889,058 for a 48-month project (June 1, 2008 — May 31, 2012)

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  The purpose of this project is to establish a Penn Center of Excellence for Regenerative Medicine at the University of Pennsylvania with collaborative partners across eastern Pennsylvania. A programmatic effort to find new treatments for diabetes will be funded involving basic, translational and clinical investigation at three institutions. There will also be an innovative program to develop a pipeline of new scientists and clinicians in the Commonwealth which will involve outreach in the Philadelphia public schools, Haverford College and Lincoln University.

  The research Specific Aims involve:
  A Research Program to develop regenerative therapies for diabetes including clinical, translational and basic studies performed by a collaborative team of investigators at three institutions within the Commonwealth. The project simultaneously advances multiple approaches to encourage islet cell growth and regeneration. Specific aims are:

  Aim 1: Determine if GLP-1 sustains or increases functional ß-cell mass in humans in vivo.
  Aim 2: Determine if GLP-1 receptor agonists stimulate human ß cell growth.
  Aim 3: Determine whether systemic Bone Morphogenetic Protein (BMP) regulates rodent and human ß cell growth.
  Aim 4: Determine whether adenoviral over-expression of GDF3 can be exploited to stimulate human ß cell proliferation.
  Aim 5: Characterize endothelially derived secreted factors for their potential to improve outcome in human islet transplantation.