International Activities Catalog

2019

Office of Global Health
Office of the Director

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

International Activities Catalog
2019

Office of Global Health
Office of the Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Table of Contents

Overview

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has supported international research since its establishment over 50 years ago and has a strong commitment to continued international research collaborations. The Office of Global Health (OGH) at NICHD resides within the Office of the Director (OD) and supports the NICHD's international activities across the institute.

OGH works in close collaboration with NICHD divisions and offices, as well as other National Institutes of Health (NIH) and U.S. Department of Health and Human Services (HHS) entities, to improve the overall health of populations worldwide by providing leadership, coordination, and support for NICHD's global heath mission and activities. Key activities include:

- Coordinating, advocating, identifying, and mobilizing policies, programs, resources, and opportunities in global health research and training
- Building and maintaining global health partnerships and collaborations
- Providing leadership in the development of cross-cutting policies, plans, and programs related to NICHD's global health research
- Assisting the institute's components in enhancing their international research portfolios and other global health activities

In implementing these activities, OGH works in partnership with multiple national and global health organizations, including the U.S. Agency for International Development (USAID), U.S. Department of State, embassies of foreign countries, foreign ministries of health, research organizations and universities in the United States and abroad, and representatives of international health and non-governmental organizations.

The NICHD International Catalog, prepared by OGH, contains the annual report of global health activities across the Institute's divisions, offices, and laboratories. These activities are described within the following sections representing the: OD, Division of Extramural Research (DER), National Center for Medical Rehabilitation Research (NCMRR), Division of Intramural Population Health Research (DIPHR), and Division of Intramural Research (DIR). Information provided includes the mission of each branch or program, current research initiatives and achievements, international collaborative partnerships, staff membership on global health committees and working groups, and points-of-contact. DIR entries also include lists of international trainees and key publications.

Office of the Director (OD)

NICHD OD provides overall leadership, planning, direction, coordination, and evaluation of the Institute's research programs and activities. OD also develops internal policies and procedures and monitors their implementation and maintenance. In addition, NICHD OD leads the institute's efforts in the assessment and dissemination of information for the scientific community, clinical practitioners, and the public.

Office of Global Health (OGH)

Mission

OGH seeks to improve health worldwide by providing leadership, coordination, and support for NICHD's global heath mission and activities.

Major International Initiatives over the Past Year

NIH – Bill and Melinda Gates Foundation (BMGF) Collaboration. A new phase of cooperation between NIH and BMGF was initiated in January 2014 in the areas of maternal and infant nutrition, reduction of premature births, healthy cognitive development, point-of-care diagnostics, vaccine development, tuberculosis (TB) drug discovery, etc. This has included annual NIH-BMGF Global Health Consultations held on the NIH campus, with NICHD representatives in several working groups (i.e., Maternal, Neonatal, and Child Health, Pediatric Pneumonia and Indoor Air Pollution, Contraceptive Research, and HIV/AIDS Working Groups). NICHD co-chairs the Maternal, Neonatal, and Child Health and Contraceptive Research Working Groups which include representation from NICHD, BMGF, the National Institute of Mental Health (NIMH), the National Institute of Drug Abuse (NIDA), and the National Institute of Neurological Disorders and Stroke. These working groups aim to identify new research collaborations in the areas of prematurity, child neurodevelopment, nutrition and growth, neurocognitive assessment, contraception development, among other areas. Joint activities have included presentations on the NIMH Data Archive (NDA) data-sharing portal, input toward planning the May 2019 BMGF Workshop in Seattle on *Modeling Neurodevelopment: Physical Growth Above the Neck*, and the launch of the NIH Infant and Toddler Toolbox funding opportunity, among others.

NIH - Canadian Institute of Health Research (CIHR) Symposium. NIH and CIHR organized a joint symposium in November 2019 framed by two panel discussions on: 1) Building the next generation scientific workforce, and 2) Emerging medical technologies (i.e., development, testing, validation, and adoption of new technologies), such as mobile health, imaging, point of care diagnostics, and big data. These opening panel discussions were followed by bilateral/multilateral meetings on an array of global health topics, including one led by NICHD on maternal and child health research. Comparable NIH research to Canada's Healthy Life Trajectories Initiative (HeLTI) was discussed. HeLTI is a 10-year study evaluating approaches to prevent overweight and obesity in children in which Canadian researchers will follow participants from preconception through childhood. Other areas of mutual interest and follow on activities include medications for children and pregnant and lactating women, data linkages, and data sharing.

NIH Common Fund, "Data Science – I in Africa Program (DS-I Africa)." NICHD staff is participating in the DS-I Africa to leverage data science technologies and prior NIH investments to develop solutions to the continent's most pressing public health problems. A robust ecosystem of new partners will be established from academic, government, and private sectors. In the next decade, rapid advances in data science are expected to transform biomedical and behavioral research and lead to improved health for individuals and populations. Plans are

underway for a DS-I Africa symposium in Uganda in June 2020, as well as the development of research hubs, training, and data coordinating centers.

World Health Organization (WHO) Nurturing Care Framework. Over the past 3 years, OGH has represented NICHD on the WHO Nurturing Care Framework Planning and Implementation Working Group. The concept of "Nurturing Care" was coined in the 2016 *Lancet* series, "Advancing Early Childhood Development: From Evidence to Scale," to refer to a cluster of evidence-based interventions aimed at enhancing health, nutrition, responsive caregiving, safety and security, and early learning. OGH participated in both the 2018 World Health Assembly launch of this WHO framework (which included over 200 participants) and subsequent technical consultations aimed at identifying research and implementation gap areas, developing plans for interagency implementation, and drafting guidelines for policymakers.

WHO Consultation: "Early Childhood Development Innovative Interventions and Approaches Mapping Exercise." This WHO consultation held in Geneva, Switzerland in June 2019 aimed to further examine evidence-based approaches and next steps of the Nurturing Care Framework for Early Child Development co-sponsored by the WHO, United Nations International Children's Emergency Fund (UNICEF), and the World Bank, to be implemented by the WHO Partners for Maternal, Neonatal, and Child Health and the Early Childhood Development Action Network. This groundbreaking, global interagency effort aims to make the shift from child survival to studying and supporting long-term child health and development outcomes at the country level globally. Objectives of the meeting included: discussing the findings of portfolio analyses and country experiences; identifying gaps in knowledge about effective implementation and scale up of nurturing care interventions for early childhood development; determining principles and enablers that are relevant for effective implementation of nurturing care interventions in different contexts; and developing recommendations to inform implementation research and guidance.

Trans-NIH Initiative on Conducting Health Research in Humanitarian Crises. For the past 3 years, OGH has represented NICHD on this trans-NIH initiative, addressing topics such as armed conflict, natural disasters, forced displacement, and disease outbreaks, as well as on follow-up activities outlined at the 2019 workshop held on the NIH campus. Toward this end, an OGH staff member served as a reviewer for a collection of case analyses of health research in humanitarian crises to be published in the journals *Conflict and Health* and the *BioMed Central Public Health*. The CIHR has also indicated an interest in working with NIH to develop joint initiatives and its own funding announcements aimed at developing mechanisms for research during humanitarian crises.

U.S. Government "Children in Adversity" Initiative. In June 2019, USAID together with interagency partners including NICHD, NIMH, the National Institute of Environmental Health Sciences (NIEHS), and the Fogarty International Center (FIC), launched the updated Children in Adversity Framework for interagency collaboration for improving long-term health and development outcomes of orphans and vulnerable children. A preliminary description of this initiative, aimed at developing a research agenda and whole-of-government strategy for work with children in adversity in low- and middle-income countries (LMICs), was published in The *Lancet* in December 2011, with the former NICHD director serving as a co-author. An NICHD

staff member served as co-editor of a special supplement in the journal *Child Abuse and Neglect*, and multiple NICHD and NIH staff members served as co-authors of several articles that described results of evidence review teams. NICHD hosted a pre-summit for this initiative at NIH in October 2011 and was a partner in the government-wide evidence summit held in December 2011 at USAID, which was supported by senior leadership of seven federal agencies, including NICHD.

Recent Achievements in International Health

Planning of International Site Visits by Senior NICHD, NIH, HHS, and Congressional Leadership

In collaboration with NICHD program staff, OGH prepared briefing materials and helped plan site visits for NICHD, NIH, HHS, White House, and Congressional senior leadership for collaborations with Belgium, Mexico, South Africa, Switzerland, and Uganda, among other countries.

- **Coordination of Visits by Foreign Delegations.** Participated in the coordination of meetings and preparation of briefing materials for visits by foreign delegations (e.g., Indian Ministry of Health, Chinese National Science Foundation).
- **Public Law 109-95 Congressional Report Data Call.** Served as the NICHD lead for preparing the trans-NIH report on research projects studying the health and developmental outcomes of orphans and vulnerable children for this annual report to Congress.
- **OGH Brown Bag Series.** Organized talks on global health and diverse scientific topics within the NICHD mission.
- **Dissemination of Global Health Information Including Current NICHD Initiatives.** Regularly updated the OGH webpage on the NICHD Insider and prepare the NICHD International Activities Catalog to facilitate information exchanges related to global health.
- **Scientific Input Provided for Interagency Global Health Documents.** OGH contributed to the writing of science and policy documents and requests for information from internal (e.g., NICHD, NIH, HHS) and external (e.g., USAID, WHO, UNICEF) sources that describe NICHD's scope of mission and international activities.

International Partnerships

International partnerships developed through involvement on working groups as described below.

Examples of Staff Membership on Global Health Committees/Working Groups

- NICHD Global Health Strategic Team. Representatives: Vesna Kutlesic & Jenelle Walker
- WHO Nurturing Care Framework Advisory Group. Representative: Vesna Kutlesic

- NIH-BMGF Child Health and Development Working Group. Representative: Vesna Kutlesic
- Children in Adversity Strategy Working Group. Representatives: Vesna Kutlesic & Jenelle Walker
- Trans-NIH Global Health Research Working Group. Representative: Vesna Kutlesic
- Trans-NIH International Clinical Research Subcommittee. Representative: Vesna Kutlesic
- FIC International Representatives Working Group. Representative: Vesna Kutlesic
- NICHD Reproductive Health Working Group. Representatives: Vesna Kutlesic & Jenelle Walker
- NICHD Maternal Mortality Working Group. Representatives: Vesna Kutlesic, Jenelle Walker, & Hannah Savage
- NICHD Pain/Opioid Working Group. Representative: Vesna Kutlesic
- Global Nutrition Coordination Plan Technical Working Group: Jenelle Walker
- NIH Dissemination & Implementation Working Group: Jenelle Walker
- NIH Global Health Interest Group: Jenelle Walker
- Trans-NIH China Working Group: Jenelle Walker

Point-of-Contact

Dr. Vesna Kutlesic
vesna.kutlesic@nih.gov
301-435-7566

Division of Extramural Research (DER)

DER develops, implements, and coordinates cross-cutting, multidisciplinary research activities within NICHD's mission. The research portfolio is quite broad, including biological, behavioral, and clinical research related to conception and pregnancy, normal and abnormal development in childhood, reproductive health, and population dynamics across the lifespan. While NICHD's DIR conducts laboratory and clinical research programs at NIH, DER coordinates and funds research and training programs across the United States and many other countries through grants and contracts.

DER advises the NICHD director on extramural research and training policies and activities. It also provides scientific peer review, grants management, and program management and oversight for roughly 3,500 competing grant applications and over 450 new and competing awards each year. With a focus on scientific priorities and research integrity, DER leads implementation of extramural policies and procedures for NICHD.

Child Development and Behavior Branch (CDBB)

Mission

CDBB develops scientific initiatives and supports research and research training relevant to the psychological, neurobiological, language, behavioral, and educational development and health of children.

Major International Activities over the Past Year

Exposure to Political Violence. The branch supports longitudinal studies examining the effects of exposure to political violence on child outcomes, including in Israel, Northern Ireland, and Palestine. The FIC provided support for at least one of these projects and expressed interest in learning about opportunities for future collaboration.

Parenting Across Cultures. The branch supports this longitudinal study conducted in nine countries, China, Columbia, Jordan, Italy, Kenya, Philippines, Sweden, Thailand, and the United States, that is examining parenting influences on impulsive, risky behaviors during late adolescence, when the transition to adulthood is beginning. This research explores how "risky behavior" is conceptualized across cultures, and how cultural contexts moderate the association between early parenting and competence and maladaptation during this point in development. Another study, set in Pakistan, is evaluating the impact of an intervention for maternal depression on child socio-emotional, cognitive, and physical outcomes, and whether improved parenting mediates child outcomes.

Integrated Early Childhood Development (ECD) Interventions. Recent neurobiological and psychological research has established that vital development occurs in language, cognitive, motor, and socio-emotional development during the first few years of life, and early life outcomes are key determinants of adult outcomes such as educational achievement, labor market outcomes, and health. Yet more than 200 million children younger than age 5 who live in LMICs will fail to reach their developmental potential as adults, predominantly due to poverty, poor health and nutrition, and inadequate cognitive and psychosocial stimulation. ECD interventions that integrate nutrition and child stimulation activities have been shown to be effective in improving children's developmental and health outcomes, at least in the short-term. The branch supports a multi-arm clustered randomized controlled trial across 60 villages and 1,200 households in rural Kenya that tests different potentially cost-effective delivery models for an ECD intervention with a curriculum that integrates child psychosocial stimulation and nutrition education.

Cognitive and Behavioral Development. The branch supports a multicomponent project with both domestic and foreign components. The project investigates how infants develop actions strategically toward goals. This ability emerges early in infancy and matures across childhood. This capacity may be supported by a common underlying neural network known as the mirror neuron system. This project combines investigations of the mirror neuron system in both an animal model as well as infants to understand typical development of the mirror neuron system and in children with autism spectrum disorder to understand whether the system is disrupted in this disorder. The foreign component at the Institut des Sciences Cognitives Marc Jeannerod,

France, and the investigator there conducts the mirror neuron system animal model work to inform and converge with the human-based research on the system.

A current study supported by CDBB is designed to understand the genes and pathways most affected by early life stress, the degree to which these effects persist over time, or the environmental, behavioral, or genetic factors that mediate inter-individual differences in susceptibility in a unique animal model. The project takes advantage of a 5-decade, multigenerational study of baboons in which genomic approaches are well-developed, and in which long-term associations between early life stressors and later life gene regulation, health, and mortality risk have already been demonstrated. This baboon population is located in the Amboseli ecosystem of Kenya and has been studied for more than 45 years by the Amboseli Baboon Research Project. For the purposes of this grant, the Kenyan component objectives are to: (1) Collect biological samples (blood) from individuals in the population for whom information on social and ecological adversity is also known; (2) Collect behavioral data important for determining social and reproductive status at the time of biological sampling.

The branch is supporting a new study to determine whether a nutritional intervention of omega-3 supplementation for adolescents and their parents will reduce externalizing behavior in the adolescent and will explore potential neurocognitive mechanisms of action of omega-3. This research is taking place in the Republic of Mauritius and participants are recruited from the ongoing, multigenerational Mauritius Child Health Study.

A Canadian study of the development of face-processing expertise is supported as well. This study involves an international team of researchers and investigates how children's face-processing expertise is tuned by experience in their unique environments. The infants and children in these studies are from several countries (e.g., Australia, China, France, and the United States) and aim to capitalize on their naturally occurring experiential differences with faces of different races, genders, and ages.

The branch is supporting a collaboration with Norway to investigate the relationship of maternal and child infection, fever and immune disorders to Attention Deficit/Hyperactivity Disorder (ADHD) risk, the potential modulation of that risk by medications (i.e., antipyretics, analgesics, antibiotics) and micronutrients using prospective data about exposures in ADHD and control mother-child pairs. This study will also characterize immune signatures of mothers during pregnancy and their children at birth, determine their association with ADHD risk, as well as examine the role of specific infectious agents on the development of ADHD.

Bilingualism and Cross-Linguistic Studies of Literacy and Language Development. The branch funds studies of infant perception, conceptual development, and early word learning in various languages. Some of these studies across languages are demonstrating which aspects of language development may be universal (the same for all languages), and which are language-specific. Published studies have indicated a cognitive advantage in some aspects of executive function in bilingual children, which supports the value of encouraging the development of bilingualism and the maintenance of first language in English learning children. Similarly, studies of reading and reading disability, including its neurobiological and genetic bases, are supported as domestic grants many of which have foreign subcomponents. Both cross-linguistic studies

and those examining bilingual and second language learning populations are helping to describe the timing and trajectory of early language development and of literacy learning. Locations for some of the data collection and/or subcontracts for this work include Australia, Canada, China, France, Israel, Mexico, the Netherlands, Spain, and the United Kingdom (U.K.).

Improving the Health and Well-being of Orphaned Children. The branch supports a study that describes existing models of care for orphans in Kenya and examines the effects of characteristics of the care environment and socioeconomic measures on children's mental and physical health. Another branch-funded study in Zambia seeks to longitudinally assess the cognitive development and educational outcomes of orphans and vulnerable children (OVC) affected by HIV/AIDS, to document and evaluate regional aid organizations that serve or intend to serve OVC, and to support Zambian collaborators in behavioral, community-oriented, and program evaluation research so that long-term studies of OVC outcomes and programs will be possible.

Recent Achievements in International Health

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. James Griffin
james.griffin@nih.gov
301-435-2307

Contraception Research Branch (CRB)

Mission

CRB supports research and research training programs on the effects of contraception on human health and new and improved methods of contraception.

Major International Initiatives over the Past Year

Hormonal Contraception and HIV/AIDS. CRB supported analyses of specimens obtained from research it had funded previously on the impact of hormonal contraception on HIV-disease acquisition and acute infection/progression in Uganda and Zimbabwe. This project is designed to understand the associations between systemic hormone levels with circulating regulators of inflammation, immunity, and soluble innate immunity mediators in the cervix, their relationship to HIV acquisition risk, and how these relationships are altered by pregnancy and by exposure to hormonal contraception, specifically depot medroxyprogesterone acetate (DMPA) and oral contraceptives. It also plans to define the effects of pregnancy and hormonal contraception on the immune system preceding, at the time of, and during established herpes simplex virus 2 (HSV-2) infection to better understand the effect of hormonal contraception and pregnancy on the risk of HIV infection associated with HSV-2.

Effects of Contraceptive Ring on Vaginal Microbiota, HIV Shedding, and Local Immunity. CRB continued support of this study in Kenya to determine whether sustained vaginal delivery of estrogen promotes desirable vaginal bacteria and thus reduces the risk of bacterial vaginosis, which is a common cause of vaginitis and increases the risk of HIV, pelvic inflammatory disease, adverse pregnancy outcomes, and HIV acquisition.

Injectable Contraception and HIV/HSV-2 Incidence in Young South African Women. CRB continued supporting this project which is one of the first studies of the relationship between the use of injectable contraceptives (DMPA and norethisterone oenanthate) and the incidence of both HIV and HSV-2. It will also study their effects on other common sexually transmitted infections (STIs) and sexual risk behaviors in this vulnerable population, which has unusually high rates of HIV and unwanted pregnancies.

Promoting Effective Condom Use. CRB supported a Small Business Innovative Research (SBIR) grant that includes collaborating on design and manufacturing of an improved male condom, with a condom manufacturing facility in Malaysia.

Pharmacological Strategies to use the Levonorgestrel (LGN) Implant in HIV-infected Women. CRB supported a research grant to study pharmacokinetics of samples collected over one year of combined use and compared to a control group of HIV-infected women on an LNG implant, but not yet on antiretroviral therapy (ART), which includes study sites in Uganda and England. The study will determine the LNG implant dosage required to ensure safe and effective combined use with ART regimens, spanning the continuum of HIV care. In turn, this work is strongly expected to improve the management of reproductive health in millions of HIV-infected women worldwide. Additionally, the models developed through this study represent a highly efficient and Food and Drug Administration (FDA)-recognized approach to predict drug-

drug interactions and will guide future contraception studies. In doing so, the study addresses three important areas for research identified by the NIH Office of Research on Women's Health, including to: actualize personalized prevention methods, create strategic partnerships that maximize the global impact of women's health research, and build a vigorous women's health research workforce.

Preclinical Development of Polyphenylene Carboxymethylene Sodium Salt (PPCM) Vaginal Contraceptive to Submit Investigational New Drug (IND) Application. This grant will develop an aesthetically acceptable, safe, and effective vaginal contraceptive gel, and complete all preclinical studies required by the FDA for submission of an IND application. PPCM has multipurpose technology potential and is also under development as an antiviral drug. This project includes work to be done in Australia to develop this product by improving the effectiveness of an existing gel through increasing its viscosity and mucoadhesion.

International Guidelines for Family Planning. Through an interagency agreement with the USAID that began 14 years ago, CRB provides both financial and technical support to the WHO's Department of Reproductive Health and Research for a series of technical documents on contraception. These documents are among the most highly respected guidelines for family planning personnel around the world and have had a significant impact on enabling family planning programs to provide evidence-based contraceptive services.

Collaboration with the BMGF. CRB staff continues to work with the BMGF and other organizations in to develop a clear picture of all the contraceptive products currently in the research pipeline worldwide and the current status of each. This effort has focused on identifying products that are particularly well-suited for South Asia and Sub-Saharan Africa.

Recent Achievements in International Health

N/A

International Partnerships

CRB has ongoing collaborations with the WHO. Through CRB's interagency agreement with USAID, the process of collecting and analyzing the world's literature on contraception continued to provide the background for the continuously revised WHO guidance documents. The *Medical Eligibility Criteria for Contraceptive Use*, the parent WHO family planning document, has been adapted and published for the United States by the Centers for Disease Control and Prevention (CDC).

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Daniel Johnston
daniel.johnston@nih.gov
301-827-4663

Developmental Biology and Structural Variation Branch (DBSVB)

Mission

The DBSVB supports basic, clinical, and translational research on normal and abnormal development relating to the causes and prevention of structural birth defects, as well as research training in relevant academic and medical areas. Among the branch's high-priority areas is basic research, primarily using a variety of animal models, on elucidating the biochemical, molecular biologic, genetic, biophysical, and cellular mechanisms of embryonic development. The DBSVB supports both basic and translational aspects of structural birth defect research by supporting and fostering collaborations among: basic developmental biologists studying developmental mechanisms at all embryonic stages and the causes of birth defects in model organisms; biophysicists studying physical/biomechanical aspects of development; and clinicians studying the causes and intervention strategies of birth defects in humans.

In addition to our emphasis on structural birth defects and transdisciplinary research, DBSVB priority research areas of emphasis include the elucidation of gene regulatory networks, the biophysics and biomechanics of development, stem cell and regeneration biology, and developmental metabolomics.

The study of developmental biology is without a doubt foundational to our understanding of birth defects or "inborn errors of morphogenesis." Whether these perturbations are due to genetics, environmental insults, or a combination of both, understanding the underlying developmental mechanisms will only be achieved through multidisciplinary, collaborative efforts among developmental biologists, geneticists, teratologists, genetic epidemiologists, obstetricians, neonatologists, and pediatricians. Consequently, the DBSVB actively promotes the collaboration of basic and clinical scientists through the NICHD's Birth Defects Initiative and encourages interactions between NIH Institutes with shared interests in birth defects research by providing leadership for the Gabriella Miller Kids First Pediatric Research Program.

Major International Initiatives over the Past Year

International Activities Involving Human Subjects

China

Birth defects are a global problem affecting about 6 percent of all births. In the United States, birth defects are the leading cause of pediatric hospitalizations, medical expenditures, and death in the first year of life. Furthermore, they continue to rank as a top cause of death for children ages 1 to 4 years (#2 cause of death), 5 to 14 years (#3), and 15 to 24 years (#6). Birth defects are, therefore, one of the most important childhood healthcare issues. However, little is known about the causes of most birth defects, and there are few truly effective prevention strategies. This collaboration with investigators in China focuses on one of the top five most common birth defects worldwide, neural tube defects (NTDs), with the goal of understanding the underlying causes in humans and developing of new strategies for prevention.

NICHD-supported investigators have established collaborations with several sites in China including investigators at Peking University, the Shanghai Institute of Medical Genetics, Fudan University in Shanghai, and the Capital Institute of Pediatric Research in Beijing. These collaborations with groups in China enable investigators on domestic NICHD-supported grants to leverage well-established clinical and research infrastructures in China and provide a unique opportunity to obtain biological specimens and information on environmental and genetic contributions to the etiology of NTDs. The scope of these collaborative studies broadly integrates multiple risk factors (environmental, nutritional, biochemical responses, and genetic) that can contribute to NTDs, using a multidisciplinary approach with state-of-the-art technologies and bioinformatic/genomic methodologies. This program tests highly novel hypotheses concerning the protective mechanism of folic acid in the prevention of NTDs and the post-translational modification of selected proteins interfering with normal neural tube closure. Understanding the underlying biology of failed closure opens the possibility of developing effective intervention strategies for preventable NTDs. This has broad implications for the 330,000 infants born with NTDs annually worldwide.

Multinational Collaborations

In an effort to obtain enough subjects for studies that will result in statistically significant findings, members of our branch's Structural Birth Defects Working Group often form collaborations with investigators in other countries to strengthen the statistical power of their studies.

France, Germany, Spain, and UK: The long-term goal of this project on craniosynostosis is to elucidate normal and abnormal craniofacial biology to ultimately improve the treatment of craniofacial disorders. Craniosynostosis and other skull abnormalities are among the most common human malformations and usually require surgical and medical intervention. This international collaboration integrates the efforts of scientists with diverse expertise including anthropology, morphometry, imaging, birth defects, developmental biology, genetics, genomics, epidemiology, statistics, and systems biology to explore the determinants of the fate of the relevant mesenchymal progenitor cells, and how abnormalities in the processes of osteogenesis contribute to disorders such as global skull growth abnormality, premature closure of sutures, in particular the coronal suture. Foreign collaborators will be involved in acquiring and processing images and DNA, fibroblasts, and osteoblast samples from subjects recruited at foreign sites to be used in performing genotyping studies.

Japan, Sweden, and Hong Kong: Adolescent idiopathic scoliosis (AIS) is a twisting condition of the spine and is the most common pediatric musculoskeletal disorder, affecting 3 percent of children worldwide. Children with AIS risk severe disfigurement, back pain, and pulmonary dysfunction later in life at great economic costs. Girls requiring treatment for AIS outnumber boys by more than fivefold, for reasons that are unknown. AIS is treated symptomatically rather than preventively because the underlying etiology is unknown. The overall purpose of this project is to understand the biologic causes of AIS as a means to early diagnosis, prevention, and non-invasive biologic treatment. AIS is a complex genetic disease. Genome-wide association studies (GWAS) of common non-coding variants have identified AIS-associated DNA variations/polymorphisms, but the mechanistic basis of these associations remains to be

defined. GWAS also require well-powered replication studies to validate the work being carried out. Presently, there are no U.S. research groups that have the necessary cohorts required to perform the validation studies. Consequently, the one investigator performing these studies in the United States interacts with investigators in Japan and Sweden through the International Consortium for Spine Genetics, Development, and Disease and electronically shares polymorphic markers found associated with scoliosis in the cohorts as well as summary statistics (e.g., allele frequencies, odds ratios, P values, etc.). In this way, investigators can test these markers in each other's cohorts of scoliosis patients and controls and thus perform very powerful validation studies of each other's GWAS data. The results of such collaborations can help to develop hypothesis-driven research aimed at early molecular diagnosis, prevention and potential therapeutic interventions. Recently, they added Hong Kong collaborators to improve validation studies.

International Activities Involving Animal and Cell Culture Models

Canada

The wide use of animal models to elucidate the causes of human disease generates a great deal of genomic data. In recent years, the need to share these data between investigators doing basic research with different animal models and physician-scientists doing clinical or translational research has become paramount. One of the best ways to share data is through the use of community databases. Xenbase, the *Xenopus* model organism database, is one of the best available and represents a strong collaboration between investigators in the United States and Canada. The Canadian component of this project provides programming and server-associated services for a database of research information obtained from research using *Xenopus*. These frogs are used as an experimental animal model system for basic biomedical studies that would be prohibitively difficult or expensive to conduct in humans. The database collects, annotates, and stores research data as well as provides access and tools for data analysis. This provides a resource to the international research community, ensuring that important data are available and easily accessible to guide further research projects and to avoid unnecessary duplication of effort. In serving this function, Xenbase provides an essential resource to the biomedical research community for understanding the molecular basis of development, health, and disease.

In the last year, a similar collaboration has been undertaken with echinoderm researchers in the United States and Canada to improve an Echinobase database using the software, hardware and infrastructure of Xenbase to provide a highly reliable platform that delivers efficient access to a broad range of data derived from this key set of model organisms. These data include genomes, genome annotations, gene ontology, gene expression, gene regulatory networks and the relevant scientific literature that will be made readily available to researchers using Echinoderms as an experimental model organism.

Embryonic stem cells (ESCs) have become an essential model system for studies of embryonic development, regenerative medicine, and stem cell therapies due to their ability to differentiate into all cell types of the body. An NICHD-funded predoctoral fellow is working to determine how protecting specific proteins from degradation regulates the differentiation of mouse ESCs. This project is highly relevant to our understanding of human development and disease, as

mutations in similar processes have been identified in a range of human neurological disorders, developmental syndromes, and cancers.

Italy

Understanding NTDs is of great importance as these are amongst the most commonly occurring birth defects. In one collaborative effort with a group in Italy, supplemented by the NIH Office of Dietary Supplements, our investigators are elucidating the mechanisms and the nutritional and genetic determinants of deoxy uridine nucleotide incorporation into DNA, and its role in the etiology of NTDs. The results from these collaborative studies will establish the pathway for NTDs and inform future human and population studies for the prevention of folate- and B12-associated pathologies including NTDs.

Switzerland

The use of different types of ribosomes within the embryo is a novel means by which the expression of key developmental regulator genes is controlled. To understand at a mechanistic level this new level of gene regulation, in collaboration with researchers in the United States, Swiss researchers are using advanced microscopy and detection systems to visualize the 3-D interaction of RNAs directly with the mammalian ribosome. This requires sophisticated structural analysis guided by electron microscopy for which the Swiss collaborators are recognized as world leaders.

Recent Achievements in International Health

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. James Coulombe
coulombeJ@mail.nih.gov
301-451-1390

Fertility and Infertility Branch (FIB)

Mission

FIB's mission is to encourage, enable, and support research aimed at alleviating human infertility, uncovering new possible pathways to control fertility, and expanding fundamental knowledge of processes that underlie human reproduction. To this end, FIB funds basic, clinical, and translational studies to enhance our understanding of normal reproduction and reproductive pathophysiology, as well as to enable the development of more effective strategies for the diagnosis, management, and prevention of conditions that compromise fertility.

Major International Initiatives over the Past Year

There are no FIB international activities to report at this time.

Point-of-Contact

Dr. Louis De Paolo
depaolol@mail.nih.gov
301-435-6970

Gynecologic Health and Disease Branch (GHDB)

Mission

GHDB supports and promotes basic science, translational and clinical research, and research training programs related to gynecologic health in women and adolescent girls. The branch portfolio emphasizes studies on the menstrual cycle, uterine fibroids, endometriosis, polycystic ovary syndrome, pelvic floor disorders, and gynecologic pain syndromes. International activities include support of research on obstetric fistula and female genital mutilation.

Major International Initiatives over the Past Year

Obstetric Fistula (OF). OF is a debilitating birth injury resulting from obstructed labor which results in constant leaking of urine and/or feces. OF is estimated to affect 50,000 to 100,000 women each year with as many as 2 million women with untreated OF in Asia and Sub-Saharan Africa. While women with OF often can be successfully treated with surgery, they may still not be reintegrated into their communities. GHDB currently supports a study which aims to assess the long-term mental health and physical sequelae of women who have had surgery for obstetric fistulae, and to determine predictors of reintegration success after surgical repair in a Ugandan population. This will be followed by design of a post-surgical reintegration intervention for these women and their households with subsequent pilot testing for feasibility, acceptability and impact on reintegration success.

Female Genital Cutting (FGC) or female genital mutilation. FGC (a.k.a., female circumcision) is a cultural/religious/social practice of removing either part or all of the external female genitalia, often with narrowing of the vaginal outlet. The practice is usually carried out by a member of the community or family on young girls up to age 15 years and can result in death from unclean practices, obstructed labor, and chronic vulvar/vestibular pain, urination problems, and sexual dysfunction. The WHO estimates that over 125 million girls and women alive today have undergone this procedure. Due to recent immigration patterns, there has been a large increase in the number girls and women in the United States who have undergone FGC. It may have been performed either abroad or domestically, as there are still immigrant communities carrying out this procedure. As such, this remains both an international and domestic area of interest.

GHDB is currently funding a study to measure the health and psychological impact of FGC in West African immigrant females now living in New York City, as well as the knowledge, attitudes and practices regarding FGC among health professionals caring for these patients. The long-term aims of this project are to identify ways to improve interactions with the health care system including the development of evidence-based approaches for providing culturally sensitive, effective interventions.

A second research project is investigating the factors that contribute to an increased risk of developing chronic sexual pain among circumcised Somali American women living in Minnesota. The overall goal is to gather information that may be used by mental health and medical professionals to provide culturally sensitive and empirically informed health care.

Menstruation: Science and Society. (September 20-21, 2018, Bethesda, Maryland). The goal of this meeting was to discuss promising new discoveries and avenues of research surrounding menstruation; speakers and attendees included leaders in the field with expertise in endometrial biology, smart technologies/apps and mHealth platforms, and health literacy and dissemination frameworks. The meeting encompassed both insights provided by the normally functioning endometrium, as well as the potential of diagnostics for abnormal functioning and disease. Importantly, the meeting incorporated the science of menstruation with the broader societal implications of that process, including the unique considerations necessary in menstrual health communications, population health research, and public health outreach both in the United States and internationally. Manuscripts from the meeting will be published this year.

Recent Achievements in International Health

N/A/

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Lisa Halvorson
lisa.halvorson@nih.gov
301-480-1646

Intellectual and Developmental Disabilities Branch (IDDB)

Mission

The IDDB sponsors research and research training aimed at preventing and ameliorating intellectual and related developmental disabilities. The branch has a longstanding history of providing support for a diverse portfolio of research projects, training programs, and research centers dedicated to promoting the well-being of individuals with intellectual and developmental disabilities (IDD). When the institute was created in 1962, at the request of then-President John F. Kennedy and with the support of Congress, one of its primary charges was to encourage investigations in human development throughout the lifespan, with an emphasis on understanding IDD.

The mission of the IDDB is to support a program of research in IDD, including common and rare neuromuscular and neurodevelopmental disorders, such as Down, Fragile X, and Rett syndromes, inborn errors of metabolism, autism spectrum disorders (ASD), and conditions currently and soon-to-be detectable through newborn screening. The IDDB has a long and respected history of providing support for a diverse portfolio of research projects, contracts, training programs, and research centers dedicated to promoting the well-being of individuals with IDD at all stages of development. Research priorities for the branch include the following: (1) Understand the etiology of IDD; (2) Understand the complexity of comorbid symptoms; (3) Improve screening and early diagnosis and develop early interventions and treatments; (4) Study natural history and neurobiological and behavioral transitions; (5) Develop appropriate, valid biomarkers and preclinical and clinical outcome measures; and (6) Support translational and implementation research.

IDD is not limited by geographic or national boundaries, though the factors that may lead to IDD such as genetics, environmental exposures, or availability of clinical care can vary from one country/region to another. The IDDB supports a portfolio of research and conference grants that serve to identify the prevalence of IDD in LMICs and to develop strategies for reducing the burden of these disorders in the population. As infant mortality falls in these countries, there is an increased need to develop interventions to prevent and ameliorate IDD.

Household air pollution due to incomplete combustion of solid cooking fuels traditionally used for cooking and heating is a leading cause of death and disability worldwide, with the highest risks for women and children due to their domestic roles. NICHD has served a leadership role in developing a research agenda to improve women's and children's health outcomes. The IDDB is currently coordinating NICHD activities on cookstove-related household air pollution.

Major International Initiatives over the Past Year

Gene and Variant Curation. The branch support studies to identify the genetic causes underlying many IDDs. With advances in genomic sequencing technologies, clinical genetic testing is becoming increasingly routine in clinical practice both in the United States and internationally. However, genome-scale sequencing is leading to the identification of many genomic variants with unknown significance, potentially leading to inappropriate medical interventions. In partnership with the Clinical Genome Resource (ClinGen) funded by the

National Human Genome Research Institute, NICHD has initiated a program that brings together international panels of experts to identify the genes and genomic variants associated with the pathogenicity of conditions of high importance to NICHD. Three expert curation panels have been funded that include international experts from the United States, UK, Italy, Germany, France, Australia, and the Netherlands.

Down Syndrome. DS-Connect®: The Down Syndrome Registry, is an online, secure registry to promote sharing of health information that will advance research to benefit individuals with Down syndrome and their families. Sponsored by the NICHD-led Down Syndrome Consortium, the registry was created by the NIH under NICHD leadership to connect families with researchers on projects of shared interest. DS-Connect® has attracted over 4,700 registrants in the United States and abroad and has supported recruitment for nearly two-dozen research projects through its membership. International partners include Down Syndrome International, T21RS, Jérôme Lejeune Foundation, and International Mosaic Down Syndrome Association, who are active members of the Down Syndrome Consortium and have promoted the registry worldwide. A Spanish translation of the website is available to increase the registry's outreach to Spanish-speaking families within the United States and in Latin America. DS-Connect® has a responsive web design to facilitate access on a wide variety of mobile platforms. Recently, DS-Connect also launched a Medication Tracker, to help inform research and to inform future clinical drug trials, participants can enter information about medication and supplement use in people with Down syndrome.

A collaboration between investigators in the United States and Canada is comparing longitudinal early brain development in infants and school aged children with Down syndrome, other developmental disabilities (ASD and Fragile X syndrome), as well as typically developing infants and children. The study is utilizing magnetic resonance imaging (MRI) to compare changes in brain structures with the goal of eventually identifying therapeutic targets for intervention for individuals with Down syndrome.

Understanding the Long-Term Outcomes of In Utero Zika Virus Exposure. The extensive outbreak of Zika in Brazil and its devastating impact on infants exposed in utero has left vulnerable families facing the long-term implications of raising a child with potentially severe and limiting disabilities. There is an urgent need for longitudinal surveillance of affected infants and their families. A new collaboration between the United States and Brazil is undertaking a comprehensive longitudinal study of infants with congenital Zika syndrome and their families to investigate early childhood development, potential treatment, and family adaptation. This project has the potential to fill the knowledge gaps about the developmental course of congenital Zika syndrome, the treatment needs of children, and supports needed by family caregivers.

Recent Achievements in International Health

Brain Disorders in the Developing World: Research across the Lifespan Initiative. IDDB participates in this FIC-led initiative to enhance research to ameliorate IDD in LMICs. A collaboration between the Democratic Republic of Congo and the United States funded under this initiative is evaluating the effectiveness of adding an early childhood development

intervention that will better sensitize mothers to their children's development to a proven method for detoxifying cassava in the Democratic Republic of Congo. Cyanide levels in cassava have been shown to lead to Konzo, a disease in which children exhibit neurodevelopmental delay that poses a serious public health threat in central and western Africa. This study will determine whether the combination of these two interventions will lead to better neurocognitive outcomes in the children.

A collaboration between the United States and Uganda is undertaking a clinical trial to evaluate the effectiveness of hydroxyurea as a treatment to prevent cognitive defects in children with sickle cell vasculopathy in Uganda. The trial is based on findings from a NICHD funded pilot study that showed that children in Uganda are particularly vulnerable to brain injury due to the combination of sickle cell disease, anemia, malnutrition, and infection.

While mortality from premature births in Sri Lanka has decreased by 50 percent, the survivors are at risk for epilepsy and developmental disorders that are unrecognized due to difficulties in accessing medical services. This collaboration with Sri Lanka will perform a proof-of-concept study by adapting mobile health technologies to transfer ambulatory electroencephalogram (EEG) and evoked potential recordings data performed remotely to a central hub for analysis. This will expand care for children with neurological disorders related to premature birth.

A longstanding prospective cohort study is seeking to quantify the progression of Fragile X-Associated Tremor Ataxia Syndrome (FXTAS) through repeated longitudinal assessment of biomarkers and clinical outcomes and to ascertain whether there is any correlation between *FMR1* CGG repeat size and the rate of clinical progression of FXTAS manifestations. This is a critical unanswered question in the field of FXTAS and *FMR1* research. Although the largest cohort of participants is being recruited in the United States, this project includes an independent validation sample of individuals being recruited by research collaborators at La Trobe University in Melbourne, Australia. The use of this independent validation sample will help to increase the generalizability of their clinical findings across multiple diverse populations.

Rare Diseases Research. Many rare disorders are first manifest during childhood and can lead to lifelong disability and early death. IDDB participates in the National Center for Advancing Translations Sciences Office of Rare Diseases Research-led Rare Diseases Clinical Research Network. This network promotes clinical trial readiness by supporting natural history, biomarker development and outcome measure studies, as well as pilot treatment studies in partnership with researchers, clinical practitioners, patient groups, and industry. The branch provides support for the Urea Cycle Disorders, Sterol and Isoprenoid Disorders, the North American Mitochondrial Disease, and the Brittle Bone Disease Consortia, all of which have international sites in Canada and Europe.

The branch supports an international collaboration on Wolfram syndrome, a rare neurodegenerative disease first appearing in children with early onset diabetes, optic nerve atrophy, and deafness and death in early-mid adulthood. With the identification of the causative gene, the investigators have discovered a broader range of phenotypes. The research team has established a partnership with the UK to increase the number of children enrolled in the study to

better understand both the neuropathophysiology of this disorder and to identify potential targets for brain-specific interventions.

Cookstove-Related Achievements

- NICHD is partnering with the National Heart, Lung, and Blood Institute (NHLBI), National Cancer Institute (NCI), NIEHS, the NIH Common Fund, and the BMGF to support a randomized controlled trial of introducing liquefied petroleum gas cookstoves in India, Guatemala, Peru, and Rwanda. Primary outcomes include low birth weight, pneumonia, and linear growth in children as well as blood pressure in the mothers. A biomarker study is being integrated with the clinical trial to explore the relationship of Household Air Pollution (HAP) exposures to health outcomes. Markers will include those relevant to HAP and second-hand smoke exposures and indicators of non-communicable disease. This study represents the first large-scale field trial utilizing clean liquefied petroleum gas cookstoves. In addition, emphasis will be placed on behavioral and economic aspects of cookstove adoption in these countries (Branch: IDDB).
- In a study of 37,870 pregnant women in six of the sites in the Global Network for Women's and Children's Health Research (see the Pregnancy and Perinatology Branch [PPB] section of this document), women who lived in households using polluting fuels were 15 percent more likely to have a low birth weight baby than those living in households using clean fuels. This risk was over and above other risk factors for having a low birth weight baby (Branch: PPB).
- In a second study of 62,111 pregnant women in the same six Global Network sites, women living in households using polluting fuels were 45 percent more likely to have a stillborn baby or baby who died in the first 7 days of life (perinatal mortality) than women living in households using clean fuels. This risk was also over and above other risk factors for perinatal mortality (Branch: PPB).

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Danuta Krotoski
Krotoskd@mail.nih.gov
301-496-5576

Maternal and Pediatric Infectious Disease Branch (MPIDB)

Mission

MPIDB supports domestic and international research, and sponsors NIH research training and career development programs related to the epidemiology, diagnosis, clinical manifestations, pathogenesis, transmission, treatment, and prevention of HIV infection and its complications in infants, children, adolescents, and pregnant and nonpregnant women. As the HIV epidemic has evolved and other infectious diseases have emerged in the United States and globally, the branch has ensured that its funded research reflects these changes and addresses important research opportunities and gaps as they arise, including HIV-associated co-infections such as TB, hepatitis, and malaria.

To meet the needs and ongoing challenges of other significant infectious diseases, MPIDB coordinates research on tropical diseases and congenital infections, such as Zika virus and cytomegalovirus, and vaccine-preventable diseases in infants, children, adolescents, and women.

The branch supports research projects in 56 countries through grants, cooperative agreements, and contracts.

Major International Activities over the Past Year

Identification of Birth Defects Possibly Related to Dolutegravir Treatment of Pregnant Women. In May 2018, a possible association was identified between NTDs involving the brain, spine, and spinal cord in babies born to women infected with HIV who were treated with dolutegravir, an antiretroviral drug of the integrase strand transfer inhibitor class. Preliminary results from an ongoing NICHD-funded observational study in Botswana indicated that women who received dolutegravir at the time of becoming pregnant appeared to be at higher risk for these defects. MPIDB helped to develop and coordinate some of the cautionary statements issued by the HHS Antiretroviral Treatment Guidelines Panels, FDA, European Medicines Agency, CDC, U.S. President's Emergency Plan for AIDS Relief (PEPFAR), and the WHO while further investigation is pursued. Those efforts include the creation of an interagency workgroup to coordinate opportunities internationally for evaluating the possible association between dolutegravir and NTDs, and reproductive toxicity studies in animal models to rapidly evaluate dolutegravir potential to cause NTDs. The findings from this ongoing study were presented at the 10th International AIDS Society Conference in Mexico City in 2019, noting although the difference in risk for children born to women on dolutegravir since conception (0.2%) is small, it is still significant to the fields of maternal and child health and HIV/AIDS. This study was also published in the *New England Journal of Medicine*.

Prevention and Treatment through a Comprehensive Care Continuum for HIV-affected Adolescents in Resource Constrained Settings (PATC^{3}H) (RFA-HD-18-032). MPIDB/NICHD issued this request for applications (RFA) for fiscal year 2018, in collaboration with the National Institute on Minority Health and Health Disparities and the NIH Office of Behavioral and Social Science Research. These eight newly funded, large cooperative agreements support research projects in South Africa, Kenya, Nigeria, Uganda, Zambia, Mozambique, and Brazil are aimed at

preventing HIV infection among youth at-risk and maintaining their HIV-negative status. They also seek to enroll youth with HIV into treatment studies to improve their health and prevent transmission to others. As a collective, the projects in PATC^{3}H aim to improve the numbers of adolescents in resource-limited settings who achieve successful outcomes across the entire HIV prevention and care continuum. Investigators have established relationships with clinical sites and national programs that have expertise in conducting research studies and in providing care for these vulnerable adolescents. Through the engagement and leveraging of multilateral relationships with local and national stakeholders, the foundation is in place for possible scale-up and sustainment of rolling out interventions in these regions should they be found effective and will maximize the impact on public health. For more information, visit the PATC3H website: https://www.patc3h.org/SitePages/Home.aspx.

The NICHD International and Domestic Pediatric and Maternal HIV Clinical Trials Network (NICHD Network). Since 1988, the NICHD Network has conducted clinical trials in infants, children, adolescents, and women, including pregnant women, with the goal of answering specific questions regarding the treatment, prevention, and persistence of HIV. This Network was responsible for the first domestic trial in children with HIV and the prevention of bacterial infections. Now, NICHD funds 17 domestic sites including Puerto Rico and 13 international sites in five countries: Brazil, Kenya, Tanzania, Peru, and Thailand. Through collaborations with the National Institute of Allergy and Infectious Diseases (NIAID), NIMH, CDC, and other international partners, the NICHD Network has been able to conduct HIV-related trials including but not limited to the International Maternal Pediatric Adolescent AIDS Clinical Trials Network, AIDS Clinical Trials Group, and the Tuberculosis Trials Consortium.

International Epidemiologic Databases to Evaluate AIDS (IeDEA). IeDEA, co-funded by NIAID, NICHD, NIMH, NIDA, and NCI, supports regional data centers in Africa, Asia, and North and South America to collect data on HIV-infected individuals receiving clinical care. NICHD plays a critical role in funding a maternal and pediatric component of IeDEA in four regions in Africa, as well as the Asia-Pacific and South America/Caribbean regions. Within these databases, data pertaining to over 180,000 children living with HIV have been collected and serve as an example for how such data can enable large multiregional studies to evaluate the effect of HIV and its treatment on children in resource-limited countries. Furthermore, these data continue to inform the Joint United Nations Programme on HIV/AIDS estimates of the global pediatric HIV epidemic. Data from IeDEA pediatric analyses were critical to informing the WHO guidelines on pediatric treatment.

Active International Initiatives

In addition to the activities and initiatives mentioned above, several research grants are evaluating the effects of HIV, its treatment, and potential remission, as well as other important co-infections such as malaria, hepatitis, and TB, in children, adolescents, and pregnant and non-pregnant women. These international studies are occurring in several countries, including Brazil, Botswana, Kenya, Malawi, Mozambique, Nigeria, South Africa, Thailand, Uganda, Zambia, and Zimbabwe. Examples of some of these studies include:

- MPIDB/NICHD in collaboration with FIC, other NIH institutes, and Office of the Global AIDS coordinator released the RFA **"Adolescent HIV Prevention and Treatment**

Implementation Science Alliance (AHISA)" in fiscal year 2016. The RFA provided supplementary funding to existing NIH grants that could advance the effective use of evidence and help overcome implementation challenges related to prevention, screening, and treatment among adolescents with HIV in sub-Saharan Africa. Grants were awarded to projects in the following sub-Saharan African countries: Kenya, Ghana, Nigeria, Malawi, Tanzania, Uganda, Zambia, Rwanda, Zimbabwe, South Africa, and Botswana. This ongoing collaboration continues to inform factors driving uptake and adherence to HIV prevention and treatment strategies for adolescents and inform policy through evidence and data. AHISA convenes a forum as a platform for collaboration among implementation scientists and other stakeholders focused on HIV in adolescents.

- **Interaction of HIV and Neurodevelopment of Children in Resource-Limited Settings: Improving Assessment (RFA-HD-18-019, RFA-HD-18-020).** MPIDB/NICHD issued this RFA for fiscal year 2018. Three awarded grants are investigating neurodevelopment assessment in South Africa, Tanzania, and Botswana. The widespread implementation of combination antiretroviral therapy for HIV prevention and treatment has changed the presentation, manifestation, and course of development and impairment in children, globally, but especially in resource-limited settings most severely affected by HIV. The importance of non-invasive assessment of child cognitive development using neuropsychological approaches is necessary for the monitoring of normally developing achievement, as well as emerging and continuing cognitive deficits related to HIV and its treatment.
- **Evaluation of the Latent Reservoir in HIV-Infected Infants and Children with Early Antiretroviral Therapy and Virologic Control (RFA-HD-14-026).** In support of the NIH Office of AIDS Research 2015 scientific research priority that targets cure (elimination or functional cure) of HIV infection, this RFA solicited studies of the latent reservoir in HIV infected children who have had early treatment (ART initiated before 6 months of age) and have had continuous viral suppression. One of the grants through this RFA is an international clinical trial of very early treatment (within 48 hours of birth) of HIV-infected infants in Johannesburg, South Africa, assessing whether this early treatment initiation results in remission of HIV and will include careful and sophisticated evaluations of immunological responses. Other studies range in geographic location, including early treated Thai children, and scientific breadth, including an infant macaque study.
- **Safety and Effectiveness of Triple Antiretroviral Drug Strategies for Prevention of Mother-to-Child Transmission (MTCT) (RFA-HD-14-027).** This RFA solicited R01 grant applications to evaluate the safety and overall population-based effectiveness of implementation of triple antiretroviral (ARV) drug strategies for prevention of MTCT in resource-constrained settings. This area includes a range of research issues, including overall long-term transmission and HIV-free survival rates for infants, and long-term health of the mother; acceptability and adherence to the regimens; linkage to care and retention of the mothers and infants; optimal service organization and comparison of models of ARV drug delivery and monitoring; issues of adverse pregnancy outcome including birth defects, preterm delivery, stillbirth, low birth weight; surveillance for drug resistance; and cost-benefit analysis and impact on overall country ARV programs. With PEPFAR providing additional funding for one grant, eight grants were awarded for

research in six African countries: Botswana, Kenya, Malawi, South Africa, Uganda, and Zimbabwe. Grantees are continuing to address the full range of research priority areas in the RFA, from evaluating birth outcomes with in utero ARV exposure, different innovative methods to promote maternal ART adherence and retention of mothers/infants in care, and population-based studies to look at long term effectiveness of maternal ART strategies for prevention of MTCT and maternal health.

- **Increasing Access and Uptake of HIV Testing and Counseling and Appropriate HIV-Related Services for Adolescents in LMICs (RFA-HD-15-017).** MPIDB/NICHD in collaboration with NIAID, NIDA, and NIMH issued this internationally focused RFA in fiscal year 2015. The aim of the RFA was to solicit R01 grant applications for implementation science projects that will provide results to directly inform HIV prevention and care service-delivery programs for HIV-infected and at-risk, uninfected adolescents in resource-limited settings to increase their impact, efficiency, and sustainability. Grants were awarded for studies in Bulgaria, Kenya, Tanzania, and Zimbabwe. Grant recipients are evaluating early detection and engagement in HIV care, community interventions for HIV testing and care linkages, sexual risk behaviors, and social media messaging for HIV testing.
- **HIV-Infected Adolescents: Transitioning from Pediatric to the Adult Care Settings RFA-HD-16-033, RFA-HD-16-034).** Issued by MPIDB/NICHD in fiscal year 2016, this RFA is currently funding active projects. For individuals with HIV emerging as young adults, one of the most challenging obstacles to preventing poor health outcomes is transition from pediatric to adult HIV care programs. The four awarded grants offer a range of approaches and geographical locations (Kenya, Thailand, Malawi, South Africa, United States) on transition of HIV-infected youth to adult care with the goal of developing an evidence base to support guidelines applicable to low, middle and high-income countries. Transitioning from pediatric to adult care has been identified as a high-priority scientific research theme in the NICHD Strategic Plan.
- **Understanding and addressing the multilevel influences on uptake and adherence to HIV prevention strategies among adolescent girls and young women (AGYW) in sub-Saharan Africa (RFA-MH-17-550, RFA-MH-17-555, RFA-MH-17-560).** MPIDB/NICHD issued this RFA for fiscal year 2017, in collaboration with NIMH. The goals are to: 1) enhance our understanding of the multilevel factors that influence HIV prevention strategy use; and 2) develop and test novel interventions to address these factors and enhance the uptake and adherence to HIV prevention strategies, both among AGYW in sub-Saharan Africa. In 2017, the NIH funded 11 grants in response to these companion RFAs, with the research taking place in Kenya, South Africa, Tanzania, Uganda, and Zimbabwe. The investigative, multidisciplinary teams on the grants are addressing a wide range of issues affecting AGYW including involvement in sex work, gender-based violence, and stigma by healthcare professionals. Different approaches are being evaluated to determine how to increase uptake and adherence to HIV prevention strategies including the evaluation of a risk screening tool, counseling using behavioral economic principles, pre-exposure prophylaxis (PrEP) knowledge, and peer-networks.
- **U.S.-South Africa Program for Collaborative Biomedical Research (RFA-AI-19-022, RFA-AI-19-023, RFA-AI-19-024, and RFA-AI-19-025).** Since the inception of this

program in 2013, this series of RFAs has solicited R01, R21, and U01 grants to establish this binational program for collaborative research in the areas of HIV/AIDS, TB, and cancer with funding also provided by the South African Medical Research Council. The first round of awards included NICHD grants in maternal and pediatric HIV and in TB. Now entering Phase 2, NICHD is one of five institutes participating in this program to continue collaborations amongst U.S., South African, and other African countries' investigators.

International Health and Data and Biospecimen Sharing

The NICHD Data and Specimen Hub (DASH) offers de-identified data from NICHD-supported clinical research on a variety of topics. As a resource for collaboration and discovery, DASH includes six studies funded by the branch with data from international sites; biospecimens are also available from the four NICHD International Site Development Initiative (NISDI) studies.

- Phase III Randomized Trial of the Safety and Efficacy of Three Neonatal Antiretroviral Regimens for Prevention Of Intrapartum HIV-1 Transmission (HPTN 040/P1043)
- A Prospective, Observational Study of HIV-Infected Pregnant Women and HIV-Exposed, Uninfected Children at Clinical Sites in Latin American Countries (NISDI LILAC)
- A Prospective, Observational Study of HIV-Exposed and HIV-Infected Children at Clinical Sites in Latin American and Caribbean Countries (NISDI Pediatric)
- A Prospective, Observational Study of HIV-Infected Pregnant Women and Their Infants at Clinical Sites in Latin American and Caribbean Countries (NISDI Perinatal)
- NISDI Pediatric Latin American Countries Epidemiological Study: A Prospective, Observational Study of HIV-infected Children at Clinical Sites in Latin American Countries (NISDI PLACES)
- Novel Strategies to Prevent Malaria and Improve Maternal-Child Health in Africa (PROMOTE II) - Prevention of Malaria in HIV-uninfected Pregnant Women and Infants - Birth Cohort 3 (PROMOTE BC3)

Staff Membership on Global Health Committees/Working Groups

- WHO Paediatric Antiretroviral Drug Optimization and Paediatric Antiretroviral Working Groups. Member: Dr. Rohan Hazra
- WHO Working group to develop PrEP implementation module for adolescents. Member: Dr. Bill Kapogiannis
- Scientific and Technical Advisory Committee for the International AIDS Society Collaborative Initiative on Pediatric HIV Research. Member: Dr. Rohan Hazra

Point-of-Contact

Dr. Rohan Hazra
hazrar@mail.nih.gov
301-435-6868

Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB)

Mission

The overarching goal of the OPPTB is to support pediatric and obstetric pharmacology efforts, including: 1) identifying, prioritizing, and sponsoring basic, translational, and clinical research and research strategies to improve understanding of interactions between therapeutics, disease, pregnancy, and development; and 2) facilitating training and other educational modalities that enhance pediatric and obstetric pharmacology expertise, as well as skills in reproductive, perinatal, and pediatric and obstetric pharmacoepidemiology.

Major International Initiatives over the Past Year

Pediatric Trials Network (PTN). As part of the Best Pharmaceuticals for Children Act (BPCA) initiative, the OPPTB sponsors clinical trials of drugs and other therapeutic approaches (including devices) used with children and adolescents. The PTN has developed international collaborations with clinical sites in Canada, Israel, Singapore, Australia, Japan, and the UK to conduct clinical studies as part of the BPCA. Currently, the international sites are participating in clinical studies that evaluate pharmacology data on children receiving standard-of-care treatments for various diseases.

Development of Global Pediatric Clinical Trials Network. Several meetings were held to discuss the formation of a global pediatric clinical trials network formed with industry, academia, U.S. federal government agencies (including NIH and FDA), and the European Medicines Agency. Through the resulting funding announcement (RFA-FD-17-014), the FDA made awards to Duke University and the Institute for the Advancement of Clinical Trials in Pediatrics (I-ACT) in September 2017.

International Neonatal Consortia. The International Neonatal Consortia was formed under the FDA's Critical Path Initiative with NICHD representation on the Steering Committee. Discussions on neonatal drug development in several specific areas are underway. Many nations are represented in this consortium such as: Canada, England, Japan, and France among others.

Collaboration with the European Pediatric Formulations Initiative (EU PFI) and U.S. Pediatric Formulations Initiative (US PFI). There is a need to improve the availability of pediatric formulations. This collaboration between the EU PFI and the US PFI discusses needs and potential solutions to this unmet need.

International Rare Diseases Research Consortium (IRDiRC). The IRDiRC is a consortium of research funding agencies, NIH among them, and other interested parties acting to accelerate research through these collaborations. Countries involved in the consortium include Australia, Canada, Germany, and Finland, as well as many others.

Opioid Use in Pregnancy. The OPPTB supports a population-based cohort study to assess the risks associated with exposure to opioids in pregnancy and examine adverse pregnancy

outcomes possibly associated with such exposure including specific birth defects, preterm birth, small for gestational age birth, and stillbirth. This study includes the entire pregnancy population with information linked to electronic health records in Ontario, Canada.

A Clinical Trial of Praziquantel in Children with Schistosomiasis. A phase II PK/PD dose finding trial investigates Praziquantel use in children younger than age 4 in Uganda and the Philippines, both with high prevalence of intestinal schistosomiasis.

Direct Quantitation of the Circulating Mycobacterium Tuberculosis Peptides for Improved Pediatric TB Diagnosis and Management. Diagnosing pediatric TB and evaluating its rapid response to pharmacotherapy is extremely challenging given the difficulties obtaining necessary samples, and the poor diagnostic value of the samples. Early detection is critical in reducing morbidity and mortality, while treatment monitoring may identify children who would respond better to novel treatment regimens minimizing side effects and treatment duration. The OPPTB has funded a study to develop a rapid blood assay for both diagnosis and treatment monitoring of active TB in children. The results generated from this project will lead to the development of a novel tool to monitor response to TB treatment and potentially guide duration of treatment. The proposed research aims will be accomplished through international collaboration with well-known TB clinical investigators at the Stellenbosch University, Western Cape, South Africa.

Recent Achievements in International Health

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

- European Medicines Agency (to develop a safety database for excipients used in pediatric formulations): Dr. George Giacoia.
- Steering Committee of the International Neonatal Consortia. Member: Dr. George Giacoia (represents NIH)
- European Society for Developmental Perinatal and Pediatric Pharmacology: Dr. George Giacoia (invited member)

Point-of-Contact

Dr. Aaron Pawlyk
aaron.pawlyk@nih.gov
301-451-7299

Pediatric Growth and Nutrition Branch (PGNB)

Mission

As the focal point within NICHD for extramural research and research training in nutrition science and pediatric endocrinology, PGNB supports research to understand basic, translational, and clinical aspects of pediatric endocrinology, growth and development, and how nutrition promotes healthy growth and development from pregnancy through adolescence.

The mission of PGNB is to foster and cultivate biomedical research in pediatric endocrinology, growth and development, and nutrition to advance scientific understanding and promote health. The branch is also committed to the development and training of investigators pursing research in branch-relevant areas, as well as supporting SBIR and small business technology transfer (STTR) programs in branch-relevant areas. To carry out this mission, the branch engages with and supports investigators and helps identify gaps and opportunities for scientific advancement, and supports research aimed at understanding the mechanisms of growth and development at the gene-molecular level and at higher levels of cell and organ function.

Areas of coverage include:

- Determining the role of nutrition throughout the life cycle, with an emphasis on the needs of women of reproductive age (including pregnant and lactating women), preterm and term infants, and children through adolescence, to promote health, optimal growth and development and to prevent disease
- Exploring the role of nutrients within specific biological systems, e.g., reproduction, immune function, and neurodevelopment (including cognition and behavioral development)
- Elucidating the interactive roles played by nutrients and hormones in growth and development of the central nervous system and its interactions with the gastrointestinal tract
- Determining the roles played by lactation and breastfeeding in infant nutrition, including studies of the non-nutrient/bioactive components of human milk and their roles in infant health, with an emphasis on the immunologic properties of human milk, the intestinal microbiome, and the role of human milk in protecting against infections and enteric diseases
- Improving our understanding of the biological antecedents and sequelae of childhood obesity as well as the nutritional and developmental origins of health and disease
- Identifying biomarkers and bioindicators of nutrient status
- Elucidating the role of specific nutrients in the neuroendocrine basis of linear growth and the onset of puberty, including studies of growth failure and precocious and delayed puberty
- Ascertaining the genetic, nutritional, and hormonal antecedents of bone health and the early origins of skeletal disorders with an aim to developing preventive strategies

- Determining and preventing the effects of hypo- and hyperglycemia on growth and development in children with diabetes
- Elucidating the molecular drivers of adverse intrauterine environments to prevent the development of obesity, insulin resistance, type 2 diabetes, and cardiovascular disease in individuals exposed to either overnutrition or undernutrition in utero

Previous Major International Initiatives

In addition to an active portfolio of investigator-initiated grants, PGNB staff has developed programs to address specific high-priority and mission-relevant issues.

Trial to Reduce Type 1 Diabetes (T1DM) in the Genetically at Risk (TRIGR). This trial was the first large international effort designed to ascertain if a simple nutritional intervention during infancy can delay or prevent the onset of T1DM in children with high genetic risk for the disease. The intervention consisted of being weaned from the breast to either standard cow milk-based infant formula, or a highly hydrolyzed casein-based formula. The rationale for this study is that the intestines of infants prone to T1DM are more permeable to foreign proteins than the intestines of infants who are not susceptible to T1DM. By supplying amino acids instead of proteins, the exposure to foreign antigens is greatly reduced, thus protecting the infant from developing a state of autoimmunity which leads to diabetes. This randomized controlled trial enrolled 2,159 genetically susceptible infants in 14 countries in addition to the United States. The primary outcome was the prevalence of T1DM in the two groups in 2017, when the last of the infants to be enrolled reached his or her tenth birthday. Autoantibodies to islet cells were measured annually, and an oral glucose tolerance test was administered when each child turned 6 years old and then again at age 10.

Studies in Other Networks and Researcher-Initiated Activities

Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. The goal of this study was to better understand the pathologic effects of levels of glycemia within what is generally considered to be the normal range in pregnant women: fasting plasma glucose levels of 70-104 mg/dL. The study examined the relationship between the glycemic state of women and their rates of cesarean section when both the women and their caregivers were blinded to the women's level of glycemia. This international study in eight countries in addition to the United States has enrolled more than 25,000 pregnant women and administered oral glucose tolerance tests to them during their second trimesters. Other outcomes of interest are macrosomia of the infants, hyperinsulinemia in the cord blood of the infants, preeclampsia in the mothers, and infant hypoglycemia. An important finding of HAPO is that the rate of preeclampsia quintuples, from 3 percent to 15 percent over the range of fasting plasma glucose noted above. The rates of operative delivery doubled from 13 percent to 26 percent over the same range of glycemia, despite the blinding. NICHD and the National Institute of Diabetes and Digestive and Kidney Diseases are collaborating on a follow-up study of the offspring of the women in this study to ascertain rates of obesity, beta cell failure, type 2 diabetes, and metabolic syndrome.

Genetic and Environmental Influences on the Metabolic Syndrome. This study follows 2,000 twin pairs in Anqing, China, to ascertain genetic vs. environmental factors that may impact body

composition and the development of metabolic risk factors. The twins were initially assessed at 6 to 21 years of age and are being examined again at 12 to 27 years of age. The large sample size and twin study design will yield significant information on the epidemiology of the metabolic syndrome.

The PGNB portfolio also reflects a historic leadership role in the effort to address micronutrient malnutrition by supporting numerous trials (in sites throughout Africa, Asia, and South America) to assess the importance of single and multiple micronutrient interventions in health and disease. Specific focal points include the importance of iron to cognitive and neurological development, the role of zinc and vitamin A in diarrheal and other infectious diseases, an expanded understanding of vitamin D biology not only for bone health but other critical biological systems, and the potential role of single or multiple micronutrient interventions for prevention, care, and treatment of HIV/AIDS.

International Partnerships

PGNB has established a close working relationship with the U.S. federal and global agencies involved in activities covering the breadth of the global food and nutrition enterprise. Agencies included in these partnerships are: the U.S. Department of Agriculture (USDA), CDC, FDA, USAID, U.S. Department of Defense, WHO, UNICEF, World Food Programme, the BMGF, and numerous other organizations and members of the private sector engaged in global efforts to address the role and impact of food and nutrition on global health.

Staff Membership on Global Health Committees/Working Groups

PGNB staff serves on numerous interagency committees involved in current and emerging efforts to address the role of nutrition in global health.

Point-of-Contact

Dr. Daniel Raiten
raitend@mail.nih.gov
301-435-7568

Pediatric Trauma and Critical Illness Branch (PTCIB)

Mission

PTCIB was established as a result of the institute's reorganization in 2012 to develop and support research and research training in pediatric trauma and critical illness. Priority areas of research include:

- Care and treatment of trauma and critical illness for pediatric populations
- Collaborative multidisciplinary research across the continuum of care
- Ethical issues related to the care of critically ill children and their families
- Interplay of physical and psychological trauma in children
- Multiple Organ Dysfunction Syndrome in critically ill children
- Prevention and treatment of life-threatening traumatic injuries in children

Major International Initiatives over the Past Year (funded projects)

Biological Pathways of Risk and Resilience in Syrian Refugee Children

This study, conducted at St. George Hospital University Medical Center, will investigate the biological underpinnings of individual differences in refugee children's response to acute war-related trauma exposure. Applying a modern multilevel perspective, the study aims to explore the intricate interplay between psychosocial, neuroendocrine, epigenetic, and genetic factors in the prediction of risk and resilience related to the experience of war in 1,000 8- to 16-year-old Syrian refugee children (and their primary caregivers) in Lebanon. A better understanding of how social, psychological, and biological factors contribute to the mental health of refugee children will be important in order to better protect war-affected children from the negative effects of political conflict and displacement, and to promote their psychological resilience.

Test of a Training Program That Uses Virtual-Reality Technology to Improve Children's Pedestrian Behaviors: A Randomized Controlled Trial (1R21HD093878-01A1)

Motor vehicle pedestrian injury is a critical issue for school children. Each year in the United States, over 4,900 pedestrians are killed and another 207,000 are injured, and about 25 percent of these pedestrian events involve school-age children. This research focuses on 7- and 8-year-olds, who constitute a high-risk group for pedestrian injury because, at these ages, children regularly cross streets without supervision, and they struggle both with selecting where to cross and determining how to cross. Research has shown, however, that they benefit from effective behavioral training in pedestrian behavior. The research addresses the issue of crossing skills deficits and will: (1) implement a randomized controlled trial to test two alternative training programs to teach the children where and how to cross streets safely; and (2) conduct an economic analysis to reveal cost-benefit indices for both programs. The results of these studies

will provide essential knowledge to inform future decisions about "best practices" in child pedestrian injury prevention through behavioral training.

Maternal Traumatic Stress and Child Development: Epigenetic Links

The broad goal of this work is to build capacity and provide preliminary resources to develop a research program to understand the influence of maternal trauma and posttraumatic stress on the development of brain and nervous system disorders of their offspring, in South Africa, with a focus on epigenetic mechanisms. This study is a collaboration between the Department of Psychiatry UCT, the Center for Molecular Medicine and Therapeutics at the University of British Columbia in Canada, the Department of Epidemiology at the Harvard School of Public Health, and the Department of Epidemiology at the Columbia University Mailman School of Public Health (CU-MSPH). The PIs will train South African partners in the bio-behavioral mechanisms, specifically epigenetic processes, via which maternal trauma and post-traumatic stress disorder (PTSD) impacts child development and collect preliminary data on such mechanisms in the Drakenstein cohort. The specific aims of this proposal are to Expand capacity of South African collaborators to investigate epigenetic mechanisms underlying the impact of maternal trauma and PTSD across generations by formal training, regular meetings, professional meetings, an annual scientific symposium, and research experience. This project capitalizes on the Drakenstein Child Study, a pregnancy cohort located at the UCT that aims to investigate longitudinally the epidemiology and etiology of childhood pneumonia and the impact on child health by following 1,000 mother-child pairs through pregnancy and for the first 2 years of life, with a planned data collection through age 7 years. The ultimate goal of this study is the development of a new program of research crucial to the well-being of future generations of South Africans.

Impact of Conflict on Mental Health and Risk Behaviors of Palestinian Youth

Conflict may seriously impact the health and wellbeing of young people not just through directly experienced trauma, such as beatings and the loss of a family member, but also less directly, through economic hardship, constraints on mobility and livelihoods, reduced access to health-related and other goods and services, lawlessness and insecurity, and breakdown of community cohesion and support. These "stressors" of conflict environments may significantly affect young people's mental health, their expectations for the future, and their engagement in risk behaviors. In order to appropriately target interventions to mitigate harm to youth, policymakers need information on effects of both trauma and indirect exposure to conflict. However, research on the effects of conflict on young people has largely been limited to consideration of direct conflict-related trauma on adolescents' mental health. Further, very little research has examined the impacts of conflict (whether through trauma or aspects of the conflict environment) on the future orientation and engagement in health risk behaviors of youth, a group that is especially vulnerable to such behaviors. This study tests an ecological model of the impacts of conflict on youth that encompasses both the broader conflict environment and direct exposure to violence, using unique representative data on Palestinian youth in the Occupied West Bank, an area of pervasive political violence and conflict-related disruptions to normal life. The survey contains information on mental health, risk behaviors (i.e., smoking, alcohol and drug use, sexual activity), future expectations, and direct exposure to

violence. Researchers will link the survey with multiyear, geocoded measures of aspects of the conflict environment in the West Bank, including barriers to mobility and events such as demonstrations and home demolitions. These linked data will provide a unique opportunity to understand the impacts of conflict environments, as well as direct experience of trauma, while providing specific insight into the vulnerabilities of Palestinian youth living under conflict, and potential measures to mitigate harm.

Neuropsychological and Genomic Signatures of Violence Exposure in Childhood

How do stressful experiences that happen in early life have such powerful direct effects on poor health decades later? When and how do these experiences become biologically embedded? To address these questions, researchers are following a 1994-1995 birth cohort of 2,232 twins from the E-Risk Study, a nationally representative 2-year birth cohort of same-sex twins born in England and Wales. Families were recruited to represent the UK population with newborns in the 1990s to ensure adequate numbers of children in disadvantaged homes and to avoid an excess of twins born to well-educated women using assisted reproduction. The cohort is well-characterized, environmentally and phenotypically, with assessments at birth, ages 2, 5, 7, 10, 12, and 18 years, and has a dedicated biobank. The research focuses on exposure to violence, one of the most common and severe sources of human stress. Researchers begin by compiling cumulative dossiers of violence exposure in childhood and adolescence, including child maltreatment, sexual abuse, domestic violence, peer victimization, dating violence, and conventional crime and then test the hypothesis: that young people who are exposed to violence in childhood and adolescence will, by young adulthood, show compromised neuropsychological functioning, telomere erosion, and differential expression, and that epigenetic regulation of genes involved in the coordination of the stress response and the regulation of immune and inflammatory reactions are affected. A key need in this research is for violence exposure to be disentangled from associated risk factors, including poverty, parents' mental health, and genetic liability.

Recent Achievements in International Health

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Valerie Maholmes
maholmev@mail.nih.gov
301-496-1514

Population Dynamics Branch (PDB)

Mission

PDB supports research and research training in demography, reproductive health, and population health. In demography, the branch supports research on the scientific study of human populations, including fertility, mortality and morbidity, migration, population distribution, nuptiality, family demography, population growth and decline, and the causes and consequences of demographic change. In reproductive health, the branch supports behavioral and social science research on STIs, HIV/AIDS, family planning, and infertility. In population health, the branch supports data collection and research on human health, productivity, behavior, and development at the population level, using such methods as inferential statistics, natural experiments, policy experiments, statistical modeling, and gene/environment interaction studies.

Data and Methods for Global Health

PDB has several programs promoting the data sharing of international data on human health, development, and productivity to the broad research community.

Data Archiving

The branch uses the standard R01 Research Project Grant mechanism to support documenting, archiving, and dissemination of many international datasets, making these resources available to the research community. Projects that curate multiple datasets also harmonize data across multiple countries and/or time periods and provide documentation in English, thereby substantially increasing the usability of these datasets. The multicountry and multitime-period datasets are crucial for identifying trends and differentials in population health and demographic characteristics and understanding the causes and consequences of these changes.

Dataset/Description	Countries	Grant	PI/Institution
Mexican Migration Project	Mexico, United States	R01HD035643	Massey, Douglas Princeton University
Latin American Censuses, Micro- and Metadata	Bolivia, Brazil, Colombia, Cuba, Ecuador, El Salvador, Jamaica, Mexico, Nicaragua, Paraguay, Peru, Puerto Rico, Saint Lucia, Uruguay	R01HD044154	Sobek, Matthew University of Minnesota
Eurasian Censuses, Micro- and Metadata	Bangladesh, Cambodia, Czech Republic, Fiji Islands, France, Hungary, India, Indonesia, Iran, Ireland, Israel, Kyrgyzstan, Palestine, Poland, Portugal, Republic of Korea, Romania, Spain, Vietnam, Armenia, Austria, Bulgaria, East Germany, Fiji, Germany, Mongolia, Nepal, Pakistan, Papua New Guinea, Russia, Switzerland, Thailand, Turkey, Turkmenistan, Ukraine, United Kingdom, and 7 others	R01HD047283	Cleveland, Lara University of Minnesota
Demographic and Health Surveys, Micro- and Metadata	Angola, Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo (Braz.), Congo Dem. Rep, Cote d'Ivoire, Egypt, Ethiopia, Gabon, Gambia, Ghana, Guinea, India, Jordan, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Morocco, Mozambique, Namibia, Nepal, Niger, Nigeria, Pakistan, Rwanda, Senegal, Sierra Leone, South Africa, Sri Lanka, Sudan, Swaziland, Tanzania, Togo, Tunisia, Uganda, Yemen, Zambia, Zimbabwe	R01HD069471	Boyle, Elizabeth University of Minnesota
Time Use Data for Health and Well Being	United States, Brazil, Mexico, Hungary, Italy, Germany, Pakistan, Republic of Korea, South Africa	R01HD053654	Hofferth, Sandra L. University of Maryland, College Park

PDB sponsored a program, open to all of NICHD, that promotes data sharing from projects supported by NICHD and that, if made widely available, would advance the scientific mission of NICHD. (See PAR-16-149: Archiving and Documenting Child Health and Human Development Data Sets [R03].) Many PDB grants funded through this program will make available data from international health and development research projects.

Dataset/Description	Country(ies)	Grant	PI/Institution
Indian Human Development Surveys	India	R03HD091315	Vanneman, Reeve University of Maryland, College Park
Impact of Microfinance on Health: Experimental Evidence	India	R03HD094985	Pande, Rohini Harvard School of Public Health
Integrating 30 Years of Settlement-Level Census Data for India	India	R03HD096193	Montgomery, Mark Randolph Population Council
Chitwan Valley Family Study	Nepal	R03HD092516	Axinn, William University of Michigan
Matlab Linked Database: 40-Year Archive of Health, Population and Development Data	Bangladesh	R03HD093987	Kuhn, Randall S. University of California, Los Angeles
Longitudinal Population-Based Data on HIV in Young Adulthood	Malawi	R03HD095690	Trinitapoli, Jenny A. University of Chicago
Fertility and Reproductive Health	United States, Uganda, Bangladesh	R03HD091468	Sully, Elizabeth Guttmacher Institute
Cross-National Equivalent Files: Health and Demographic Measures	United States, Germany, Canada, United Kingdom, Australia, Switzerland, Korea, Russia	R03HD091871	Lillard, Dean Ohio State University

Developing Methodology to Improve Global Health

PDB is at the forefront of supporting research to develop methodologies to project populations globally and to estimate fertility and mortality rates and disease prevalence in low-income countries (LICs) and LMICs that lack adequate vital registration systems and health information systems.

Dataset/Description	Country(ies)	Grant	PI/Institution
Population Projection—Estimating how Population Size and Composition Will Change in the Future	All countries	R01HD070936	Raftery, Adrian University of Washington
Estimating and Addressing Non-Sampling Error in Fertility Rates	LMICs	K01HD078452	McCormick, Tyler University of Washington
Developing a Standard, Automated Method to Assign Causes of Death Using Verbal Autopsy Data	LMICs	R01HD086227	Clark, Samuel Ohio State University

Dataset/Description	Country(ies)	Grant	PI/Institution
Developing Data Collection Tools to Improve the Quality of Survey Data on Neonatal Mortality	LICs in sub-Saharan Africa and South Asia/Elsewhere; validated in Guinea-Bissau	R21HD087811	Helleringer, Stephane Johns Hopkins University
Improving the Measurement of Adolescent and Adult Mortality in LICs	Bangladesh, Malawi, Uganda, Guinea-Bissau	R01HD088516	Helleringer, Stephane Johns Hopkins University
Identifying Disparities in Early-Life Mortality Among Population Subgroups, Examining Impact of Practices Aimed at Reducing Child Mortality	LMICs	K99HD088727	Ramos, Antonio University of California, Los Angeles
Improving Understanding of Age Patterns of Under-5 Mortality	LMICs	R01HD090082	Guillot, Michel University of Pennsylvania
Estimating Age- and Cause-Specific Child Mortality	LMICs	R21HD095451	Li, Liu University of Washington
Workshop on Migration Data and Analysis	Various	R25HD094676	Bloemraad, Irene University of California, Berkeley
Improving Statistical Methods for Small Area Estimates of Public Health Indicators and Demographic Characteristics	United States, United Kingdom	R01HD092580	Waller, Lance A. Emory University

Global Partnerships

Country/Major Foreign Institution	Grant	PI/U.S. Institution
Vietnam / Hanoi Medical University	R24HD056691	Hirsch, Jennifer Columbia University Health Sciences
South Africa / University of Cape Town	R24HD077976	Lurie, Mark Brown University

PDB currently supports two grants under the Global Partnerships for Social Science AIDS Research (R24), which supports collaborative grants between institutions in the United States, or other high-income countries, and research institutions in LMICs affected by the HIV/AIDS epidemic, with the goal of strengthening the research infrastructure of local institutions in LMICs and supporting small portfolios of research on HIV/AIDS. The partnerships supported are in Vietnam and South Africa; both involve a U.S. partner.

Scientific Pipeline

PDB supports the training and mentorship of young scientists interested in research in global health through its individual fellowships and individual career development awards.

Topic	Country(ies)	Grant	PI/Institution
Early Menarche and Reproductive Health	Ghana	F31HD089592	Ibitoye, Mobolaji Columbia University Health Sciences
Effects of Co-Resident and Non-Coresident Fathers and Grandparents on Child Growth and Cognitive Development	Chile	K99HD088751	Reynolds, Sarah University of California, Berkeley
Measuring and Identifying Disparities in Early-Life Mortality Among Population Subgroups, Examining Impact of Practices Aimed at Reducing Child Mortality	LMICs	K99HD088727	Ramos, Antonio University of California, Los Angeles**
Adolescent Fertility and Social Networks	Honduras	K01HD087551	Shakya, Holly University of California, San Diego
Intervention Research Addressing Reproductive Coercion Among Medically Underserved Female Adolescents	Mexico	K23HD084756	Servin, Argentina University of California, San Diego
Influence of Service Delivery Factors on Contraceptive Use	Kenya	R00HD086270	Tumlinson, Katherine University of North Carolina, Chapel Hill
Estimating and Addressing Non-Sampling Error in Fertility Rates	LMICs	K01HD078452	McCormick, Tyler University of Washington**
Health and Well-Being after Large Scale Shocks	Indonesia, Mexico	R00HD083519	Ho, Jessica Yu University of Southern California
Children's Health and Migration	Nepal	F32HD093145	Treleaven, Emily University of Michigan at Ann Arbor
Trends, Predictors, and Consequences of Child Undernutrition	India	F30HD091975	Soni, Apurv University of Massachusetts Medical School, Worcester
Biocultural Investigation of Maternal Adversity on Gene Expression and DNA Methylation in the Placenta	Democratic Republic of Congo	F30HD097935	Hsiao, Chu University of Florida

Topic	Country(ies)	Grant	PI/Institution
Contraceptive Side Effects, Method Dissatisfaction, and Early Discontinuation	Kenya	F31HD097841	Rothschild, Claire Watt University of Washington
Reproductive Coercion and Related Risk Factors	Niger	F31HD100019	Boyce, Sabrina Christine University of California, Berkeley

* Countries studied or applicable to

** See also Developing Methodology section

Supporting Offices of Research and Sponsored Programs

Country	Grant	PI/Institution
Uganda	G11HD085538	Kiweewa, Francis/Makerere University
Peru	G11HD088113	Chan, Michelle/Universidad Peruana Cayetano Heredia
Zimbabwe	G11HD088121	Kangwende, Rugare/Africa University

PDB supports the establishment and enhancement of Offices of Research and Sponsored Programs or similar entities at international institutions of higher learning through the Biomedical/Biobehavioral Research Administration Development Award (G11) program (PAR-14-333). Institutions in sub-Saharan Africa, India, and LMICs in the Caribbean and South America are eligible to apply. The branch currently supports programs in Zimbabwe, Peru, and Zimbabwe.

Additional International Research Projects

PDB supports international research on HIV/AIDS, other STDs, and other aspects of reproductive health. In addition, the branch also supports international research on the health of sexual and gender minority populations and on family dynamics and child health and development in international settings. Some of these grants are mentioned in the tables shown here.

Topic	Country(ies)	Grant	PI/Institution
Enhanced STI/HIV Partner Notification in South Africa	South Africa	R01HD074560	Kalichman, Seth University of Connecticut, Storrs
Causal Pathways to Population Health Impact of HIV Antiretroviral Treatment	South Africa	R01HD084233	Tanser, Frank Kwazulu-Natal Research Institute TB-HIV
Health Needs of First Generation-HIV Infected Adolescents	South Africa	R21HD089825	Harrison, Abigail Brown University
Young Africans' Changing Understandings of HIV/AIDS Risk	Burkina, Kenya, Nigeria, Senegal, Swaziland	R01HD085877	Winskell, Samantha Emory University
Integrating Counseling to Transform HIV Family Planning Services	Uganda	R01HD090981	Wagner, Glenn RAND Corporation

Topic	Country(ies)	Grant	PI/Institution
Addressing Disparities in HIV Testing and Care among Displaced Men who have Sex with Men (MSM)	Lebanon	R21HD089820	Heimer, Robert Yale University
Enhancing Male Participation in Interventions to Prevent Unintended Pregnancy	India	R01HD084453	Raj, Anita University of California, San Diego
Fathers' Time Spent with Sons and Daughters	India	R21HD094158	Luke, Nancy Pennsylvania State University
India Human Development Survey	India	R01HD041455	Desai, Sonalde University of Maryland, College Park
Promoting Condom Use among Women in Established Relationships	Vietnam	R01HD084637	Gallo, Maria Ohio State University
Improving the Reproductive Health of Families	Botswana	R01HD094512	St Lawrence, Janet Portland State University
Intimate Partner Coercion and Implications for Women's Health and Well-being	Bangladesh	R21HD093027	Yount, Kathryn Emory University
Multilevel Protective Factors for Lesbian/Gay/Bisexual (LGB) Youth in North America	Canada	R01HD078470	Eisenberg, Marla University of Minnesota
HIV Risk and Access to Health Care Among Mobile Populations	Mexico	R01HD046886	Martinez-Donate, Ana P. Drexel University
Factors affecting Food Choice and Childhood Health	Mexico	R03HD094019	Gracner, Tadeja Rand Corporation
Effects of Age at Marriage and Education on Health of Mothers and Children	Bangladesh	R01HD095189	Field, Erica M. Duke University
Male Absence Due to Migration and the Health of Left-Behind Wives in India	India	R03HD098377	Lei, Lei Rutgers, State University of New Jersey
Household Income at Birth and Child Health During Preschool	Indonesia	R03HD097425	Majid, Muhammad Farhan Rice University
Family Processes and Rural-Urban Migration Among Adolescents	Ghana	R21HD091534	Sensoy Bahar, Ozge Washington University
Intergenerational Impacts of Health Investments	Kenya	R01HD090118	Miguel, Edward Andrew University of California, Berkeley
Surviving an Epidemic: Families and Well-Being, Malawi 1998-2020	Malawi	R01HD087391	Kohler, Hans-Peter University of Pennsylvania

Topic	Country(ies)	Grant	PI/Institution
Adverse Childhood Experiences and Adolescent HIV Risk: Causal Inferences from a High HIV Prevalence Context	Malawi	R01HD090988	Kidman, Rachel State University of New York, Stony Brook
Prospective Determinants of Unintended Pregnancy and Its Health Consequences	Malawi	R03HD097360	Yeatman, Sara University of Colorado, Denver
Improving Perinatal Outcomes Using Conditional and Targeted Transfers	Nigeria	R01HD090231	Okeke, Edward N. RAND Corporation
Migration, Urbanization and Health in a Transition Setting	South Africa	R01HD083374	White, Michael J. Brown University
Training for Health Professionals	Tanzania	R01HD092655	Rosser, B.R. Simon University of Minnesota
Structural and Social Transitions Among Adolescents in Rakai	Uganda	R01HD091003	Santelli, John S. Columbia University Health Sciences
Population Dynamics in Africa: Selected Outcomes and Causes	Botswana, Burkina Faso, Cameroon, Kenya, Mali, Mozambique, Uganda, Zambia	R03HD098357	Gray, Clark University of North Carolina, Chapel Hill
Trends in the Stratification of Premarital Childbirth	Benin, Burkina, Cameroon, Cote d'Ivoire, Ghana, Kenya, Liberia, Madagascar, Malawi, Mali, Namibia, Niger, Nigeria, Rwanda, Senegal, Tanzania, Togo, Uganda, Zambia, Zimbabwe	R03HD099449	Stoebenau, Kirsten University of Maryland, College Park
Estimating the Returns to Provider Human Capital	Nigeria	R01HD083444	Okeke, Edward N. RAND Corporation
Father Involvement Interventions and Child Mental Health	Denmark, Sweden	R03HD096184	Rossin-Slater, Maya Stanford University
Fertility Trends, Changing Maternal Characteristics, and Children's Health	United States, United Kingdom, Ireland, Canada, Australia, and New Zealand	R03HD094042	Cavanagh, Shannon E. University of Texas, Austin
An Internet-Based Preconception Cohort Study in North America and Denmark	United States, Canada, Denmark	R01HD086742	Wise, Lauren A. Boston University Medical Campus

Topic	Country(ies)	Grant	PI/Institution
Microsimulation of Obesity Policies	United States, Australia, Mexico, France, Hungary, Spain, United Kingdom	R01HD087257	Sturm, Roland RAND Corporation

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Rebecca L. Clark
rclark@mail.nih.gov
301-496-1175

Pregnancy and Perinatology Branch (PPB)

Mission

The mission of PPB is to: (1) improve the health of women before, during, and after pregnancy; (2) reduce the number of preterm births and other birth complications; (3) increase infant survival free from disease and disability; and (4) ensure the long-term health of mothers and their children.

Major International Initiatives over the Past Year

Global Network for Women's and Children's Health Research (Global Network)

The Global Network supports and conducts clinical trials in resource-limited countries by pairing foreign and U.S. investigators, with the goal of evaluating low-cost, sustainable interventions to improve maternal and child health and, simultaneously, to build local research capacity and infrastructure. This collaboration has led to improvements in the targeted maternal and infant health outcomes, a substantial expansion of the skills of local health workers and physicians, and improved use of evidence-based practices. It also has afforded opportunities to local scientists to develop protocols, abstracts, manuscripts, and presentations. Local capabilities in information technology, as well as data collection and management have been augmented. These activities are designed to facilitate independent continuation of local research activities that will ultimately lead to improved heath, health care systems, and independent funding. It also provides opportunities for other NIH institutes and funders to collaborate with the Global Network. As of 2018, NICHD has funded eight U.S. sites, each of which has an international partner institution to conduct human subject research. A Data Coordinating Center has also been funded. More information is available at: https://globalnetwork.azurewebsites.net/.

Current studies in the Global Network include the following.

Maternal Newborn Health Registry. This registry is a prospective, population-based study of pregnancies and outcomes at eight sites in seven LMICs, including the Democratic Republic of the Congo, Bangladesh , Guatemala, India, Kenya, Pakistan, and Zambia. With the addition of a new site in Bangladesh, it is anticipated that all pregnant women at participating sites are being registered and their outcomes tracked for 6 weeks post-delivery. The primary purpose of this observational study of approximately 60,000 women per year is to quantify and understand the trends in pregnancy services and outcomes over time in defined, low-resource geographic clusters. The goal is to provide population-based statistics on stillbirths and neonatal and maternal mortality that can help inform health care policy. The data from the registry also provide the mortality and morbidity outcomes for Global Network trials and help investigators plan future network studies. Data collection began in 2008 and is ongoing. To date, the registry has collected data from more than 600,000 mother-baby dyads.

Women First: Preconception Maternal Nutrition Study. The primary hypothesis of this project is that, for women in low resource communities, a comprehensive maternal nutrition intervention (i.e., commencing at least 3 months prior to conception and continuing throughout pregnancy) will be associated with a significantly greater newborn length than for offspring

whose mothers start to receive the same intervention at 12 weeks gestation, or who do not receive the intervention at all. The trial is complete and the primary paper was published in February 2019: PMID 30721941. Data collected on infants followed through age 2 years to assess growth and neurodevelopmental outcomes is complete and the analysis will be published shortly.

Aspirin Supplementation for Pregnancy Indicated Risk Reduction in Nulliparas (ASPIRIN). This multicountry, individual randomized trial will assess the impact of first trimester administration of aspirin on the risk of preterm birth among nulliparous women with a singleton pregnancy. ASPIRIN has two treatment arms: daily administration of low-dose (81 mg) aspirin (LDA), also known as acetylsalicylic acid, initiated between 6 0/7 weeks and 13 6/7 weeks gestational age and continued to 36 0/7 weeks gestational age; compared to an identical-appearing placebo. The primary objective is to determine whether daily LDA initiated between 6 0/7 and 13 6/7 weeks gestational age and continued to 36 0/7 weeks gestational age reduces the risk of preterm birth. Secondary outcomes of interest are the rate of preeclampsia/eclampsia, small for gestational age, perinatal mortality, and the impact of malaria on pregnancy. Enrollment initiated in February 2016 and completed in April 2019. A total of 11,960 women were enrolled. Data is currently being analyzed and the primary paper is slated for publication later in 2020.

Studies in Other Networks and Researcher-Initiated Activities

Prenatal Alcohol in SIDS and Stillbirth (PASS) Network. The PASS Network, co-funded by NICHD, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Institute on Deafness and Other Communication Disorders, conducted community-linked studies to investigate the role of prenatal alcohol exposure in the risk for sudden infant death syndrome (SIDS) and adverse pregnancy outcomes, such as stillbirth and fetal alcohol syndrome (FAS) and how they may be interrelated. The Network completed enrollment of 11,899 pregnant women from the Northern Plains to include American Indian Tribal communities and the Cape Colored communities in the Western Cape of South Africa into the Safe Passage Study, a part of PASS. This prospective longitudinal study will provide important information on understanding the regulation of fetal and infant brain development, shed light on the etiology and pathogenesis of stillbirth, SIDS, and FAS, and produce improved strategies to prevent these disorders. The study has ended, and primary and secondary manuscripts are under review.

Human Cytomegalovirus (HCMV) Vaccines: Reinfection and Antigenic Variation (Brazil). The goal of this study is to define the natural history and the characteristics of HCMV-related hearing loss in children infected in utero following non-primary maternal infections. HCMV infection represents the most common viral infection transmitted in utero and is a significant cause of neurodevelopmental disorders in children. The rate of congenital HCMV infection ranges from 0.2 to 1.0 percent of live births in the United States and exceeds 1 percent in many parts of the world. This study will help identify host responses associated with intrauterine transmission and damaging fetal infections in a population of Brazilian women with non-primary infection. Findings may also aid in the rationale development of effective prophylactic and possibly therapeutic vaccines to limit the morbidity from this congenital infection.

University of North Carolina Global Women's Health Fellowship. NICHD funds a T32 Institutional Training Award program to provide training in global women's health research with experienced research mentors from Malawi, Zambia, and at the University of North Carolina, Chapel Hill. This program provides 2 years of dedicated research time abroad, where trainees will learn the professional and cultural nuances of international settings, ensure proper oversight of research activities, and foster the collaborations necessary for successful international research.

The T32 program will:

- Provide a sustained training opportunity for obstetrician/gynecologists pursuing academic careers in global women's health
- Allow trainees to complete degree requirements for a master of science degree in clinical research, providing the necessary theoretical framework for later practical training
- Leverage the vast global health expertise at the University of North Carolina School of Medicine and Gillings School of Global Public Health to expand the scope and depth of academic mentorship
- Introduce the University of North Carolina Project-Malawi in Lilongwe, Malawi, as a second training site for women's health research, in addition to the established obstetrics/gynecology post-residency training in Lusaka, Zambia. Trainees will thus have access to two established, internationally renowned institutions where they can gain valuable field experience and mentored research training. By the end of the 3-year fellowship, graduates will obtain the necessary skills and experience to become independent investigators, and leaders, in the field of global women's health.

A Cohort Study of Preterm Delivery in Relation to Partner Abuse, Mood, and Anxiety (Peru). There is increasing evidence that preterm delivery is a complex cluster of problems with a set of overlapping factors and influences. As summarized by the Institute of Medicine, the causes of preterm delivery include individual-level behavioral and psychological factors, environmental exposures, medical conditions, biological factors, and genetics, many of which occur in combination. Previous studies have not rigorously evaluated the independent and joint effects of potent highly relevant social and neuropsychological risk factors of preterm delivery in high risk populations. To address these gaps, investigators are developing a prospective cohort of 6,000 Peruvian women to study the relation of maternal history of childhood sexual abuse and lifetime and pregnancy interpersonal violence with the prevalence of mood and anxiety disorders (e.g., major depression, minor depression, generalized anxiety disorder and PTSD). They will also study associations of preterm delivery risk with mood disorder and anxiety disorder early in pregnancy and the extent to which risk of preterm delivery is influenced by alternations in multiple biological markers of maternal neuroendocrine, vascular, and immune status.

Triggers of Abruptio Placentae (AP): A Case-Crossover Study of an Ischemic Placental Disease (Peru). AP is a life-threatening obstetric condition that complicates roughly 1 to 2 percent of all pregnancies. Results from previous studies suggest a significant genetic component in the pathogenesis of AP. The investigators are conducting a large multicenter

epidemiologic study of AP in Lima, Peru. A self-matched case-crossover design will be used to evaluate the acute effects of: 1) maternal smoking and alcohol consumption; 2) physical exertion; 3) sexual activity; 4) abdominal trauma secondary to falls or motor vehicle crashes; and 5) exposure to intimate partner violence as potential "triggers" of AP. They will also study genetic variants that influence the pathogenesis of AP in well-characterized 900 mother-infant abruption case pairs and 900 mother-infant control pairs. Collectively, these new insights may facilitate the development of new approaches for the primary prevention of AP at the public health level and may also facilitate the development of new therapies and methods for diagnosis.

Maternal Genitourinary (GU) Infections and Adverse Perinatal Outcomes (Bangladesh). Maternal GU infections, particularly bacterial vaginosis and urinary tract infections (UTI) are common but inadequately quantified in LMICs. Preterm birth and infections account for the majority, or 60 percent, of the estimated 4 million annual global neonatal deaths. About one-half of preterm births and the majority of early onset neonatal sepsis are attributed to maternal GU infections. The primary aim of this study is to determine the impact of community-based screening and treatment of abnormal vaginal flora and UTI in early pregnancy, from 12 to 16 weeks, on preterm live birth in Sylhet District, Bangladesh. The researchers will conduct a cluster randomized, controlled trial enrolling 8,134 pregnant mothers from that district. Findings will enhance understanding of the burden of abnormal vaginal flora and UTI, and the impact of a screening-treatment program on perinatal outcomes, and will help inform public health recommendations for screening and treatment of maternal GU infections in low-resource settings.

Ambient and Indoor Air Pollution and Fetal Growth (China). It has long been postulated that ambient air pollution affects the health of all, especially children and women of reproductive age. However, precise mechanisms of adverse outcomes are debated. Moreover, socio-economic factors lending to the potential exposures remain confounders. There has been an intensive effort to mitigate the negative effects of indoor air pollution, especially due to burning of fossil fuel for cooking purposes in rural parts of many LMICs. NICHD-funded scientists from Yale University are studying the effects of ambient and indoor air pollution on fetal growth in a large urban population in southern China. Nearly 10,000 women are in the study. They will be prospectively evaluated assessing the speed of growth of their fetuses, as well as longitudinal assessment of air pollution data in the region. In a subset of the study participants, additional studies will be carried out to evaluate the combined effects of indoor air pollution.

Neonatal Infections and Memory T Cell Repertoire: A K99/R00 Pathway to Independence Award, Cornell University with subcontract to University of South Wales, Australia. In this grant, researchers will determine the capacity of neonatal and adult CD8+ T cells to generate appropriate immune responses against acute and chronic pathogens. The Australian subcontract provides bioinformatics support for data analyses.

Mechanisms of Fetal Inflammatory Response Syndrome Induced by Chorioamnionitis: University of Cincinnati, with subcontract to University of Western Australia, Perth, Australia. Investigators are testing how chorioamnionitis, inflammation in the fetal membranes that is present in about 70 percent of preterm infants born before 30 weeks gestation, becomes

a major contributor to morbidity and mortality in this population. Because fetal inflammatory response syndrome is present in about 50 percent of preterm infants exposed to chorioamnionitis, the study will try to decipher the mechanisms behind this response. They will use the sheep lab facilities at the University of Western Australia, Perth, for these studies.

Pregnancy and Early LifeStyle Improvement (PEARL) Study. The primary grant for PEARL is an R01 to a PI in Puerto Rico, with subcontract to a consultant from University of Lund, Sweden. Researchers will conduct a randomized controlled trial in 400 overweight or obese pregnant Puerto Rican women (free of diabetes) and their infants to study ways to favorably impact metabolic health in mothers and infants. Women presenting before 20 gestational weeks will be block randomized to a lifestyle modification intervention or standard care control group. Puerto Rico is a predominantly Hispanic U.S. territory with among the lowest levels of physical activity and fruit, vegetable, and whole grain intake, as well as the highest rates of diabetes, childhood obesity, and infant mortality of all U.S. jurisdictions. Nevertheless, recruitment rates for research studies are higher here than elsewhere in the United States. The intervention conducted in pregnant women and their infants focuses on improving: (1) physical activity levels, (2) diet quality and caloric intake, (3) behavioral imprinting, and (4) prenatal care. Conducting this study in Puerto Rico will address a major health disparity common to many parts of the United States, whilst also advancing knowledge about how early life risk factors could be influenced to reduce metabolic risk in young women and their offspring.

Human Placenta Project (HPP). HPP is an initiative aimed at developing tools and technologies that will enable safe, non-invasive, real-time assessment of placental development and function across pregnancy. Multiple initiatives have been funded since the project's inception in 2014. Translation of technologies globally, especially into low-resource settings, is a major goal for the project. The following HPP grants to U.S. entities had international components.

- **HD086313-01: Novel Tools for the Non-Invasive Evaluation of the Human Placenta**
  Mounting evidence suggests that abnormal placental development in early gestation is highly associated with many maternal and fetal pathologic conditions, which can manifest later in pregnancy. The ability to evaluate in real time human placental structure and function in early gestation using novel ultrasound tools will allow for the identification of early markers of placental dysfunction with the ultimate long-term goal of prevention of adverse pregnancy outcomes. As initial steps in accomplishing this long-term goal, this study was designed to find which of the novel ultrasound tools are best at discriminating between women who will develop adverse pregnancy outcomes and those who will not. To date, 420 pregnant women have been enrolled, and 282 patients have completed the study with delivery. It is anticipated that in the coming months it will be possible to develop normograms for the novel ultrasound tools and begin interim analysis of blood sample and imaging data.
- **HD089660-01: Lipidomics: A Novel Tool to Define Human Placental Development and Function Across Pregnancy**
  Among the most intractable pregnancy pathologies are preeclampsia, intrauterine growth restriction and gestational diabetes, all of which are associated with placental

dysfunction. The onset of these disorders occurs likely in late first and early second trimesters before the onset of the clinical manifestations. Currently no tools to assess placental health/function in these crucial trimester periods have been developed that could be utilized for routine clinical diagnosis. This study applies cutting-edge high-throughput lipidomic technologies that provide measurements of the lipidome in exosomes of placental origin in the circulation of pregnant mothers. To date, it has been determined that some lipid classes change markedly across gestation. Preeclamptic pregnancy profiles are revealing differences from control pregnancy profiles, and this is being explored for potential diagnostic value.

- **HD089685-01: Maternal Molecular Profiles Reflect Placental Function and Development Across Gestation**
  Maternal, fetal, and infant health relies on the crosstalk between the mother, placenta, and fetus. The placenta is key to pregnancy success as it is responsible for the exchange of all nutrients, gases, and wastes between the maternal and fetal circulations and importantly it orchestrates maternal adaptations to pregnancy by secreting many hormones and peptides into the maternal circulation. This study hypothesizes that the maternal plasma miRnome and maternal circulating leukocyte DNA methylome reflect dynamic changes in the placental transcriptome, miRnome and DNA methylome that correlate with placental function and health and that these can be assessed non-invasively across gestation. miRNA sequencing, RNA sequencing, and DNA methylation arrays will be used to create molecular profiles in paired maternal blood and placental samples at multiple time points across gestation. To date, a full miRnome dataset has been obtained from 96 plasma and placenta samples from first and second trimester pregnancies and are being analyzed.

- **HD089713-01: Using 'Omics to Build an Atlas of Placental Development and Function Across Pregnancy**
  The placenta is both responsive and adaptive to maternal exposures, including many that affect stress/immune signaling. However, how it does this and the intricacies of normal developmental biology of the human placenta are still poorly understood. To tackle key questions in this area, this study will employ two unique tools: 1) cell sorting techniques that allow isolation of understudied placental cell types; and 2) deep-sequencing technologies that have hugely expanded the number of known short, non-coding RNAs in the human genome. To date, several aspects of the data pipeline have been optimized and validation of the ancestry verification approach has been completed.

- **HD087181-01: Hyperpolarized 13C MRI of Placental Metabolic Abnormalities Resulting from the Western Diet**
  Current methods for assessing the metabolic function of the placenta during pregnancy provide only indirect measures, greatly limiting their utility. This means that researchers have a very limited understanding of how obesity and Western diet consumption affect placental metabolism. There is a critical need for direct measurement of metabolic changes in the placenta. This study seeks to develop a new technology based on MRI that will, for the first time, allow direct measurement of metabolic processes in the placenta during pregnancy. To date, several technical aspects of the approach have been

optimized using the guinea pig model so that the metabolic fate of 13C peptides can be followed.

- **HD087202-01: Structure and Function of the Placenta from Implantation to Delivery: A Next Generation MRI Approach**
  The goal of this study is to develop four MRI methodologies to assess placental structure, microstructure, and function across gestation, integrate these into one comprehensive MRI examination that is acceptable to pregnant women, and combine this with continuous fetal electrocardiogram (ECG) recordings. The work aims to provide a step change in antenatal assessment of the normal and abnormally developing placenta when compared to current methods, such as those based on ultrasound, velocimetry, and serum markers. The project will deliver a new capability to assess and monitor the placenta in at-risk pregnancies. To date, several technical aspects of the MRI approaches have been addressed including management of motion artifacts. Fetal ECG studies are ongoing to evaluate the utility of this approach for detecting pregnancy problems.

Recent Achievements in International Health

Neonatal Hypoglycemia and Long-Term Outcome. Hypoglycemia, or low blood sugar, occurs very commonly in newborn infants. If severe, it can lead to significant brain injury. Yet there are many aspects of newborn hypoglycemia that remain unknown, including the definition of "normal" and "abnormal," and the severity of hypoglycemia that causes brain injury. Researchers from Liggin's Institute and University of Auckland, New Zealand, used a unique monitoring system (not available in the United States) to measure infants' blood sugar each second, continuously, for as long as clinically needed. Using this monitoring device, the course of glucose changes in the blood of 500 newborn infants was followed. NICHD funded these investigators to help them conduct follow-up evaluation of these infants at age 4 to 5 years. Several recent papers from this study have begun to provide better definitions for neonatal hypoglycemia and its clinical course (See Harding JE et al). In 2017, this group published the results of 4.5-year outcomes and concluded that, in this prospective cohort study of 477 at-risk children, neonatal hypoglycemia (<47 mg/dL) was not associated with combined neurosensory impairment at 4.5 years but was associated with impaired executive function and visual motor function. Severe, recurrent, and clinically undetected episodes increased this risk. Work from this group continues to help clinical caregivers all over the world.

Reducing Neonatal Infections and Infection-Related Infant Mortality. Infections during the neonatal period are the major causes of infant mortality in low- and middle-income regions of the world. In a study by scientists at the University of Nebraska, the benefits of oral administration of an FDA-registered symbiotic preparation or a placebo were studied in healthy term infants in a randomized controlled study during the first week after birth in rural communities in northern India. The study recruitment was halted at 70 percent of the intended subject number, approximately 6,000 participants, because infants treated with probiotics encountered significantly fewer infections and fewer of them died of sepsis. A paper has been published in *Nature Medicine*.

Individual Patient Meta-Analysis of Oxygen Therapy in Preterm Infants. University of Alabama, Birmingham, with subcontract to international sites in four countries: Australia, Canada, England, and New Zealand. The NICHD/ NHLBI-funded study, Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT), tested the effects of oxygen supplementation using oxygen saturation targets in the recommended range. Four other multicenter randomized controlled trials (BOOST II Australia, COT Canada, BOOST II New Zealand, and BOOST II United Kingdom) used the same intervention as SUPPORT as part of a planned prospective analysis. The group formed the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration to undertake the first prospective individual participant data meta-analysis in neonatal medicine. The investigators of all five trials collaborated in the design and data collection.

Physiology of Postnatal Respiratory Transition. Monash University, Victoria, Australia. The transition from fetus to newborn is one of the most complex and challenging transitions that all humans have to undertake. While most infants make this transition with remarkable ease, a significant number of infants require some form of intervention to survive. The primary aim of this study is to increase the understanding of the physiological underpinning of the transition from fetal-to-newborn life and to use this information to improve the strategies used to support infants in the delivery room, during this vital stage of their lives.

Pregnant Women with Parasitic Infestation and their Offspring's Responses to Childhood Vaccinations: A Secondary Study. The study sought to determine the effect of parasitic infections in pregnant women on the responses to *Haemophilus* influenzae type B (Hib) and diphtheria vaccination in their offspring, by following 510 Kenyan maternal-infant pairs every 6 months from birth to 3 years of age. Mothers were tested for malaria, filariasis, and schistosomiasis. It was found that 64 percent of the pregnant women were infected with parasites: 46 percent with single infection and 18.0 percent with multiple parasites (polyparasitism). Children of malaria-infected women had significantly lower protective responses (a rise in immune globulin levels in the blood) at 12, 18, and 24 months, compared to the offspring born to women without malaria. Offspring of schistosomiasis-infected women also had lower levels of protective immune globulins compared to offspring born to women without schistosomiasis. Similarly, diphtheria and Hib immune globulin levels also declined at higher rates in children of malaria-infected mothers than in children born to mothers without malaria. But the researchers also showed that if mothers were treated for malaria and other parasitic infections, the immune responses in their respective offspring were restored. This public health message is important: to aggressively test for and treat malaria, schistosomiasis, and other parasitic infections in women during pregnancy because such treatment not only helps cure the mother, but also helps to strengthen the immune responses of their offspring, preventing the latter from getting routine childhood illnesses.

Zika Virus

- **Rapid Assessment of Zika Virus Complications (R21) PAR-16-106**
  The purpose of this RFA was to provide an expedited funding mechanism for research on Zika virus and its complications. This rapid RFA, in conjunction with several other participating NIH institutes, was a targeted effort to address the growing concerns of transmission and outcomes in at risk populations such as women who are pregnant. In response to this public health emergency, PPB participated in MPIDB-funded grants on the natural history and pathogenesis of Zika in reproductive-age women and the fetus, whether in utero, postpartum, or through breastfeeding.
- PPB was part of a MPIDB-led effort to develop the **ZIP Study (Zika in Infants and Pregnancy)**, which will enroll up to 10,000 pregnant women in the first or early second trimester in multiple sites throughout South America and the Caribbean. This study will help guide medical and public health responses to Zika as discoveries regarding the virus and the full scope of its impact on at-risk populations continues to unfold. At the forefront of the epidemic, investigators are working to better understand the underlying complications of Zika to protect the health of women and their children throughout the world.

Individual Studies Utilizing International Collaboration

Many investigators supported by NICHD have utilized various international sites for collaboration, and most include sites that contribute to the primary study hypotheses, and/or to help recruit appropriate patient population at an accelerated pace. Clinical studies with international sites include the following.

Hernia in Prematurity Study. This study based at Vanderbilt Medical Center is testing the most appropriate time to repair of inguinal hernia in preterm infants. Infants randomized to one of the arms of the study will undergo repair prior to their initial hospital discharge, and those randomized to an alternate arm will undergo 15 to 20 weeks after discharge. The study will evaluate the safety and complication rates in these arms, and a subset will also undergo an assessment of neurodevelopmental outcome at 2 years. International sites contributing to the study are in Canada and the Netherlands.

Premature Infants Receiving Cord Milking or Delayed Cord Clamping (DCC) (R01HD088646). Preterm brain injury from intraventricular hemorrhage (IVH) is a pressing worldwide public health problem. Delaying clamping the umbilical cord at birth for 30 to 60 seconds provides the newborn with a significant autologous transfusion of blood from the placenta and has been shown to reduce IVH. DCC has been shown to reduce overall IVH (mainly lower grades 1 and 2) by 50 percent but has not reduced the incidence of severe IVH or death. This study is being done to find out whether umbilical cord milking (UCM) is at least as good as or better than DCC in reducing bleeding in the brain or preventing death in premature newborns. The investigators will study short- and long-term outcomes of infants delivered before 32 weeks gestation that receive either UCM or DCC. In addition to six U.S. sites, University of Alberta, Canada, University College Cork, Ireland, and University of Ulm, Germany, are participants. The specific aims of this trial are to: compare the incidence of severe IVH and/or

death in premature newborns <32 weeks gestational age delivered by caesarean section receiving UCM to those receiving DCC; compare the safety and efficacy profiles of premature newborns <32 weeks gestational age delivered by caesarean section receiving UCM vs. DCC during their hospitalization and at 24 months corrected age; compare the outcomes of premature newborns <32 weeks gestational age delivered by caesarean section.

UCM in Non-Vigorous Infants (MINVI) (R01HD096023). At birth, it is critical that an infant begins breathing quickly. The infant has to switch from relying on the placenta for oxygen to using its lungs for the first time. The currently recommended practice for infants who need resuscitation is to immediately clamp the umbilical cord. Animal studies show that clamping the cord before the baby breathes can cause the heartbeat to slow and can decrease the amount of blood being pumped out of the heart each minute. MINVI will test whether these infants benefit from UCM. The cord will be quickly milked four times before cutting and will not delay the resuscitation procedures. This study is important because when there is need for resuscitation, neither UCM or DCC are recommended by national and international organizations due to lack of evidence. Yet, several large studies from around the world have identified that infants needing resuscitation are more likely to develop conditions such as cerebral palsy, autism, and other developmental problems. The trial is a cluster crossover design in which each hospital will be randomly assigned to use either early cord clamping or UCM for any infant needing resuscitation over a period of 12 months. Then sites will change to the other method for an additional 12 months. Besides eight U.S. sites, the study sites include Alberta Canada, Dallhousie University, New Brunswick, Canada, and University of Ulm, Germany.

VentFirst: A Multicenter Randomized Clinical Trial of Assisted Ventilation During DCC for Extremely Preterm Infants (HD087413-01). The purpose of this study is to determine whether providing ventilatory assistance prior to umbilical cord clamping influences the occurrence of IVH in extremely preterm infants, compared to standard care of providing ventilatory assistance after cord clamping. In addition to seven U.S. sites, the collaboration includes University of Calgary, Canada.

Group Antenatal Care to Promote a Healthy Pregnancy and Optimize Maternal and Newborn Outcomes: A Cluster Randomized Controlled Trial (R01HD096277-01). The goal of this project is to improve health literacy and reduce preventable maternal and newborn morbidities and mortality with a focus on preparing for birth, identifying complications, and understanding care-seeking patterns. The research team will test the efficacy of providing antenatal care in groups of 8 to 12 women of similar gestational age. Women will meet with the same group and the same provider over the course of their pregnancy for a 60-minute facilitated discussion in addition to their individual assessments. The research team will recruit 845 women less than 24 weeks' gestation, over the age of 15 years at their first antenatal care visit from health facilities in rural Ghana. Participants will be surveyed in person at the health facility or by cellphone at six time points: (1) initial enrollment in antenatal care, (2) third trimester (prior to delivery), (3) immediately postpartum, (4) 6-weeks postpartum, (5) 6-months postpartum, and (6) 1-year postpartum. Additional data will be collected from antenatal care and hospital medical records.

Addressing Provider Stress and Unconscious Bias to Improve Quality of Maternal Health Care (K99HD093798-01A1). The goal of this project is to improve quality of maternal health care, using person-centered maternal health care (PCMHC), and reduce disparities in PCMHC, focusing on the role of health care provider stress and unconscious bias. In the K99 phase researchers will: (1) conduct secondary data analysis using existing data from about 1,000 women, 50 providers, and facility level data to examine factors associated with PCMHC, focusing on the role of provider stress; and (2) conduct structured and in-depth interviews with 100 and 20 to 40 providers respectively, to examine the levels of provider stress and unconscious bias, and the types of stressors and biases in Kenya. In the R00 phase researchers will: (1) design an intervention that enables providers to identify and manage their stress and unconscious bias; (2) pilot the intervention to assess its feasibility and acceptability; and (3) assess preliminary effect of the intervention. The study will recruit 80 providers for the pilot and its evaluation. All study participants (providers) will be older than 18 years and recruited from health facilities in Migori County, Kenya. They will participate in surveys at one time point in the K99 phase and two time points in the R00 phase. They will also provide hair samples for cortisol levels to measure stress in the R00 phase.

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Points-of-Contact

NICHD Global Network for Women's and Children's Health Research

Dr. Marion Koso-Thomas
kosomari@mail.nih.gov
301-435-6896

Dr. Menachem Miodovnik
Menachem.Miodovnik@nih.gov
301-451-5031

NICHD Maternal-Fetal Medicine Units Research Network

Dr. Menachem Miodovnik
Menachem.Miodovnik@nih.gov
301-451-5031

Dr. Caroline Signore
signorec@mail.nih.gov
301-496-5577

For General Global Health Research Support from PPB

Dr. Andrew A. Bremer
Acting PPB Chief
andrew.bremer@nih.gov
301-402-7886

National Center for Medical Rehabilitation Research (NCMRR)

Mission

NCMRR is designed to foster development of scientific knowledge needed to enhance the health, productivity, independence, and quality of life of persons with disabilities. This is accomplished by supporting research on enhancing the functioning of people with disabilities in daily life and on developing and evaluating new methods and technologies for rehabilitation. A primary goal of the center is to bring the health-related problems of people with disabilities to the attention of America's best scientists to capitalize upon the myriad advances occurring in the biological, behavioral, and engineering sciences. These advances are emphasized through six areas:

- Adaptation and Plasticity
- Devices and Technology Development
- Rehabilitation Diagnostics and Interventions
- Chronic Symptom Management
- Health-Services Research
- Environmental Factors

Major International Initiatives over the Past Year

NCMRR is working with the WHO during the planning stages of the Rehabilitation 2030 initiative, which is led by the Rehabilitation and Disability component of WHO. This includes working to facilitate a research agenda for the initiative and identifying the priority package of interventions that would be included in the launch of rehabilitation care in the universal health care system effort. NCMRR co-hosted the meeting to establish the research agenda for rehabilitation in July of 2019 in Geneva, Switzerland.

Recent Achievements in International Health

N/A

International Partnerships

Big Data Neuroimaging to Predict Motor Behavior after Stroke. Stroke is a leading cause of serious long-term adult disability around the world. There is huge variability among stroke survivors in terms of lesion location, age, gender, and time since stroke that may affect a person's likelihood of recovery and response to different types of rehabilitation treatments. This research seeks to combine the best neuroimaging techniques with functional assessments from stroke survivors from across the globe to identify neural and behavioral biomarkers that predict

recovery of motor impairment as illustrated by research conducted at the ENIGMA Center for Worldwide Medicine, Imaging, and Genomics. This approach has the potential to revolutionize the way that rehabilitation research is validated, to ensure robust, reliable, and reproducible results.

Diet Composition and Cardiometabolic Risk Reduction in Adults with Spinal Cord Injury (SCI). This study, a collaboration with McMaster University in Canada, seeks to assess the impact of a restricted carbohydrate diet on dietary adherence and cardiometabolic risk factors among adults with SCI. Cardiometabolic diseases, including cardiovascular disease and diabetes, are among the leading causes of illness and death in adults living with SCI. The impact of these conditions can be reduced by following a healthy diet, but many people have trouble with long-term adherence. Research in non-injured adults has shown that reduced carbohydrate diets may mitigate risk and lead to increased dietary adherence over low fat diets; however, no research has examined this in individuals with SCI.

Dynamic Stability in the Anterior Cruciate Ligament (ACL)-Injured Knee. The continuation of this prospective international cohort study of patients after acute unilateral ACL injury will help influence the care of the 200,000 or more Americans who rupture their ACLs each year by answering important clinical questions regarding the role and impact of dynamic knee stability on patient outcomes. The inclusion of an international sample allows for an opportunity to test the conventional wisdom that drives surgical decision-making in the treatment of ACL rupture in the United States. The 10-year collaboration between the University of Delaware and Oslo University Hospital in Norway, where the practice pattern requires a substantial period of rehabilitation prior to reconstructive surgery, provided the platform for this unique cohort. In addition, the further elucidation of how those with different early compensation strategies for the injury are affected by neuromuscular training and reconstructive surgery will enable researchers to derive and test meaningful prediction rules for clinical management.

Early Childhood Constraint Therapy for Sensory/Motor Impairment in Cerebral Palsy (CP). The goal of this research is to overcome developmental disregard during the early rehabilitation of children with CP. This form of neglect that starts in infancy impairs the ability to infer new and effective movements and contributes to neurodevelopmental trajectories that rarely equal those of typically developing children. The short-term objective of this proposal is to show that Constraint-induced movement therapy (CIMT) at or before age 2 years can improve upper extremity sensory and motor function and thereby mitigate developmental disregard. To accomplish this, the study uses a randomized controlled trial design with a wait-list control, in children 12 to 24 months of age with asymmetric CP. The CIMT intervention includes 1 month of soft constraint wear on the less affected arm (1/2 day sessions, electronically monitored) combined with a validated parent-implemented home-based program of reach training and sensory exposures for the more affected extremity, in addition to routine therapy sessions (current standard CP treatment). Typically developing age-matched children will also be tested. This work will be done in collaboration with the Centre Hospitalier Universitaire Vaudois (Switzerland), which will assist with complex modeling of EEG data gathered in this project.

Multicenter Trial of Augmented Sensory Feedback in Children with Dyskinetic CP. The lack of theoretical and practical understanding of the impact of early brain injury on subsequent

motor skill development is a major deficit in knowledge, yet it provides an important opportunity for significant improvement in the treatment of childhood brain injury, such as that seen in CP, stroke, and Traumatic Brain Injury (TBI). This research, in collaboration with Istituto Neurologico Carlo Besta and Politecnico di Milano in Italy, will explore the impact of decreased sensory function on motor learning in dyskinetic CP and primary dystonia by: 1) performing a multicenter clinical trial to test the effect of one month of wearable sensory feedback on real-world skill learning in children with dyskinetic CP and primary dystonia; and 2) testing the effect of enhanced sensory feedback during drawing movements and a self-feeding task in children with dyskinetic CP, primary dystonia, and controls. These experiments create a theoretical and experimental foundation for a new understanding of how early brain injury interacts with motor development and skill acquisition in childhood.

Neural Predictors of Hand Therapy Efficacy in Children with CP. Unilateral CP is an extremely common pediatric neurological disorder. Through a collaboration with Catholic University of Louvain in Belgium, this research seeks to test the novel hypothesis that the efficacy of different types of hand therapy depends on the connectivity and integrity of motor pathways in the brain. Understanding the impact of brain connectivity on recovery will provide important insights into how to develop and tailor therapies for children most likely to benefit.

Neuromuscular Mechanisms Underlying Poor Recovery from Whiplash Injuries. In the majority of whiplash cases, structural damage on objective imaging is rarely present. Pilot data from this group has demonstrated the rapid and early expression of muscle fatty infiltrates on MRI, signs of disturbed descending control, and muscle weakness in the 25 percent of individuals with whiplash associated disorders (WAD) with poor functional recovery. The goal of this collaboration with University of Queensland (Australia), Zurich University of Applied Sciences, University of Otago (New Zealand), Macquarie University (Australia), and the University of Western Ontario is to test the central hypothesis that chronic WAD is an expression of a mild incomplete SCI. The team aims to: 1) understand the neurophysiological mechanisms underlying poor functional recovery in the 25 percent of individuals with a seemingly more complex injury, and 2) consider and integrate the bio-psycho-social drivers of the clinical course on a patient-by-patient basis. This new knowledge will set the stage for future studies investigating more objective and integrated assessments as well as the development of targeted science-based interventions for a cohort that does not respond well to current intervention strategies.

Optimizing Rehabilitation for Phantom Limb Pain (PLP) Using Mirror Therapy and Transcranial Direct Current Stimulation (tDCS). This study, in collaboration with University of Milano Bicocca in Italy, is investigating a novel rehabilitation approach combining a behavioral therapy (mirror therapy) with a method of brain modulation, tDCS, to treat and investigate the mechanisms of chronic PLP. Extensive evidence indicates that PLP is a phenomenon related to significant maladaptive brain changes. PLP is recognized as very difficult to treat as it is often resistant to classical pharmacological and surgical treatment approaches. It is a major cause of disability and a main detriment to quality of life for those affected.

Subject-Specific Diffusion MRI Profiles of Injury in TBI and PTSD. While mild TBI (mTBI) has become the focus of many neuroimaging studies, the understanding of mTBI, particularly in patients who exhibit no radiological evidence of injury and yet experience clinical and cognitive

symptoms, has remained a complex challenge. Sophisticated imaging tools are needed to delineate the kind of subtle brain injury that is extant in these patients, as existing tools are often ill-suited for the diagnosis of mTBI. The goal of this study, in collaboration with the French Institute for Research in Computer Science and Automation, is to develop a robust framework to perform subject-specific neuroimaging analyses of diffusion MRI, as this modality has shown excellent sensitivity to brain injuries and can locate subtle brain abnormalities that are not detected using routine clinical neuroradiological readings.

Staff Membership on Global Health Committees/Working Groups

Priority Package of Interventions Working Group, Rehabilitation 2030, Rehabilitation & Disability Component, WHO. Representative: Dr. Alison Cernich

Point-of-Contact

Dr. Ralph Nitkin
R21e@nih.gov
301-402-4206

Division of Intramural Population Health Research (DIPHR)

Mission

The DIPHR has an ambitious three-fold mission consistent with the intramural research program at the NIH, to:

- Design and conduct original and collaborative public health research consistent with our Institute's mission
- Develop and mentor the next cadre of public health and clinical researchers
- Proactively provide professional service throughout the NIH community, other federal agencies, and professional entities served by our research mission and the public at large

The DIPHR designs research responsive to critical data gaps to advance our understanding of factors that impact human health. This research is particularly relevant for the health and well-being of the public and its special populations and utilizes novel methodologies and statistical tools including those developed by DIPHR investigators. DIPHR investigators identify critical data gaps and design research initiatives to answer etiologic questions or to evaluate interventions aimed at modifying behavior.

Major International Initiatives over the Past Year

Hydrocephalus. In collaboration with the Statens Serum Institut (SSI) in Copenhagen, Denmark, this research seeks to find genetic variants associated with hydrocephalus. Confirmatory testing is being performed on cases identified through a collaboration with the New York State Department of Health.

Gestational and Type 2 Diabetes. In collaboration with investigators at the SSI, NICHD investigators are working on the Danish National Birth Cohort for a study on Diabetes and Women's Health to identify genetic and non-genetic determinants for the conversion from gestational diabetes to type 2 diabetes and related cardiometabolic disorders among women and their children.

Developmental Origins of Health and Disease. In collaboration with Danish National Birth Cohort investigators at the SSI, NICHD investigators established the Intergenerational Health Study to examine the impact of maternal obesity and gestational diabetes on cardiometabolic and reproductive health among adolescents and young adults.

In collaboration with investigators in National University of Singapore, the Growing Up in Singapore Towards Healthy Outcomes Study aims to evaluate the transgenerational impact of maternal glycemia in pregnancy and offspring abdominal adiposity as measured by MRI in a multi-ethnic Asian population—a high-risk population for both gestational and type 2 diabetes.

Development of Preeclampsia. In collaboration with investigators in Canada, Norway, and the UK, a study will investigate the role of angiogenesis factors in the development of preeclampsia by pooling data from studies worldwide.

Tryptophan Metabolites and Inflammation in Pregnancy. This study is a collaboration with Trinity College, Dublin, to examine changes in tryptophan metabolites during pregnancy and how they relate to markers of inflammation.

Recent Achievements in International Health

- **Tryptophan and Inflammation.** The collaboration with Trinity College, Dublin, has shown that the markers for inflammation, neopterin and interleukin 10, are strongly related to tryptophan metabolism in healthy adults. This study also reported that tryptophan and vitamin B6 in young adults are affected by gender and alcohol consumption.
- **In Utero Glycemia Levels and Risk of Childhood Obesity.** Maternal fasting plasma glucose concentrations were significantly and positively associated with birth size and overweight/obesity risk at age 7 years.

International Partnerships

- NTDs: Biochemistry related to birth defects and GWAS with Trinity College in Dublin, Ireland. PI: Dr. J. Mills
- Formate metabolism and genetic factors with Memorial University in Newfoundland, Canada. Co-investigator: Dr. J. Mills
- Tryptophan metabolism and its role in immune response with University of Bergen in Bergen, Norway. Co-investigator: Dr. J. Mills
- In collaboration with investigators at SSI in Copenhagen, Denmark, NICHD investigators are working to investigate congenital hydrocephalus genetics and are conducting GWAS. Co-investigator: Dr. J. Mills
- In collaboration with SSI, genetic determinants for the progression from gestational diabetes to type 2 diabetes. PI: Dr. C. Zhang; co-investigators: E. Schisterman, J. Mills, E. Yeung, A. Liu
- In collaboration with the SSI, NICHD investigators are working on the Danish National Birth Cohort to investigate the intergenerational impact of gestational diabetes and maternal obesity. PIs: Drs. C. Zhang, S. Mumford, E. Yeung; co-investigators: P. Mendola, J. Mills, A. Liu
- International consortium project on angiogenesis factors and preeclampsia. Investigators: Drs. C. Zhang and E. Schisterman
- Global pregnancy collaborative consortium on major pregnancy outcomes. Investigators: Drs. C. Zhang and E. Schisterman

- Reproductive effects of in utero exposure to Chernobyl fallout in an iodine-deficient region of Ukraine. Investigators: Drs. K. Grantz and J. Mills
- In collaboration with investigators at SSI, NICHD investigators are working to investigate pyloric stenosis genetics and are conducting GWAS. Co-investigator: Dr. J. Mills

Epidemiology Branch Investigators Involved in International Activities

Enrique F. Schisterman, Ph.D., M.A.
schistee@mail.nih.gov

Aiyi Liu, Ph.D.
liua@mail.nih.gov

James L. Mills, M.D., M.S.
millsj@exchange.nih.gov

Cuilin Zhang, M.D., Ph.D., M.P.H.
zhangcu@mail.nih.gov

Katherine Laughon Grantz, M.D., M.S.
katherine.grantz@nih.gov

Edwina Yeung, Ph.D.
yeungedw@mail.nih.gov

Sunni Mumford, Ph.S.
mumfords@mail.nih.gov

Staff Membership on Global Health Committees/Working Groups

WHO Advisory Committee for developing a practice guide to implementation research on non-communicable disease prevention and control. Committee member: Dr. C. Zhang

Point-of-Contact

Dr. Enrique F. Schisterman
schistee@mail.nih.gov
301-435-6893

Division of Intramural Research (DIR)

DIR plans and conducts the institute's laboratory and clinical research programs to seek fundamental knowledge about the nature and behavior of living systems through basic, clinical, and population-based research and to determine how to apply such knowledge to illuminate developmental origins of health and disease and help the NICHD achieve its mission.

The DIR research program utilizes a multidisciplinary environment to investigate the physics, chemistry, and biology of cells, the processes that govern and regulate cellular function, and the effects when these processes fail. The division includes more than 60 tenured and tenure-track investigators, organized into 13 affinity groups (AGs), and approximately 300 postbaccalaureate, clinical, and postdoctoral fellows and graduate students.

Each of the 13 AGs is an intellectual hub for a group of investigators, creating a forum to share ideas and to collaborate around common themes in support of the DIR mission. The AGs serve as catalysts for new initiatives. Each investigator has a primary affiliation with an AG most closely aligned with his or her scientific interests. Secondary affiliations allow for communication across specialties in support of translational research and new collaborations. Each AG has its own mission statement, shared research goals and objectives, and resources. Collectively, the AGs contribute to recruitment, mentoring, and the annual DIR scientific retreat.

- Aquatic Models of Human Development
- Basic Mechanisms of Genome Regulation
- Bone and Matrix Biology in Development and Disease
- Cell and Structural Biology
- Cell Regulation and Development
- Developmental Endocrine Oncology and Genetics
- Genetics and Epigenetics of Development
- Maternal-Fetal Medicine, Imaging, and Behavioral Development
- Metals Biology and Molecular Medicine
- Neurosciences
- Pediatric Endocrinology, Metabolism, and Genetics
- Physical Biology and Medicine
- Reproductive Endocrine and Gynecology

DIR research addresses several fundamental questions:

- How do cells transmit signals from the outside environment to the nucleus, initiate gene expression and replication, and then translate molecular responses into changes in function, differentiation, and communication with the cells' neighbors and environment?
- How do cells talk to one another, identifying their properties and location to give rise to tissues and organs?
- How are these processes integrated during embryonic, fetal, and postnatal development?
- When these processes go awry and disease ensues, how may we intervene in this pathologic sequence and treat the disease?

Section on Clinical Neuroendocrinology (SCN)

PI: Karel Pacak, M.D., Ph.D., D.Sc.
AG: Developmental Endocrine Oncology and Genetics

Mission

Focus in on endocrine tumors

Major International Initiatives

Member of the International Advisory Panel of the Czech Government Board for Science, Technology and Innovation, 2017-Present

Recent Achievements in International Health

N/A

International Trainees

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

Working Group on Endocrine Hypertension: Pheochromocytoma Research and Support Organization (PRESSOR)

Point-of-Contact

Dr. Karel Pacak
Karel.Pacak@nih.gov
301-402-4594

Section on Endocrinology and Genetics (SEGEN)

PI: Constantine A. Stratakis, M.D., M. (Med) Sci.
AG: Developmental Endocrine Oncology and Genetics

Mission

This program focuses on understanding the genetic and molecular mechanisms leading to disorders that affect the adrenal cortex, with emphasis on developmental and hereditary disorders and those associated with adrenal hypoplasia or hyperplasia, multiple tumors, and abnormalities in other endocrine glands especially the pituitary gland and, to a lesser extent, the thyroid gland.

Major International Initiatives

- Dr. Jerome Bertherat and colleagues: Institut National de la Santé et de la Recherche Médicale, Paris, France: Cloning of new genes for Carney complex, 06/2003-2013; and others in France
- Prof. A. Beckers and colleagues: Department of Endocrinology, Chu de Liège, Domaine Universitaire du Sart-Tilman, Liege, Belgium; and others in Belgium
- Prof. Stefan Bornstein and colleagues: Medizinischen Klinik und Poliklinik III und des Zentrums für Innere Medizin Universitätsklinikum Carl Gustav Carus an der TU Dresden, Germany; and others in Germany
- Dr. Jan Maarten Wit and colleagues: Leiden University Medical Center, The Hague Area, Netherlands; and others in Netherlands
- Dr. Annalisa Vetro and colleagues: Università degli Studi di Pavia: Dipartimento di Medicina Molecolare, Genetica Medica, Pavia, Italy
- Prof. Massimo Mannelli and colleagues: Dept. Experimental and Clinical Biomedical Sciences, Sez. Endocrinologia, Universita Degli Studi – Firenze, Italy
- Prof Francesto Brancati and colleagues: Ambulatori Genetica Clinica – Genetica Medica, Policlinico Universitario Tor Vergata – Rome, Italy
- Dr. Maria Candida Fragoso and colleagues: Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Unidade de Endocrinologia do Desenvolvimento, Unidade de Neuroendocrinologia, Laboratório de Hormônios e Genética Molecular/LIM42, Sao Paulo, Brazil
- Prof. Amilcar Tanuri and colleagues: Laboratório de Virologia Molecular, Instituto de Biologia - Departamento de Genética, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; and others in Brazil
- Dr. Paraskevi Xekouki: Department of Endocrinology, King's College Hospital, London, UK

Selected Publications with International Collaborators in the Past 5 Years

1. Xekouki P, Brennand A, Whitelaw B, Pacak K, Stratakis CA. The 3PAs: An update on the association of pheochromocytomas, paragangliomas, and pituitary tumors. *Horm Metab Res. 2019 Jul;51*(7):419-436.
2. Rossi ÁD, Faucz FR, Melo A, Pezzuto P, de Azevedo GS, Schamber-Reis BLF, Tavares JS, Mattapallil JJ, Tanuri A, Aguiar RS, Cardoso CC, Stratakis CA. Variations in maternal adenylate cyclase genes are associated with congenital Zika syndrome in a cohort from Northeast, Brazil. *J Intern Med. 2019 Feb;285*(2):215-222.
3. Espiard S, Knape MJ, Bathon K, Assié G, Rizk-Rabin M, Faillot S, Luscap-Rondof W, Abid D, Guignat L, Calebiro D, Herberg FW, Stratakis CA, Bertherat J. Activating PRKACB somatic mutation in cortisol-producing adenomas. *JCI Insight. 2018 Apr 19;3*(8). pii: 98296.
4. Hernández-Ramírez LC, Gam R, Valdés N, Lodish MB, Pankratz N, Balsalobre A, Gauthier Y, Faucz FR, Trivellin G, Chittiboina P, Lane J, Kay DM, Dimopoulos A, Gaillard S, Neou M, Bertherat J, Assié G, Villa C, Mills JL, Drouin J, Stratakis CA. Loss-of-function mutations in the CABLES1 gene are a novel cause of Cushing's disease. *Endocr Relat Cancer. 2017 Aug;24*(8):379-392.
5. Stratakis CA, Kelestimur F, Bertherat J. PDE 2015: cAMP signaling, protein kinase A (PKA) and phosphodiesterases (PDEs): How genetics changed the way we look at one of the most studied signaling pathways. *Horm Metab Res. 2017 Apr;49*(4):237-239.
6. Bram Z, Louiset E, Ragazzon B, Renouf S, Wils J, Duparc C, Boutelet I, Rizk-Rabin M, Libé R, Young J, Carson D, Vantyghem MC, Szarek E, Martinez A, Stratakis CA, Bertherat J, Lefebvre H. PKA regulatory subunit 1A inactivating mutation induces serotonin signaling in primary pigmented nodular adrenal disease. *JCI Insight. 2016 Sep 22;1*(15):e87958.
7. Drelon C, Berthon A, Sahut-Barnola I, Mathieu M, Dumontet T, Rodriguez S, Batisse-Lignier M, Tabbal H, Tauveron I, Lefrançois-Martinez AM, Pointud JC, Gomez-Sanchez CE, Vainio S, Shan J, Sacco S, Schedl A, Stratakis CA, Martinez A, Val P. PKA inhibits WNT signaling in adrenal cortex zonation and prevents malignant tumour development. *Nat Commun. 2016 Sep 14;7*:12751.
8. Iacovazzo D, Caswell R, Bunce B, Jose S, Yuan B, Hernández-Ramírez LC, Kapur S, Caimari F, Evanson J, Ferraù F, Dang MN, Gabrovska P, Larkin SJ, Ansorge O, Rodd C, Vance ML, Ramírez-Renteria C, Mercado M, Goldstone AP, Buchfelder M, Burren CP, Gurlek A, Dutta P, Choong CS, Cheetham T, Trivellin G, Stratakis CA, Lopes MB, Grossman AB, Trouillas J, Lupski JR, Ellard S, Sampson JR, Roncaroli F, Korbonits M. Germline or somatic GPR101 duplication leads to X-linked acrogigantism: A clinico-pathological and genetic study. *Acta Neuropathol Commun. 2016 Jun 1;4*(1):56.
9. Daly AF, Lysy PA, Desfilles C, Rostomyan L, Mohamed A, Caberg JH, Raverot V, Castermans E, Marbaix E, Maiter D, Brunelle C, Trivellin G, Stratakis CA, Bours V, Raftopoulos C, Beauloye V, Barlier A, Beckers A. GHRH excess and blockade in X-LAG syndrome. *Endocr Relat Cancer. 2016 Mar;23*(3):161-70.

10. Naves LA, Daly AF, Dias LA, Yuan B, Zakir JC, Barra GB, Palmeira L, Villa C, Trivellin G, Júnior AJ, Neto FF, Liu P, Pellegata NS, Stratakis CA, Lupski JR, Beckers A. Aggressive tumor growth and clinical evolution in a patient with X-linked acro-gigantism syndrome. *Endocrine. 2016 Feb;51*(2):236-44.

11. Rostomyan L, Daly AF, Petrossians P, Nachev E, Lila AR, Lecoq AL, Lecumberri B, Trivellin G, Salvatori R, Moraitis AG, Holdaway I, Kranenburg-van Klaveren DJ, Chiara Zatelli M, Palacios N, Nozieres C, Zacharin M, Ebeling T, Ojaniemi M, Rozhinskaya L, Verrua E, Jaffrain-Rea ML, Filipponi S, Gusakova D, Pronin V, Bertherat J, Belaya Z, Ilovayskaya I, Sahnoun-Fathallah M, Sievers C, Stalla GK, Castermans E, Caberg JH, Sorkina E, Auriemma RS, Mittal S, Kareva M, Lysy PA, Emy P, De Menis E, Choong CS, Mantovani G, Bours V, De Herder W, Brue T, Barlier A, Neggers SJ, Zacharieva S, Chanson P, Shah NS, Stratakis CA, Naves LA, Beckers A. Clinical and genetic characterization of pituitary gigantism: an international collaborative study in 208 patients. *Endocr Relat Cancer. 2015 Oct;22*(5):745-57.

12. Perez-Rivas LG, Theodoropoulou M, Ferraù F, Nusser C, Kawaguchi K, Stratakis CA, Faucz FR, Wildemberg LE, Assié G, Beschorner R, Dimopoulou C, Buchfelder M, Popovic V, Berr CM, Tóth M, Ardisasmita AI, Honegger J, Bertherat J, Gadelha MR, Beuschlein F, Stalla G, Komada M, Korbonits M, Reincke M. The gene of the ubiquitin-specific protease 8 is frequently mutated in adenomas causing Cushing's disease. *J Clin Endocrinol Metab. 2015 Jul;100*(7):E997-E1004.

13. Zilbermint M, Xekouki P, Faucz FR, Berthon A, Gkourogianni A, Schernthaner-Reiter MH, Batsis M, Sinaii N, Quezado MM, Merino M, Hodes A, Abraham SB, Libé R, Assié G, Espiard S, Drougat L, Ragazzon B, Davis A, Gebreab SY, Neff R, Kebebew E, Bertherat J, Lodish MB, Stratakis CA. Primary aldosteronism and ARMC5 variants. *J Clin Endocrinol Metab. 2015 Jun;100*(6):E900-9.

14. Espiard S, Drougat L, Libé R, Assié G, Perlemoine K, Guignat L, Barrande G, Brucker-Davis F, Doullay F, Lopez S, Sonnet E, Torremocha F, Pinsard D, Chabbert-Buffet N, Raffin-Sanson ML, Groussin L, Borson-Chazot F, Coste J, Bertagna X, Stratakis CA, Beuschlein F, Ragazzon B, Bertherat J. ARMC5 mutations in a large cohort of primary macronodular adrenal hyperplasia: clinical and functional consequences. *J Clin Endocrinol Metab. 2015 Jun;100*(6):E926-35.

15. Trivellin G, Daly AF, Faucz FR, Yuan B, Rostomyan L, Larco DO, Schernthaner-Reiter MH, Szarek E, Leal LF, Caberg JH, Castermans E, Villa C, Dimopoulos A, Chittiboina P, Xekouki P, Shah N, Metzger D, Lysy PA, Ferrante E, Strebkova N, Mazerkina N, Zatelli MC, Lodish M, Horvath A, de Alexandre RB, Manning AD, Levy I, Keil MF, Sierra Mde L, Palmeira L, Coppieters W, Georges M, Naves LA, Jamar M, Bours V, Wu TJ, Choong CS, Bertherat J, Chanson P, Kamenický P, Farrell WE, Barlier A, Quezado M, Bjelobaba I, Stojilkovic SS, Wess J, Costanzi S, Liu P, Lupski JR, Beckers A, Stratakis CA. Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutation. *N Engl J Med. 2014 Dec 18;371*(25):2363-74.

16. Haller F, Moskalev EA, Faucz FR, Barthelmeß S, Wiemann S, Bieg M, Assie G, Bertherat J, Schaefer IM, Otto C, Rattenberry E, Maher ER, Ströbel P, Werner M, Carney JA, Hartmann

A, Stratakis CA, Agaimy A. Aberrant DNA hypermethylation of SDHC: a novel mechanism of tumor development in Carney triad. *Endocr Relat Cancer. 2014 Aug;21*(4):567-77.

17. Faucz FR, Zilbermint M, Lodish MB, Szarek E, Trivellin G, Sinaii N, Berthon A, Libé R, Assié G, Espiard S, Drougat L, Ragazzon B, Bertherat J, Stratakis CA. Macronodular adrenal hyperplasia due to mutations in an armadillo repeat containing 5 (ARMC5) gene: a clinical and genetic investigation. *J Clin Endocrinol Metab. 2014 Jun;99*(6):E1113-9.
18. Beuschlein F, Fassnacht M, Assié G, Calebiro D, Stratakis CA, Osswald A, Ronchi CL, Wieland T, Sbiera S, Faucz FR, Schaak K, Schmittfull A, Schwarzmayr T, Barreau O, Vezzosi D, Rizk-Rabin M, Zabel U, Szarek E, Salpea P, Forlino A, Vetro A, Zuffardi O, Kisker C, Diener S, Meitinger T, Lohse MJ, Reincke M, Bertherat J, Strom TM, Allolio B. Constitutive activation of PKA catalytic subunit in adrenal Cushing's syndrome. *N Engl J Med. 2014 Mar 13;370*(11):1019-28
19. Forlino A, Vetro A, Garavelli L, Ciccone R, London E, Stratakis CA, Zuffardi O. PRKACB and Carney complex. *N Engl J Med. 2014 Mar 13;370*(11):1065-7.
20. Assié G, Libé R, Espiard S, Rizk-Rabin M, Guimier A, Luscap W, Barreau O, Lefèvre L, Sibony M, Guignat L, Rodriguez S, Perlemoine K, René-Corail F, Letourneur F, Trabulsi B, Poussier A, Chabbert-Buffet N, Borson-Chazot F, Groussin L, Bertagna X, Stratakis CA, Ragazzon B, Bertherat J. ARMC5 mutations in macronodular adrenal hyperplasia with Cushing's syndrome. *N Engl J Med. 2013 Nov 28;369*(22):2105-14.

Recent Achievements in International Health

Work on the genetics of protein kinase A, phosphodiesterases, G-Protein coupled receptors and related genes (all involved in the cAMP pathway) has led to the discovery of new diseases and decreased morbidity and mortality of the disorders caused by these defects. New medical treatments are being designed as a result of this research.

International Trainees

- Annabel Berthon, Ph.D.
  Postdoctoral Visiting Fellow
  University of Clermont Ferrand, France
  Issoire, France
- Laura Cristina Hernández Ramírez, Ph.D.
  Postdoctoral Visiting Fellow
  Queen Mary University of London
  Barts and The London School of Medicine
  Centre for Endocrinology
  William Harvey Research Institute
- Giampaolo Trivellin, Ph.D.
  Postdoctoral Visiting Fellow
  University of Padova
  Bassano Del Grappa, Italy

- Nikolaos Settas, Ph.D.
  Postdoctoral Visiting Fellow
  National and Kapodistrian University of Athens, School of Medicine
  Department of Genetics
  Athens, Greece
- Christina Tatsi, M.D., Ph.D.
  Clinical and Research Fellow in Pediatric Endocrinology
  National and Kapodistrian University of Athens, School of Medicine
  Department of Pediatrics
  Athens, Greece
- Ludivine Drougat Charlier, Ph.D.
  Postdoctoral Visiting Fellow
  Institut Cochin
  Paris, France
- Andrea Gutierrez Maria, Ph.D.
  Special Volunteer
  Universidade de Sao Paulo
  Department of Pediatrics
  Sao Paulo, Brazil
- Mingming Ho
  Special Volunteer
  Peking Union Medical College Hospital
  Department of Endocrinology
  Beijing, China

International Partnerships

Memoranda of Understanding (MOU) with:

- Dr. Albert Beckers, Liege, Belgium
- Dr. Jerome Bertherat and others in France
- Prof. Stefan Bornstein and others in Germany
- Dr. Maria Candida Fragoso and others in Brazil
- Dr. Annalisa Vetro and others in Italy
- Dr. Jan Marteen Wit and others in Holland

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Fabio Rueda Faucz
fabio.faucz@nih.gov
301-451-7177

Section on Environmental Gene Regulation (SEGR)

PI: Gisela Storz, Ph.D.
AG: Cell and Structural Biology

Mission

Currently, SEGR has two main interests: the identification and characterization of small noncoding RNAs, and the identification and characterization of small proteins of less than 50 amino acids. Both small RNAs and small proteins have been overlooked because they are not detected in biochemical assays and the corresponding genes are poorly annotated and missed in genetic screens. However, mounting evidence suggests that both classes of these small molecules play important regulatory roles.

Major International Initiatives

N/A

Publications with International Collaborators

Olejniczak, M. and Storz, G. (2017) ProQ/FinO-domain proteins: another ubiquitous family of RNA matchmakers? *Mol. Microbiol. 104*, 905-915.

Recent Achievements in International Health

The review listed above was written together with Dr. Mikolaj Olejniczak, a colleague at the Institute of Molecular Biology and Biotechnology, Faculty of Biology, Adam Mickiewicz Univeresity in Poznan, Poland. We have followed up the review with discussions of possible collaborative projects.

International Trainees

Mr. Hanbo Wang completed the requirements for a Ph.D. degree through The Chinese University of Hong Kong-NICHD graduate partnership program this year.

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Gisela Storz
storz@helix.nih.gov
301-402-0968

Section on Intercellular Interactions (SII)

PI: Leonid Margolis, Ph.D.
AG: Maternal-Fetal Medicine, Imaging, & Behavioral Determinants

Mission

To identify basic mechanisms of cell interactions in norm and pathologies

Major International Initiatives

- Development of ex vivo models of atherosclerotic plaques: A collaborative project with Moscow University of Medicine and Dentistry, Moscow, Russia (PIs: Dr. Elena Vasilieva and Alexander Shpektor)
- Morphological analysis of extracellular vesicles generated by CMV-infected cells and their role in HIV infection: A collaborative project with Cochin Institute, Paris, France (PI: Dr. Morgan Bomsel)
- Investigation of the role of *Lactobacillus*-generated of extracellular vesicles in protection against vaginal HIV transmission: A collaborative project with the University of Bologna, Bologna, Italy (PI: Dr. Beatrice Vitali)
- Development of anti-HIV/ anti-CMV dual-targeted antivirals: A collaborative project with the Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russia (PI: Dr. Sergey Kochetkov)
- Educational project, Ilia University, Tbilisi, Republic of Georgia (Prof. D. Mikeladze)

Publications with International Collaborators

N/A

Recent Achievements in International Health

N/A

International Trainees

- Dr. Rogers Palomina
  International Trainee
  University of Bologna, Italy
- Ms. Daria Vorobyeva
  Ph.D. Student
  Moscow Medical University
- Mr.Vincenzo Mercurio
  Ph.D. Student
  University of Milan

International Partnerships

SII is an international partner in the framework of the NIH Office of AIDS Research Intramural-to-Russia Program.

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Leonid Margolis
margolil@helix.nih.gov
301-594-2476

Section on Molecular Morphogenesis (SMM)

PI: Yun-Bo Shi, Ph.D.
AG: Cell Regulation and Development

Mission

The SMM studies the gene-regulatory mechanisms controlled by thyroid hormone (TH) receptor that establish the postembryonic developmental program in vertebrates. The main model system is amphibian metamorphosis. The laboratory recently showed that TH receptor is both necessary and sufficient for metamorphosis by recruiting cofactors in a TH-dependent manner and revealed the origin of the TH-induced adult intestinal epithelial stem cells. The laboratory has also identified many TH target genes and is currently investigating their regulation and function during larval organ degeneration and adult organ development.

Major International Initiatives

The SMM has collaborated with laboratories in several different countries. Summarized below are collaborations that have resulted in publications within the last 5 years.

The work of this section on intestinal remodeling during thyroid hormone-dependent *Xenopus* metamorphosis, in conjunction with researchers at Nippon Medical School in Japan and Wuhan University in China, has led to a new understanding of the formation of organ-specific adult stem cells during vertebrate development. As intestinal maturation in frog metamorphosis resembles that in human neonatal development, these findings may aid development of stem cell-based tissue therapies for human diseases such as necrotizing enterocolitis, the most common gastrointestinal emergency in neonates, especially premature infants.

Tail resorption during amphibian metamorphosis is perhaps the most dramatic developmental events controlled by TH. In collaboration with researchers at Hiroshima University, Japan, and Chengdu Institute of Biology, China, we have recently discovered a unique role of TH receptor β in regulating notochord resorption during *Xenopus* metamorphosis and analyzed the expression program underlying tail resorption during metamorphosis of the ornamented pygmy frog, *Microhyla* fissipes, revealing conserved gene expression profiles in tail resorption between terrestrial and aquatic frog species.

To investigate the function of endogenous genes during metamorphosis, there has been a recent collaboration with scientists in South University of Science and Technology of China to adapt the transcriptional activator-like effector nuclease (TALEN) and clustered regularly interspaced short palindromic repeat (CRISPR) for efficient disruption of *Xenopus* genes, leading to novel discoveries on the functions of thyroid hormone receptor alpha and a histone methyltransferase. Though this collaboration concluded, continued data analysis resulted in recent publications listed below.

Through collaboration with researchers at the University of Dundee in the UK, a conditional knockout mouse line has been generated to investigate the role of a transporter for TH and amino acids that has been previously shown to be induced by TH during frog intestinal

metamorphosis. Analysis of the mouse knockout line indicates that the transporter facilitates nutrient signaling in mouse skeletal muscle. More recently, a collaboration with researchers in Kanazawa University Graduate School, Japan, has shown that the transporter also regulates osteoclastogenesis and bone homeostasis via the mTORC1 pathway.

The likely conservation of TH function in vertebrate development prompted investigation of the role of TH in mouse intestinal development. A collaboration with scientists at NCI, NIH, and Xi'an Jiaotong University School of Medicine, China, recently showed that in a mouse model mimicking human patients with resistance to TH due to TH receptor α mutations, a heterozygous dominant negative TH receptor α mutation leads to stem cell defects in the adult intestine, consistent with our finding on the role of TH in adult intestinal stem cell development in *Xenopus*.

In addition, a collaboration with Wuhan University has revealed that hepatitis B virus induces autophagy to increase viral replication by regulating NFkB signaling via the miR-192-3p-XIAP axis. Though this collaboration concluded, continued data analysis resulted in recent publications listed below.

Finally, in collaboration with researchers at Wuhan University, it was demonstrated that fluorescent-magnetic-biotargeting of multifunctional nanoparticles can be used as probes for concurrent and efficient detection and isolation of multiple types of tumor cells. More recently, *Staphylococcus* aureus cells have been successfully transformed into fluorescent probes for pathogen detection by synthesizing fluorescent quantum dots in the cells. These findings should find applications in clinical diagnosis and facilitate cancer research involving clinical samples. Though this collaboration formally concluded, continued data analysis resulted in recent publications listed below.

Publications with International Collaborators

1. Sun, G., Fu, L., and Shi, Y.-B. (2014) Epigenetic regulation of thyroid hormone-induced adult intestinal stem cell development during anuran metamorphosis. *Cell & Bioscience 4:73*, 1-8.
2. Sun, G., Fu, L., Wen, L., and Shi, Y.-B. (2014) Activation of Sox3 gene by thyroid hormone in the developing adult intestinal stem cell during *Xenopus* metamorphosis. *Endocrinology.155*(12):5024–5032.
3. Sun, G., Roediger, J., and Shi, Y.-B. (2016) Thyroid hormone regulation of adult intestinal stem cells: Implications on intestinal development and homeostasis. *Reviews in Endocrine and Metabolic Disorders. 17*, 559-569.
4. Wen, L., Hasebe, T., Miller, T.C., Ishizuya-Oka, A., and Shi, Y.-B. (2015) A requirement for hedgehog signaling in thyroid hormone-induced postembryonic intestinal remodeling. *Cell & Bioscience 5*:13, 1-12.
5. Hasebe, T., Fujimoto, K., Kajita, M., Fu, L., Shi, Y.-B., and Ishizuya-Oka, A. (2017) Thyroid hormone-induced activation of Notch signaling is required for adult intestinal stem cell development during *Xenopus* laevis metamorphosis. *Stem Cells 35*:1028–1039.

6. Wang, S., Liu, L., Liu, J., Zhu, W., Tanizaki, Y., Fu, L., Bao, L., Shi, Y.-B., Jiang, J. (2019) Gene expression program underlying tail resorption during thyroid hormone-dependent metamorphosis of the ornamented pygmy frog *Microhyla* fissipes. *Frontiers in Endocrinology 10*:11, 1-12; doi: 10.3389/fendo.2019.00011
7. Nakajima, K., Tazawa, I., and Shi, Y.-B. (2019) A unique role of thyroid hormone receptor β in regulating notochord resorption during *Xenopus* metamorphosis. *General and Comparative Endocrinology 277*: 66–72.
8. Wen, L., Fu, L., Guo, X., Chen, Y., and Shi, Y.-B. (2015) Histone methyltransferase Dot1L plays a role in postembryonic development in *Xenopus* tropicalis. *FASEB J. 29*, 385-393.
9. Wang, F., Shi, Z., Cui, Y., Guo, X., Shi, Y.-B., and Chen, Y. (2015) Targeted gene disruption in *Xenopus* laevis using CRISPR/Cas9. *Cell & Bioscience 5*:15, 1-5.
10. Poncet, N., Mitchell, F.E., Ibrahim, A.F.M., McGuire, V.A., English, G., Arthur, S.C., and Shi, Y.-B., and Taylor, P.M. (2014) The catalytic subunit of the System L1 amino acid transporter (Slc7a5) facilitates nutrient signaling in mouse skeletal muscle. *PLoS One 9*(2): e89547,1-14.
11. Ozaki, K., Yamada, T., Horie, T., Ishizaki, A., Hiraiwa, M., Iezaki, T., Park, G., Kazuya Fukasawa, K., Kamada, H., Kaneda, K., Ogawa, K., Ochi, H., Sato, S., Kobayashi, Y., Shi, Y.-B., Taylor, P.M., Hinoi, E. (2019) The L-type amino acid transporter LAT1 inhibits osteoclastogenesis and maintains homeostasis through the mTORC1 pathway. *Science Signaling, Jul9;12*(859).
12. Bao, L., Roediger, J., Park, S., Fu, L., Shi, B., Cheng, S.-Y., and Shi, Y.-B. (2019) TRα mutations lead to stem cell defects in the adult intestine in a mouse model of resistance to thyroid hormone. *Thyroid 29*: 439-448.
13. Wang, J., Chen, J., Wei, M., Wu, S., Zeng, X., Xiong, Q., Song, F., Xiao, Y., Bao, Y., Liu, Z., Li, C., Guo, M., Shi, Y.-B., Sun, G., and Guo, D. (2019) HBV inducing autophagy to increase its replication by the axis of miR-192-3p-XIAP via NFkB signal. *Hepatology. 69*:974-992.
14. Xiong, L.-H., Cui, R., Zhang, Z.-L., Yu, X., Xie, Z.-X., Shi, Y.-B., and Pang, D.-W. (2014) Uniform fluorescent nanobioprobes for pathogen detection. *ACS Nano 8*(5), 5116–5124.
15. Liu, S.-L., Zhang, L.-J., Zhang, Z.-L., Wang, Z.-G., Wu, Q.-M., Sun, E.-Z., Shi, Y.-B., and Pang, D.-W. (2014) Globally visualizing the microtubule-dependent infection behaviors of influenza virus in live cells. *Analytical Chemistry 86*(8), 3902–3908.
16. Xiong, L.-H., Cui, R., Zhang, Z.-L., Tu, J.-W., Shi, Y.-B., and Pang, D.-W. (2015) Harnessing intracellular biochemical pathways for in vitro synthesis of designer tellurium nanorods. *Small, 11*(40): 5416–5422.

Recent Achievements in International Health

N/A

International Trainees

- Shouhong Wang
  Graduate Student
  Chengdu Institute of Biology, China
- Lingyu Bao
  Graduate Student
  Xi'an Jiaotong University School of Medicine, China

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Yun-Bo Shi
shi@helix.nih.gov
301-402-1004

Section on Molecular Neurobiology (SMN)

PI: Andres Buonanno, Ph.D.
AG: Cell and Structural Biology

Mission

Project A

The SMN aims to elucidate how Neuregulin and its receptor ErbB4, both of which are genetically associated with psychiatric disorders, function in the developing brain to regulate synaptic plasticity, neuronal network activity (i.e., gamma oscillations) and behaviors that model features of psychiatric disorders in rodents. Researchers are using multidisciplinary approaches, including electrophysiological, neurochemical, gene targeting, molecular/cellular and behavioral techniques, to achieve these aims. The ultimate goal of this multidisciplinary approach is to generate holistic models to investigate the developmental impact of genes that modulate excitatory/inhibitory balance and neuronal network activity, and that consequently affect behaviors and cognitive functions altered in psychiatric disorders.

Project B

A second aim of the SMN is to understand how distinct activity patterns (i.e., exercise regiments) regulate the contractile properties of adult muscles. Multidisciplinary approaches, including gene targeting, molecular/cellular, whole genome-wide scans, in vivo muscle stimulation, and live imaging of transcription in adult skeletal muscles are being used to identify transcription factors that selectively regulate the slow- and fast-twitch muscle programs in response to distinct stimulation (depolarization) patterns.

Major International Initiatives

Project A

In collaboration with Dr. Oh-Bin Kwon at the Department of Life Science, Pohang University of Science and Technology, South Korea, and Dr. Elias Leiva-Salcedo at the Department of Chemistry and Biology, Universidad de Santiago, Chile, SMN has been studying how gene-targeted NRG2 mice (knockouts) exhibit deficits in synaptic plasticity and glutamatergic transmission, and the many behavioral phenotypes relevant to psychiatric disorders. Ms. Larissa Erben, a graduate student at the University of Bonn, Germany, has joined the laboratory to pursue her dissertation project on analyzing ErbB4 splice variants (co-mentor Dr. Andreas Zimmer). Dr. Tanveer Ahmed at the Department of Biochemistry, University Grants Commission (UGC) at New Dehli is studying trafficking of NRG3 in neurons.

Project B

The major initiative of this project, in collaboration with Dr. Kristian Gundersen's group at Oslo University, Norway, is to identify transcription factors that are differentially modulated by slow (10 Hz) and fast (100 Hz) patterns of motorneuron activity and that, in turn, regulate genes

encoding the contractile properties that determine the slow- and fast-twitch properties of skeletal muscles.

Publications with International Collaborators

Project A

1. Vullhorst, D. Mitchell, RM., Keating, C., Roychowdhury, S., Karavanova, I., Tao-Cheng, J-H., Buonanno, A. (2015) A negative feedback loop controls NMDA receptor function in cortical interneurons via neuregulin 2/ErbB4 signalling. *Nature Comm 6, 7222 DOI: 10.108/ ncomms8222*.
2. Yan, L., Shamir, A., Skirzewski, M., Leiva-Salcedo E., Kwon O.B., Karavanova I., Paredes D., Malkesman O., Bailey K.R., Vullhorst D., Crawley J.N. and Buonanno A. (2017) Neuregulin-2 ablation results in dopamine dysregulation and severe behavioral phenotypes relevant to psychiatric disorders. *Mol Psychiatry Mar 21. doi: 10.1038/mp.2017.22*.
3. Skirzewski M., Karavanova I., Shamir A., Erben L., Garcia-Olivares J., Shin J.H., Vullhorst D., Alvarez V.A., Amara S.G. and Buonanno A. (2017) ErbB4 signaling in dopaminergic axonal projections increases extracellular dopamine levels and regulates spatial/working memory behaviors. *Mol Psychiatry, 2017 Jul 20. doi: 10.1038/ mp.2017.132*.
4. Vullhorst D., Ahmad T., Karavanova I., Keating C., Buonanno A. (2017) Structural similarities between Neuregulin 1-3 isoforms determine their subcellular distribution and signaling mode in central neurons. *J Neurosci. 37,* 5232-5249.

Project B

Rana, ZA., Bruusgaard JC, Wendland, JR, Wenje, I, Karavanova, I, Gundersen, K. and Buonanno, A. (2017) Ets2 is an activity-dependent transcriptional regulator of a fast-twitch muscle program. *Nature Comm* (in revision).

Recent Achievements in International Health

We work on basic science projects with a potential for translational research, particularly in Project A.

International Trainees (alphabetical order)

- Tanveer Ahmed, Ph.D.
  Assistant Professor
  Department of Biochemistry, University Grants Commission
  New Delhi, India
- Sharmila Basu, Ph.D.
  President and Chief Scientific Officer
  MindSpec
  McLean, Virginia

- Swagata Roychowdhury-Basu, Ph.D.
  Technical Writer for Neuroscience Advances
  Inscopix, Inc.
- Soledad Calvo, M.D., Ph.D.
  Assistant Professor
  Facultad de Medicina at Alicante University
  Spain
- Claudia Colina-Prisco, Ph.D.
  Postdoctoral Fellow
  NIAAA, NIH
- Rolando Garcia, Ph.D.
  Senior Scientist
  Wellstat Therapeutics
  Gaithersburg, Maryland
- Carmen M. Gonzalez, Ph.D.
  Department of Pathology and Exp Therapy
  University of Barcelona, Spain
- Ryoichi Kimura, Ph.D.
  Assistant Professor
  Department of Physiology, Hyogo College of Medicine
  Nishinomiya, Japan
- Oh-Bin Kwon, Ph.D.
  Assistant Professor
  Molecular NeuroScience Lab
  Department of Life Science, POSTECH
  South Korea
- Marines Longart, Ph.D.
  Principal Investigator
  Center for Biosciences, Institute for Advanced Studies
  Caracas, Venezuela
- Elias Leiva-Salcedo
  Assistant Professor
  Facultad de Química y Biología, Universidad de Santiago
  Chile
- Joerg Neddens, Ph.D.
  Senior Scientist,
  Department of Histology
  JSW Life Sciences, Austria

- Daniel Paredes, Ph.D.
  Investigator
  Lieber Institute for Brain Development
  Baltimore, Maryland
- Zaheer Rana, Ph.D.
  Staff Scientist
  Department of Molecular Biosciences
  University of Oslo, Norway
- Alon Shamir, Ph.D.
  Head of Research Laboratory
  Mazra Mental Health Center, Israel
- Miguel Skirzewski, Ph.D.
  Postdoctoral Fellow
  NICHD, NIH
- Raluca Yonescu, Ph.D.
  Senior Research Specialist
  Johns Hopkins Cytogenetics, Maryland

International Partnerships

- Universidad de los Andes, Merida, Venezuela. MOU and joint graduate student stipend for Dr. Miguel Skirzewski
- University of Bonn. MOU for graduate student stipend for Ms. Larissa Erben
- Oslo University, Norway. MOU for Dr. Zaheer Rana to perform his dissertation

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Andres Buonanno
buonanno@mail.nih.gov
301-496 0170

Section on Nutrient Control of Gene Expression (SNCGE)

PI: Alan Hinnebusch, Ph.D.
AG: Cell Regulation and Development

Mission

Work from the SNCGE on the mechanism of protein synthesis initiation in budding yeast provided the foundation for a collaboration with researchers at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, on high-resolution cryo-electron microscopy of reconstituted preinitiation complexes, which reveal conformational changes that occur on the transition from the scanning phase of initiation to that of start codon recognition. Collaborative work with researchers at Shimane University School of Medicine, Shimane, Japan, provided structural analysis of interactions among translation initiation factors using nuclear magnetic resonance spectroscopy. Collaborative work with researchers at Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Moscow, Russia, provided biochemical analysis of the mechanism of ribosome recycling. Collaborative work with researchers at the John Curtin School of Medical Research, the Australian National University, Canberra, Australia, provided protocols and bioinformatics analysis of small subunit ribosome profiling that unveiled the role of the RNA helicase Ded1 in promoting ribosomal scanning through structured mRNAs during translation initiation. Collaborative work with researchers at Universidad de Salamanca, Spain, and the University Duisburg-Essen, Germany, provided molecular genetic data revealing the effects of human cancer-related mutations in the initiation factor eIF1A on the mechanism of scanning and start codon selection in translation initiation.

Major International Initiatives

N/A

Publications with International Collaborators

1. Llácer JL, Hussain T, Marler L, Aitken CE, Thakur A, Lorsch JR, Hinnebusch AG, Ramakrishnan V. Conformational differences between open and closed states of the eukaryotic translation initiation complex. *Mol Cell. 2015 Aug 6;59*(3):399-412.
2. Hussain T, Llácer JL, Fernández IS, Munoz A, Martin-Marcos P, Savva CG, Lorsch JR, Hinnebusch AG, Ramakrishnan V. Structural changes enable start codon recognition by the eukaryotic translation initiation complex. *Cell. 2014 Oct 23;159*(3):597-607. doi: 10.1016/j.cell.2014.
3. Obayashi E, Luna RE, Nagata T, Martin-Marcos P, Hiraishi H, Singh CR, Erzberger JP, Zhang F, Arthanari H, Morris J, Pellarin R, Moore C, Harmon I, Papadopoulos E, Yoshida H, Nasr ML, Unzai S, Thompson B, Aube E, Hustak S, Stengel F, Dagraca E, Ananbandam A, Gao P, Urano T, Hinnebusch AG, Wagner G, Asano K. Molecular landscape of the ribosome pre-initiation complex during mRNA scanning: structural role for eIF3c and its control by eIF5. *Cell Rep. 18*:2651-2663, 2017.
4. Martin-Marcos P, Zhou F, Karunasiri C, Zhang F, Dong J, Nanda J, Kulkarni SD, Sen ND, Tamame M, Zeschnigk M, Lorsch JR, Hinnebusch AG. eIF1A residues implicated in cancer

stabilize translation preinitiation complexes and favor suboptimal initiation sites in yeast. *Elife*. *6*: e31250, 2017.

5. Young DJ, Makeeva DS, Zhang F, Anisimova AS, Stolboushkina EA, Ghobakhlou F, Shatsky IN, Dmitriev SE, Hinnebusch AG, Guydosh NR. Tma64/eIF2D, Tma20/MCT-1, and Tma22/DENR recycle post-termination 40S subunits in vivo. *Mol Cell*. *71*:761-774, 2018.
6. Llácer JL, Hussain T, Saini AK, Nanda JS, Kaur S, Gordiyenko Y, Kumar R, Hinnebusch AG, Lorsch JR, Ramakrishnan V. Translational initiation factor eIF5 replaces eIF1 on the 40S ribosomal subunit to promote start-codon recognition. *Elife*. *2018 Nov 30*;7. pii: e39273.
7. Sen ND, Gupta N, K Archer S, Preiss T, Lorsch JR, Hinnebusch AG. Functional interplay between DEAD-box RNA helicases Ded1 and Dbp1 in preinitiation complex attachment and scanning on structured mRNAs in vivo. *Nucleic Acids Res*. *2019 Jul 12*. pii: gkz595. doi: 10.1093/nar/gkz595. [Epub ahead of print]

Recent Achievements in International Health

N/A

International Trainees

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Alan Hinnebusch
alanh@mail.nih.gov
301-496-4480

Section on Protein Biosynthesis (SPB)

PI: Thomas Dever, Ph.D.
AG: Cell Regulation and Development

Mission

The SPB is studying cellular protein synthesis. The lab has long-standing interests in characterizing the structure and function of translation factors, the molecular principles of kinase-substrate recognition by the stress-responsive eIF2a kinases, and the functions of unique modifications on the translation factors eIF5A and eEF2. The group recently reported that the translation factor eIF5A functions generally in translation elongation and termination, and that it is especially required for the synthesis of peptides containing polyproline sequences. The group has also characterized mutations in the translation factor eIF2 that cause MEHMO syndrome, an X-linked intellectual disability syndrome.

Major International Initiatives

Molecular, genetic, and biochemical studies in yeast and mammalian cells on the mechanism and regulation of protein synthesis from this section established the groundwork for collaborations with human molecular geneticists and with molecular biologists. Studies in collaboration with human geneticists in London identified mutations in the translation factor eIF2gamma that cause a novel form of MEHMO syndrome marked by hypopituitarism and glucose dysregulation and revealed that the mutation impairs protein synthesis and relax the stringency of translation start site selection. Work with molecular biologists in Cork, Ireland, revealed a novel form of translational control whereby polyamines interfere with eIF5A function to cause pausing and queuing of ribosomes to control synthesis of the polyamine regulatory factor antizyme inhibitor.

Publications with International Collaborators

1. Gregory LC, Ferreira CB, Young-Baird SK, Williams HJ, Harakalova M, van Haaften G, Rahman SA, Gaston-Massuet C, Kelberman D, GOSgene, Qasum W, Camper SA, Dever TE, Shah P, Robinson ICAF, Dattani MT. Impaired EIF2S3 function associated with a novel phenotype of X-linked hypopituitarism with glucose dysregulation. *EBioMedicine 42*:470-480, 2019. PMID:30878599.
2. Ivanov IP, Shin BS, Loughran G, Tzani I, Young-Baird SK, Cao C, Atkins JF, Dever TE. Polyamine control of translation elongation regulates start site selection on antizyme inhibitor mRNA via ribosome queuing. *Mol Cell 70*:254-264, 2018. PMID:29677493.

Recent Achievements in International Health

N/A

International Trainees

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

Dr. Thomas Dever
Thomas.Dever@nih.gov
301-496-4519