NICHD International Activities Catalog

2020

Office of Global Health
Office of the Director

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

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Overview

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) was founded in 1962 to investigate human development throughout the entire life process, with a focus on understanding disabilities and important events that occur during pregnancy. Since then, research conducted and funded by NICHD has helped save lives, improve wellbeing, and reduce societal costs associated with illness and disability. NICHD's mission is to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all.

NICHD has supported international research since its establishment nearly 60 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 international activities across the institute.

OGH works in close collaboration with NICHD divisions and offices, as well as with 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, provides an annual reporting of global health activities across the NICHD'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 scientific scope of each component, 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)

The NICHD OD provides overall leadership, planning, direction, coordination, and evaluation of the institute's research programs and activities. The 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)

Scientific Scope

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

COVID-19 Pandemic Research Response. The COVID-19 pandemic brought biomedical research to a grinding halt and, more recently, slowed it in the United States and around the globe. OGH has represented NICHD in several meetings to discuss the U.S. government COVID-19 response organized by the HHS Office of Global Affairs (OGA), Fogarty International Center (FIC), and USAID Children in Adversity (APCCA) Interagency Working Group. Discussions focused on the consequences of disrupted research and training in multiple countries, and on the potential impact and next steps related to the Trump administration's petition on July 6, 2020, to withdraw the United States as a member state from the World Health Organization (WHO).

NICHD Strategic Planning Process – The Wefting of Global Health. OGH has contributed in two capacities to the NICHD Strategic Planning Process: 1) as co-chair for Research Theme 4 focused on child health and development, and 2) as the lead for the "wefting" of global health research priorities throughout the different components of the strategic plan. In the next phase of NICHD Strategic Plan implementation, OGH will seek to further improve real-time communication about global health priorities between the NICHD OD, including OGH, and other NICHD components, particularly with regard to key global health research issues, science advances, and interagency activities.

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 preterm births, healthy cognitive development, point-of-care diagnostics, vaccine development, tuberculosis (TB) drug discovery, and other areas. This work has included annual NIH-BMGF Global Health Consultations held on the NIH campus. 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), the National Institute of Neurological Disorders and Stroke (NINDS), National Heart, Lung, & Blood Institute (NHLBI), the NIH Environmental Influences on Child Health Outcomes (ECHO) Program, among others. These working groups aim to identify new research collaborations in the areas of pregnancy outcomes, nutrition and growth, child neurodevelopment, neuroimaging, contraception development, and sickle cell research, among other areas. Examples of joint activities have included the launch of the Azithromycin-Prevention in Labor Use Study (A-PLUS), and the NICHD intramural collaboration aimed at using the HyperFine Scanner to translate new imaging biomarkers for effective neurodevelopmental applications on this instrument.

NIH Common Fund: Data Science – I in Africa Program (DS-I Africa). NICHD staff has been participating in the DS-I Africa Common Fund Initiative to leverage data science technologies and prior NIH investments to develop solutions to Africa's most pressing public health problems. The DS-I Africa Virtual Conference and events extended August through October 2020, and NICHD organized a Maternal and Child Health Panel in October on Innovative Data Science Approaches to Improve Maternal and Child Health. Related NIH funding opportunities have focused on four areas: open data science platform

and coordinating center; research hubs; research training programs; and ethical, legal, and social implications (ELSI) research. In addition, the DS-I Africa Data Scholar Program was established, and the first scholar joined NIH in fall 2020.

Fogarty Fellows and Scholars Program. For the first time, NICHD will be participating in the Fogarty Fellows and Scholars Program which supports predoctoral (Scholars) and postdoctoral (Fellows) students from the United States and partners low- and middle-income country (LMIC) institutions for a year of mentored research at an established U.S.-based or comparable academic institution in an LMIC. Each grant is led by a consortium of U.S. universities with strong global health research and their LMIC partner institutions. The program has trained over 1,000 Fellows and Scholars, at over 80 research sites in 27 LMICs, and has published over 1,200 peer-reviewed papers. OGH and the NICHD Maternal and Pediatrics Infectious Diseases Branch (MPIDB) organized an internal peer-review process for the selection of candidates working on HIV/AIDS research and on topics in line with the NICHD mission.

OGH Brown Bag Seminar on the Prevention of Podoconiosis. In February 2020, OGH organized a global health seminar featuring the research of Dr. Fasil Tekola-Ayele in NICHD's DIPHR on Integrating Genetic Research on Podoconiosis with Prevention Strategies in Ethiopia. Podoconiosis, also known as elephantiasis, is the progressive swelling of the lower legs caused by years of exposure to inorganic irritants (i.e., silica particles) in red clay soil. It mainly affects barefooted farmers with high genetic susceptibility, including children as young as 10 years of age. Genetic research has identified the susceptibility locus (HLA class II Region) and helped characterize the potential functional mechanisms, enabling early identification of individuals who are most vulnerable to the disease for both more precise prevention and intervention approaches.

NICHD OGH Panel on Implementation Science. In fall 2020, OGH organized an NICHD panel on implementation science with participation from the NICHD Pregnancy and Perinatology Branch (PPB), the National Cancer Institute (NCI), and the NIH Office of Behavioral and Social Science Research (OBSSR). The purpose of the panel was to: 1) provide NICHD staff with an overview of Implementation Science as a research methodology; 2) provide examples of the use of Implementation Science across NIH and within interagency partnerships; and 3) share examples of the benefits of Implementation Science for NICHD research and specific populations, as described by NICHD funded grantees.

WHO Nurturing Care Framework. Over the past four 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 series in *The Lancet*, "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 (WHA) 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.

U.S. Government Children in Adversity Initiative. Since the onset of the COVID-19 pandemic earlier in 2020, this USAID-led, U.S. government working group for the Children in Adversity Initiative has focused on the impact of the COVID-19 outbreak on vulnerable children and families in LMICs. Particular focus areas have included the disruption of health services for children and families due to the COVID-19 outbreak, and the simultaneous rise in domestic violence, including child abuse, as a result of at-risk children spending more time in the home and not attending school. OGH has kept this working group apprised of trans-NIH research efforts targeting the COVID-19 outbreak of most relevance for at-risk

children and their families. A preliminary description of this initiative, aimed at developing a research agenda and whole-of-government strategy for work with children in adversity in LMICs was published in *The Lancet* in December 2011, with then-NICHD Director Dr. Alan Guttmacher serving as a co-author. In addition, an NICHD staff member served as co-editor of a special supplement in the journal *Child Abuse and Neglect* about the initiative, and multiple NICHD and NIH staff members were co-authors of several articles describing evidence review results.

Recent Achievements in International Health

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

Given the recent COVID-19 outbreak, some global health activities, such as visits to NIH by foreign delegations, high-level U.S. government staff visits to NIH international research sites, and international travel to scientific conferences have been postponed or canceled. Nonetheless, in collaboration with NICHD program staff, OGH has represented NICHD and prepared briefings for high-level global health leadership (e.g., White House Group of 7 Meeting, HHS OGA, HHS Health Attachés in Geneva, Kenya, and South Africa), and provided input on relevant maternal and child health research for interagency documents (e.g., WHA, WHO Regional Meetings).

- **Coordination of Visits by Foreign Delegations.** In early 2020, participated in the coordination of meetings and preparation of briefing materials for visits by foreign delegations (e.g., congressional delegation site visits in Norway, Finland, Denmark, Switzerland, and the United Kingdom)
- **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 prepared the NICHD International Activities Catalog to facilitate information exchanges related to global health
- **Scientific Input Provided for Interagency Global Health Documents.** Contributed to the writing of scientific and policy documents and requests for information from internal (e.g., NICHD, NIH, HHS) and external (e.g., USAID, WHO, United Nations International Children's Emergency Fund [UNICEF]) sources that describe NICHD's mission and international activities

International Partnerships

International partnerships developed through involvement on working groups are as follows.

Examples of Staff Membership on Global Health Committees/Working Groups

- NICHD Global Health Strategic Planning Team. Representatives: Drs. Vesna Kutlesic and Jenelle Walker
- NIH-BMGF Maternal, Neonatal, & Child Health Working Group. Representative: Dr. Vesna Kutlesic

- WHO Nurturing Care Framework Advisory Group. Representative: Dr. Vesna Kutlesic
- Children in Adversity Strategy Working Group. Representatives: Drs. Vesna Kutlesic and Jenelle Walker
- Trans-NIH Global Health Research Working Group. Representative: Dr. Vesna Kutlesic
- Trans-NIH International Clinical Research Subcommittee. Representative: Dr. Vesna Kutlesic
- FIC International Representatives Working Group. Representative: Dr. Vesna Kutlesic
- Fogarty International Interest Group. Representatives: Drs. Vesna Kutlesic and Jenelle Walker
- NICHD Reproductive Health Working Group. Representatives: Drs. Vesna Kutlesic and Jenelle Walker
- NICHD Maternal Mortality Working Group. Representatives: Dr. Vesna Kutlesic, Dr. Jenelle Walker, and Hannah Savage
- NICHD Male Health Working Group. Representatives: Dr. Vesna Kutlesic, Dr. Jenelle Walker, and Hannah Savage
- Global Nutrition Coordination Plan Technical Working Group: Dr. Jenelle Walker
- NCI Trans-NIH Dissemination & Implementation Working Group: Dr. Jenelle Walker
- NIH Global Health Interest Group: Dr. Jenelle Walker
- Trans-NIH China Working Group: Dr. Jenelle Walker

Point-of-Contact

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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, encompassing 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)

Scientific Scope

CDBB supports basic and translational research and training that addresses the typical neurocognitive, psychological, behavioral, physical, and social-emotional development and health of infants, children, and adolescents. The branch explores how individual differences in development, as well as family and other social relationships, are affected by emerging societal trends (e.g., increased reliance on technology and digital media), as well as public health emergencies (e.g., COVID-19 pandemic). The branch also supports basic research to identify the mechanisms by which atypical development and related health outcomes in children and adolescents from diverse backgrounds (e.g., low socioeconomic status, racial/ethnic and language minorities) and subpopulations (e.g., individuals with Specific Learning Disorders) arise from or are differentially affected by genetic and environmental risk/protective factors. The branch uses these findings to inform translational prevention, intervention, and health promotion studies designed to enhance the lives of children and adolescents.

Major International Activities over the Past Year

Parenting Across Cultures. CDBB is funding a longitudinal study in nine countries (China, Columbia, Jordan, Italy, Kenya, Philippines, Sweden, Thailand, and the United States) to examine 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. In addition, one study examines the role of parental socialization on early neurophysiological moral development across cultures, comparing Japanese and American parents and children. Specifically, this research tests cross-cultural differences in neurophysiological responses to social evaluation in preschool years; intergenerational transmission of moral evaluation across cultures; and the role of parental socialization on neurophysiological moral sensitivity and prosocial behaviors in preschool children.

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 that 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 to test different potentially cost-effective delivery models for an ECD intervention with a curriculum that integrates child psychosocial stimulation and nutritional education.

Cognitive and Behavioral Development. One CDBB multicomponent project on cognitive development includes both domestic and international research on how infants develop actions strategically toward goals. This ability emerges early in infancy, matures across childhood, and 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 an animal model as well as in 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, under the direction of Pier Francesco Ferrari at the Le Centre National de la Recherche Scientifique, France, conducts mirror neuron system animal model work to inform and converge with the human-based research on the system (P01HD064653).

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, and the environmental, behavioral, or genetic factors that mediate inter-individual differences in susceptibility in a unique animal model (R01HD088558). 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. The baboon population is 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; and 2) collect behavioral data important for determining social and reproductive status at the time of biological sampling.

CDBB is also supporting research on a nutritional intervention of omega-3 supplementation for adolescents and their parents aimed at reducing externalizing behavior in the adolescent and exploring potential neurocognitive mechanisms of action of omega-3. This research is taking place in the Republic of Mauritius, and participants are being recruited from the ongoing, multigenerational Mauritius Child Health Study.

The branch also supports a Canadian study of the development of face-processing expertise. 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 the effort aims to capitalize on their naturally occurring experiential differences with faces of different races, genders, and ages.

CDBB is also supporting research in Norway on the relationship of maternal and child infection, fever, and immune disorders to Attention Deficit/Hyperactivity Disorder (ADHD) risk, and the potential modulation of that risk by medications (i.e., antipyretics, analgesics, antibiotics) and micronutrients. The study uses prospective data about exposures in ADHD and control mother-child pairs (5R01HD090051-04). 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 their neurobiological and genetic bases, are supported as domestic grants but many 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 Canada, China, Hong Kong, Israel, Spain, and the United Kingdom.

Recent Achievements in International Health

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

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Contraception Research Branch (CRB)

Scientific Scope

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

Major International Initiatives over the Past Year

Contraceptive Method and HIV Risk. The goal of this research is to evaluate objective biological markers of HIV risk by a randomized contraceptive method within the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial to inform interpretation of the primary trial results. The ECHO trial, initiated in 2015, is the first clinical trial to randomize HIV-negative women to depot medroxyprogesterone acetate (DMPA), the copper T intrauterine device (IUD), and a levonorgestrel (LNG) implant to compare HIV acquisition rates. The ECHO trial was conducted in Eswatini, Kenya, South Africa, and Zambia with the goal of providing high-quality evidence to inform women, service providers, and normative bodies (e.g., the WHO) on the comparative HIV risks associated with these three highly effective contraceptive methods. With support from ECHO trial leadership, this study is testing stored genital specimens from a subset of ECHO trial participants who provided consent for future research on prostate-specific antigen (PSA) and sexually transmitted infections (STIs). These data will be combined with ECHO trial demographic, behavioral, laboratory, and clinical data to:

- Determine whether women randomized to DMPA have more or less frequent condomless vaginal sex than women randomized to the intrauterine device or implant during trial follow-up by comparing vaginal PSA, a marker of recent semen exposure, between randomized contraceptive groups across multiple ECHO sites, and secondarily, the prevalence of non-viral STIs.
- Evaluate whether women randomized to DMPA are more or less likely to misreport condomless sex than women randomized to the IUD or implant during trial follow-up by evaluating the concordance of self-reported condom use or abstinence during trial follow-up with PSA detection overall, and by randomized contraceptive group, to inform use of self-reported data in planned trial causal modelling.

The research will provide data, including objective markers of post-randomization sexual behavior change within the ECHO trial by randomized group, critical to the accurate interpretation of trial results, which policymakers, providers, and contraceptive users can use to minimize the risk of both unwanted reproductive outcomes and HIV among reproductive-age women worldwide.

Understanding the Impact of Lower Dose DMPA on Female Genital Tract Microbiome and Immunology. Depo-Provera 150mg delivered intramuscularly (150-IM), the most widely used injectable contraceptive worldwide, has been associated with increased HIV acquisition in multiple observational studies. This grant is leveraging three randomized trials to conduct timely, innovative, and cost-efficient research evaluating the impact of multiple contraceptives—the LNG implant 150-IM, the copper IUD, Sayana® Press, and novel low-dose DMPA formulations—on the female genital tract microbial and immune environments. These clinical studies were conducted in South Africa, Kenya, Zambia, Swaziland, Dominican Republic, Chile, and Brazil. This research grant is 1) analyzing the vaginal microbiome of women before and after use of these contraceptive products; 2) evaluating levels of vaginal cytokines

and antimicrobial proteins before and after use of these contraceptive products; 3) evaluating changes in the frequency and activation of defined immunological markers during use of these contraceptive products; 4) evaluating changes in the vaginal microbiome, cytokines, and antimicrobial proteins with use of lower DMPA doses; and 5) conducting discovery metaproteomics analysis to evaluate alterations in vaginal human and microbial proteins following initiation of these contraceptive products. These data will inform contraceptive use and policy, as well as provide targets and safety endpoints for the development of future contraceptives.

Clinical Trial with the LNG Intrauterine System to Measure Changes in Hemoglobin and Serum Ferritin Among Anemic Women in Kenya. Anemia continues to disproportionately affect marginalized women in resource-poor countries. In Africa and Southeast Asia, over 270 million women of reproductive age are anemic. Iron-deficiency anemia causes 18 percent of maternal deaths worldwide. Though the relationships between iron loss from menstruation, absorption of dietary intake of iron, iron storage, and the impacts on hematologic parameters are complex, higher levels of menstrual blood loss are associated with lower hemoglobin values. The LNG intrauterine system is a highly effective contraceptive product that also generally reduces menstrual blood loss. In research spanning 4 decades, the product consistently raises hemoglobin levels and increases iron stores in broad populations of women, but particularly for women with heavy menstrual bleeding. The overall goal of the grant is to give anemic women in Kenya an opportunity to try the LNG intrauterine system and to measure the impact on hemoglobin and iron stores. If the LNG intrauterine system is found to work as hypothesized, then the product can become another tool to alleviate anemia among reproductive-age women, resulting in healthier living and healthier beginnings to pregnancy when desired.

Pharmacological Strategies to Use the LNG Implant in HIV-infected Women. Family planning options are essential for improving reproductive health among HIV-infected women. Prevention of unintended pregnancy decreases maternal and child mortality, as well as reduces the risk of mother-to-child HIV transmission. Antiretroviral therapy (ART) is essential for reducing morbidity and mortality among HIV-infected individuals, in addition to preventing HIV transmission. It is of critical public health importance to safely combine hormonal contraceptives and ART. Millions of HIV-infected women on ART currently use subdermal progestin-releasing implants as a preferred method of long-acting, reversible contraception despite the lack of critically needed pharmacokinetic (PK) drug-interaction data to inform their safe and effective concomitant use. Preliminary data demonstrated that combined use of efavirenz (EFV)-based ART, the only preferred first-line ART regimen in LMICs, with an LNG-releasing implant for one year reduced LNG plasma concentrations by approximately 50 percent compared to women not on ART. Importantly, a 15-percent unintended pregnancy rate was seen in the study group of women on EFV-based ART plus the LNG implant, in contrast to the <1 percent expected failure rate of the implant for women without drug interactions. This study is building upon and extending these observations to provide comprehensive, evidence-based guidance on the use of LNG implants with ART in HIV-infected women. The study will use samples obtained from woman in Uganda to: 1) identify a strategy to overcome the drug-drug interaction between LNG and EFV-based ART; 2) advance contraceptive therapeutic options for HIV-infected women; and 3) advance the science of the drug-drug interaction field. The study is an evidence-based approach to safely combine LNG implants with ART regimens spanning the continuum of HIV care. The collaborative study is expected to improve the management of reproductive health in millions of HIV-infected women worldwide.

A Prospective Cohort of HIV-infected Malawian Women on EFV initiating the LNG Implant or the DPMA Injectable. Sub-Saharan Africa (SSA) has high rates of unintended pregnancy, maternal mortality, and perinatal HIV. The LNG implant is a highly effective and reversible contraceptive that is particularly

well-suited to settings like Malawi. It provides up to 5 years of protection and is not dependent upon external factors. The LNG implant's typical-use failure rate is 0.1 percent in the first year. The DMPA injectable is the most used contraceptive in SSA, and it requires repeat injections every 3 months, leading to a higher typical-use failure rate of 6 percent in the first year. Small studies suggest co-administration of the antiretroviral EFV may reduce the contraceptive efficacy of the LNG implant possibly due to PK interaction between the two drugs, causing some countries in SSA to consider policy recommendations against use of implants for women on EFV. This award compares the typical-use pregnancy rates of the LNG implant versus the DMPA injectable in a prospective cohort of 1,420 HIV-positive women on EFV (710 initiating the LNG implant and 710 initiating DMPA). Women will be followed in the study after 1 month and then every 3 months for at least 2 years and up to 4 years. In addition, a second study of 240 women in a 2:1 nested case-control study of women from the cohort will determine if higher EFV concentrations are associated with LNG implant contraceptive failure.

Recent Achievements in International Health

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

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Developmental Biology and Structural Variation Branch (DBSVB)

Scientific Scope

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, to elucidate the biochemical, molecular biologic, genetic, biophysical, and cellular mechanisms of embryonic development. The DBSVB supports both basic and translational aspects of structural birth defects 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 for birth defects in humans.

In addition to an emphasis on structural birth defects and transdisciplinary research, DBSVB priority research areas 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, 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 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 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 (e.g., 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 raises the possibility of developing effective intervention strategies for preventable NTDs, which has broad implications for the 330,000 infants born with NTDs annually worldwide.

Multinational Collaborations

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

France, Germany, Spain, and United Kingdom: 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 interventions. 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 learn how abnormalities in the processes of osteogenesis contribute to disorders such as global skull growth abnormality and premature closure of sutures, in particular the coronal suture. Foreign collaborators are 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 as well as 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 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 researchers to the collaboration 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 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,* an experimental frog 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, providing a resource to the international research community, and ensuring that important data are available and easily accessible to guide further research projects without 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.

On another front, 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.

Finally, short-stature syndromes are a family of structural birth defects important to the mission of NICHD. Short stature homeobox (*SHOX*) gene is associated with several short-stature syndromes, including Léri-Weill dyschondrosteosis and Langer syndrome. An NICHD-funded investigator at University of Calgary is the only investigator in North America working on *SHOX* genes, and his unique expertise and experience regarding this gene is not currently found in the United States. Better understanding of the *SHOX* gene has the potential for significantly advancing this area of birth defects research.

China

Some animals can regenerate their limbs after injury, but humans cannot. In this grant, the Principal Investigator (PI) proposed to establish an approach for stimulating digit regeneration in a mammalian system (the mouse). The investigators will engineer a transplantable, re-vascularizable, 3D fibrin scaffold containing a combination of multiple types of progenitor cells and growth factors, and will test its ability to stimulate regeneration by transplanting to the mouse digit stump after middle-phalanx amputation.

This grant is based on a frog limb regeneration study conducted in China. With no expenditure of NIH funds, the work on the non-mammalian frog model will inform/benefit the NIH study of limb/digit regeneration in mammals.

Germany

Over the course of an animal's lifetime, cell-fate decisions allow for normal development and growth as well as the health of the adult organism. The long-term goal of this project is to define the molecular mechanisms by which developmentally important RNA binding proteins select their target mRNAs and control their expression to affect specific cell-fate decisions, and to understand how defects in these processes contribute to cell dysfunction and organismal disease. Branch-funded U.S. investigators, in collaboration with colleagues in Germany, are functionally manipulating one such essential RNA binding protein in developing frog embryos and identifying the cellular and molecular consequences. Together, they have discovered a critical role for this protein in controlling the events of left-right patterning in vertebrate embryos. Their results provide new insights into this critical, but poorly understood, regulation of organ position within developing organisms.

Netherlands

The objective of this project is to understand how errors in cell-cell communication systems cause human birth defects and degenerative conditions. This work focuses on a specific cell communication system that controls formation of the limbs, lungs, and face during development and controls stem cells in many adult organs such as the intestine, bones, and liver. The investigators seek to understand how specific signals produced by the "transmitter cells" act on neighboring "receiver" cells to alter their function. The collaboration with Netherlands provides technical assistance to help the U.S. investigators establish a specialized cell-culture system called intestinal organoid culture. This technology enables the investigators to study the cell communication system in the organoid culture in a dish, avoiding the use of expensive and complex animals or human studies that would be impossible within the scope of a short-term grant.

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, Swiss researchers, in collaboration with researchers in the United States, are using advanced microscopy and detection systems to visualize the 3D interaction of RNAs directly with the mammalian ribosome. This work requires sophisticated structural analysis guided by electron microscopy, a process 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

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Fertility and Infertility Branch (FIB)

Scientific Scope

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.

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Gynecologic Health and Disease Branch (GHDB)

Scientific Scope

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 that results in constant leaking of urine and/or feces. It is estimated to affect 50,000 to 100,000 women each year, with as many as 2 million women having untreated OF in Asia and sub-Saharan Africa (SSA). 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 that aims to assess the long-term mental health and physical sequelae of women who have had surgery for OF, and to determine predictors of reintegration success after surgical repair in a Ugandan population. This work 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). FGC (a.k.a., female circumcision or female genital mutilation) is a cultural/religious/social practice that removes either part or all 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 of 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 healthcare providers caring for these patients. The long-term aims of this project are to identify ways to improve interactions with the healthcare 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 studies of the normally functioning endometrium, as

well as the potential of diagnostics for addressing abnormal functioning and disease. Importantly, the meeting incorporated the science of menstruation within 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. NICHD described the meeting and some of the discussions in a July web spotlight.

Additional details of the Menstruation: Science and Society meeting are available at:

- Meeting overview: https://www.nichd.nih.gov/about/meetings/2018/092018
- Videocast recording Day 1: https://videocast.nih.gov/watch=28461
- Videocast recording Day 2: https://videocast.nih.gov/watch=28465

1. Tingen C et al. (2020). Revisiting menstruation: the misery, mystery, and marvel. *AJOG*: https://www.ajog.org/article/S0002-9378(20)30622-0/fulltext.

2. Critchley H et al. (2020). Menstruation: Science and Society. *AJOG*: https://www.ajog.org/article/S0002-9378(20)30619-0/fulltext

Recent Achievements in International Health

N/A/

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

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Intellectual and Developmental Disabilities Branch (IDDB)

Scientific Scope

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) studies emphasizing the cellular, genetic, epigenetic, and environmental factors that contribute to the cognitive and behavioral manifestations of IDD conditions; 2) research on comorbid conditions of IDD, such as disordered sleep, self-injurious behaviors, obesity, gastrointestinal dysfunction, seizures/epilepsy, ADHD, anxiety, depression, psychosis, and related mental health disorders; 3) development and/or implementation of new screening tests for the prenatal, newborn, and early childhood periods; 4) validation of biomarkers and outcome measures for IDD symptoms, severity assessments, and treatments; 5) research on transitional time periods of interest for IDD, including pre-symptomatic, adolescent to adulthood, middle adulthood to aging, and causes of mortality; and 6) development and implementation of treatments for IDD that impact clinical care and improve quality of life.

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. 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 also 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. 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, United Kingdom, Italy, Germany, France, Australia, and the Netherlands to study mitochondrial diseases, neonatal diabetes conditions, and brain malformation disorders. A new competition in fiscal year 2020 will expand the program to other institutes and centers at NIH.

Down Syndrome. DS-Connect®: The Down Syndrome Registry, is an online, secure registry that promotes sharing of health information to advance research for the benefit of 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. The DS-Connect® website has attracted over 5,000 registrants in the United States and abroad and has supported recruitment for over 50 research projects through its membership. International partners include Down Syndrome International, T21RS, Jérôme Lejeune Foundation, and International Mosaic Down Syndrome Association, all active members of the Down Syndrome Consortium that 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. The DS-Connect® website has a responsive web design to facilitate access on a wide variety of mobile platforms. Most recently, the DS-Connect platform launched a Medication Tracker, allowing participants to enter information about medication and supplement use in people with Down syndrome, to help inform research and to inform future clinical drug trials. Currently, DS-Connect® registry leaders are working to implement search functionality that will pull information about NIH clinical trials and studies in Down syndrome that are active and recruiting from ClinicalTrials.gov.

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. This effort builds off the Infant Brain Imaging Study (IBIS) project, studying the baby siblings of children diagnosed with autism who are at high-risk to develop the condition themselves, to look for the earliest brain signatures and neuropsychological features of autism. The project uses a data coordinating center at the Montreal Neurological Institute in Canada.

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 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 knowledge gaps about the developmental course of congenital Zika syndrome, the treatment needs of children, and supports needed by family caregivers (Dr. Don Bailey).

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 United States and Guatemala will identify developmental disabilities in children resulting from stunting. Researchers are trying to determine the relationship between earliest spontaneous limb movements and developmental outcomes at 12 months of age in at-risk infants by using wearable motion sensors to measure this relationship. They also aim to determine whether wearable sensor assessment is more accurate than current clinical assessments in predicting developmental outcomes in at-risk infants. A cohort of children from birth to 6 months of age who will use wearable sensors will be enrolled in the study. There is also a focus on a multidisciplinary capacity-building project involving pediatric medicine, physical therapy, and biostatistics. The project will build research capacity in Guatemala utilizing a partnership between the University of Southern California (Dr. Peter Rohloff) and the Maya Health Alliance in Guatemala.

- 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, which will better sensitize mothers to their children's development, to a proven method for detoxifying cassava. Cyanide levels in cassava have been shown to lead to Konzo, a disease in which children exhibit neurodevelopmental delay; Konzo poses a serious public health threat in central and western Africa. This study will determine whether the combination of these interventions leads to better neurocognitive outcomes in the children (Dr. Michael Boivin).

- 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 found children in Uganda to be particularly vulnerable to brain injury due to the combination of sickle cell disease, anemia, malnutrition, and infection (Dr. Richard Idro).

- While mortality from preterm births in Sri Lanka has decreased by 50 percent over the last several years, the survivors are at risk for epilepsy and developmental disorders that often go unrecognized due to difficulties in accessing medical services. This collaboration with Sri Lanka is a proof-of-concept study to adapt mobile health technologies for the transfer of remotely recorded ambulatory electroencephalogram (EEG) and evoked potential recordings data to a central hub for analysis. These data will expand care for children with neurological disorders related to preterm birth (Dr. John Phillips).

- A collaboration between investigators in the United States and India will use whole-exome sequencing (WES) technology to investigate genetic causes of inherited neurodevelopmental disorders (NDDs). The high incidence of children with inherited NDDs is a significant healthcare issue in LMICs, and this study aims to establish genetic diagnostic tools and build the research capacity in India to address the needs of these children. One of their aims is also to test and adopt tools for optimizing analysis and reanalysis of WES data to streamline variant identification, annotation, and interpretation by research scientists and medical professionals and to build an integrative outreach portal to make de-identified population-specific genetic data publicly available. This availability could have greater implications in adopting lessons learned from integrating genetic counseling into clinical practice in other LMICs globally (Dr. Stephanie Bielas).

- 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 the size of the *FMR1* CGG repeat and the rate of clinical progression of FXTAS manifestations—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 (Dr. Randi Hagerman).

Rare Diseases Research. Many rare disorders are first manifest during childhood and can lead to lifelong disability and early death. IDDB participates in the Rare Diseases Clinical Research Network (RDCRN), led by the Office of Rare Diseases Research at the National Center for Advancing Translational Sciences. 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. Many of the RDCRN consortia have international sites in Canada and/or Europe. The IDDB provides support for six existing Consortia: Urea Cycle Disorders, Sterol and Isoprenoid Disorders, North American Mitochondrial Disease, Rett syndrome and related *MECP2* Disorders, Developmental Synaptopathies, and Brittle Bone Disease. New consortia added in 2019 include one focusing on Congenital Disorders of Glycosylation and one on Phenylketonuria and related disorders.

The branch also supports an international collaboration on Wolfram syndrome, a rare neurodegenerative disease that first appears in children with early onset diabetes, optic nerve atrophy, and deafness and death in early to 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 United Kingdom to increase the number of children enrolled in the study in hopes of better understanding the neuropathophysiology of this disorder and identifying potential targets for brain-specific interventions.

Cookstove-Related Achievements

- NICHD is partnering with NHLBI, NCI, the National Institute of Environmental Health Sciences (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.

- In a study of 37,870 pregnant women in six of the sites in the Pregnancy and Perinatology Branch (PPB)-funded Global Network for Women's and Children's Health Research (see the PPB section of this document), women who lived in households using polluting fuels were 15 percent more likely to have a low birthweight baby than those living in households that used clean fuels. The risk from polluting fuels was over and above all other risk factors for having a low birthweight baby.

- In a second study—conducted at the same six sites in the PPB-funded Global Network—of 62,111 pregnant women, those living in households using polluting fuels were 45 percent more likely to have a stillborn baby or a baby who died in the first 7 days of life (called perinatal mortality) than women living in households using clean fuels. This risk was also over and above all other risk factors for perinatal mortality.

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

International Rare Diseases Research Consortium (IRDiRC): Dr. Melissa Parisi serves as the NICHD representative to this organization, which officially launched in 2011 to support the development of 200 new therapies for rare diseases and the means to diagnose most rare diseases by the year 2020. Having achieved these goals by 2017, the Consortium has developed more ambitious goals for the next decade, including: diagnosis of all patients suspected of a rare disease within 1 year of initial testing; development of 1,000 new therapies for rare diseases, with a focus on conditions without approved treatments; and development of methodologies to assess the impact of diagnosis and therapies on patients with rare diseases. The governance structure includes a Consortium assembly, composed of representatives from each member organization, including members of the Funders Constituent Committee. At least eight NIH institutes and centers, including NICHD, have representatives who serve on the Funders Committee; each organization is required to commit at least $10 million over 5 years of future funding towards IRDiRC goals.

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Maternal and Pediatric Infectious Disease Branch (MPIDB)

Scientific Scope

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 tuberculosis (TB), hepatitis, and malaria.

To meet the needs and ongoing challenges of other significant infectious diseases, MPIDB coordinates research on congenital infections, such as Zika virus and cytomegalovirus; emerging infectious diseases, most notably severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease (COVID-19); and vaccine-preventable diseases in infants, children, adolescents, and women.

The branch supports research projects in 59 countries through grants, cooperative agreements, and contracts.

Major International Activities over the Past Year

Multisystem Inflammatory Syndrome in Children (MIS-C). Early in the pandemic, it appeared that children were less likely than adults to be infected with SARS-CoV-2 and, if infected, most had only mild to moderate illness. Despite limited data indicating severe complications in children, recent findings have identified increased risk of MIS-C among children infected with SAR-CoV-2. MIS-C began to surface across the world as a rare but serious condition in children weeks after they had or were exposed to someone with COVID-19. The severity of MIS-C disease in children follows trends like those of adults, with severity increasing in the presence of co-morbidities, such as obesity. World reports are linking cases and deaths in children to a previous SARS-CoV-2 viral infection and MIS-C. Most MIS-C related cases are presenting in school-age children. MIS-C has been characterized as a spectrum of inflammatory processes with features like those of toxic shock syndrome and Kawasaki disease. Given the rise in child related cases and deaths, MPIDB/NICHD is leading a trans-NIH initiative to support the development of laboratory diagnostics integrated with digital health technologies and AI-based algorithms to rapidly diagnose and characterize SARS-CoV-2 associated illness in children and predict disease severity, including MIS-C. This initiative, called Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIds) is part of NIH's Rapid Acceleration of Diagnostics (RADx) initiative to speed innovation in the development, commercialization, and implementation of technologies for COVID-19 testing. MPIDB/NICHD is also engaging in NIH collaborations, building upon and further utilizing existing infrastructures, and contributing to calls for research proposals and projects to understand the effects of the virus among the branch's and the institute's populations. Areas of research supported by NICHD in relation to SARS-CoV-2 and COVID-19 include but are not limited to the dosing and safety of drugs being used clinically to treat children, type and length of respiratory and hospital support needed, effects on the placenta and lung tissues, disparities in COVID-19 morbidity and mortality, the safe return to the workplace and schools, risk of transmission during pregnancy and/or breastfeeding, and innovative testing strategies.

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, the U.S. Food and Drug Administration (FDA), European Medicines Agency, Centers for Disease Control and Prevention (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 that 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 (NIMHD) and the NIH OBSSR. 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 at-risk youth and maintaining their HIV-negative status. The studies 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 PATC^{3}H 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. Network research activities have expanded to include additional focus on co-infections, especially TB. This Network was responsible for the first domestic trial in children with HIV (Intravenous immunoglobulin for prevention of bacterial infections). Now, NICHD funds 14 domestic sites including Puerto Rico and nine international sites in four countries: Brazil, Kenya, Tanzania, 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 TB 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 in 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.

Zika in Pregnant Women, Infants, and Children. MPIDB/NICHD currently coordinates and sponsors or co-funds three epidemiologic cohort studies to investigate the risk and outcomes of Zika infection during pregnancy in Latin America and the Caribbean. Zika in Infants and Pregnancy (ZIP) is an international prospective observational cohort study that has enrolled over 6,000 pregnant women and follows the infants born to them through the first year of life. The International Cohort Study of Children Born to Women Infected With Zika Virus During Pregnancy (ZIP 2.0) is a prospective longitudinal study following neuro-psychosocial development in children born to women with Zika infection during pregnancy and in children born to women without Zika infection during pregnancy. The Prospective Cohort Study of HIV and Zika in Infants and Pregnancy (HIV ZIP) is a two-phase prospective international cohort study of pregnant women with HIV infection and pregnant women without HIV infection that follows the infants born to them through the first year of life.

Active International Initiatives

In addition to the activities and initiatives mentioned previously, 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 include the following.

Emergency Awards: Rapid Acceleration of Diagnostics-Radical (RADx-rad) Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIds) (RFA-OD-20-023). Despite substantial numbers of children becoming infected with SARS-CoV-2 globally, the risk of severe disease or mortality was thought to be a concern exclusively for adults and the elderly. However, within the past several months, reports from Europe and the United States of MIS-C associated with prior SARS-CoV-2 exposure and/or infection of varying severity, including shock and death, have increased attention to the varied pediatric manifestations of the infection and its post-infectious complications. To address these and other vital questions in this emerging and potentially devastating health threat among children, PreVAIL kIds was developed as an emergency phased innovation funding opportunity announcement administered by NICHD in collaboration with other NIH institutes and offices (NIH OD, NHLBI, NIAID, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIDA, NIMHD, and FIC). The goal is to support innovative research to develop novel, new or unique and non-traditional approaches (e.g., diagnostic and prognostic biomarkers and/or biosignatures) to identify and characterize the spectrum of SARS-CoV-2 associated illness, including MIS-C and, through a prognostic algorithm, predict the longitudinal risk of disease severity after a child is exposed to and may be infected with SARS-CoV-2 to properly tailor management and optimize health outcomes.

Innovative Epidemiologic Approaches for Understanding Long-Term Health Outcomes of HIV-Exposed Uninfected (HEU) Populations (RFA-HD-20-008). Utilizing a phased research approach (R61/R33), the purpose of this initiative was twofold: 1) demonstrate the capacity to enroll HEU infants, children, adolescents, and young adults in clinical studies; and 2) utilize innovative epidemiological approaches to

assess overall health in the established HEU cohort. Seeking to further understand the effects of in utero/perinatal exposure to ART and/or HIV on health outcomes, NICHD is supporting research projects in Kenya, Malawi, Botswana, Zimbabwe, and South Africa. Innovative epidemiologic approaches and assessments in these populations include but are not limited to the utilization of robust platforms of linked maternal-child data augmented by new recruitment to answer lifecourse questions about HEU populations and establishment and sustainability of a life-long evaluation model of in utero and postnatal HIV and antiretroviral (ARV) exposure.

Utilizing Archived Data and Specimen Collections to Advance Maternal and Pediatric HIV/AIDS Research (RFA-HD-19-018 and RFA-HD-20-020). Supporting research and data translation and sharing, this call for secondary analyses using archived HIV/AIDS data and specimen collections builds upon original research. Awards presented rigorous and new analysis methodologies to answer scientific questions about the epidemiology, pathogenesis, treatment, clinical manifestations, cure, and complications of HIV/AIDS in maternal, pediatric, and adolescent populations. Research topics include TB immune responses in HIV-infected and HIV-uninfected women, maternal and fetal physiologically based PK models of maternal/fetal antiviral drug disposition, and Epstein-Barr virus viremia and malaria parasitemia in HIV-infected children. Data and specimens for these studies came from Kenya and Thailand.

Fogarty HIV Research Training Program for LMIC Institutions (D43 Clinical Trial Optional) (PAR-18-717). FIC, in collaboration with other NIH institutes, including NICHD, encourage applications for research training programs to strengthen the scientific capacity of institutions in LMICs to conduct HIV research relevant to the evolving HIV epidemic in their country. NICHD-supported training programs include focuses on implementation science, adolescent HIV, child mental health, and community-based research. LMICs in which this research is being supported include Peru, Kenya, Malawi, Haiti, Malaysia, Zimbabwe, Ghana, and Uganda.

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 in 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. As a result of this collaboration, NICHD continues to pursue and support research in adverse birth outcomes, continuity of care, and biomarkers in south African HIV-infected women and their infants.

Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA). MPIDB/NICHD, in collaboration with FIC, other NIH institutes, and the Office of the Global AIDS coordinator released this RFA in fiscal year 2016. It 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 (SSA). Grants were awarded to projects in the following SSA 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 and awarded three grants to investigate neurodevelopment assessment in South Africa, Tanzania, and Botswana. The widespread implementation of combination ART 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 ART and Virologic Control (RFA-HD-14-026). In support of the NIH Office of AIDS Research 2015 scientific research priority targeting 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 ARV drug strategies for prevention of MTCT in resource-constrained settings. This research area includes a range of 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, developing different innovative methods to promote maternal ART adherence and retention of mothers/infants in care, and conducting 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 several 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 SSA (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, 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 SSA. 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 multidisciplinary investigative 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.

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 72 studies funded by the branch. Six of those offer data from international sites, with biospecimens available from five, including the four NICHD International Site Development Initiative (NISDI) studies.

Examples of MPIDB-supported research networks and initiatives available in DASH include the following:

- 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

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Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB)

Scientific Scope

OPPTB aims to assure that there are safe and effective therapeutics for children and pregnant and lactating women and that these medications are used optimally according to individual needs. The branch promotes basic, translational, and clinical research to improve the safety and efficacy of therapeutics, primarily pharmaceuticals. It is responsible for developing and supporting a comprehensive national effort to increase the knowledge base for understanding how to appropriately treat disease during pregnancy, lactation, infancy, childhood, and adolescence using evidence-based therapeutic approaches. This includes expanding the genomic understanding, phenotypic characterization, and use of advanced 'omics technologies to inform prevention and treatment strategies. The goal of these efforts is to assure that medications are appropriately tested for dosing, safety, and effectiveness for individuals within their target populations.

Multiple gaps in knowledge regarding the use of therapeutics in children and pregnant and lactating women have led to inadequate labeling and frequent off-label use of prescription drugs. One of the branch's major activities is implementation of the Best Pharmaceuticals for Children Act (BPCA). The BPCA legislation promotes the prioritization of off-patent drugs and therapeutic areas that need further study in pediatrics and allows NICHD to sponsor clinical research of the prioritized therapeutics and disseminate results to improve drug labeling.

Major International Initiatives over the Past Year

Pediatric Trials Network (PTN). As part of the 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 United Kingdom to conduct clinical studies as part of the BPCA Clinical Program. Currently, the international sites are primarily participating in clinical studies that evaluate pharmacology data on children receiving standard-of-care treatments for various diseases.

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. Plans for harmonizing activities are being developed.

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/pharmacodynamic dose finding trial investigates praziquantel use in children younger than age 4 in Uganda, where there is a 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 that minimize 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 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

Steering Committee of the International Neonatal Consortia. Member: Dr. George Giacoia (represents NIH)

Point-of-Contact

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Pediatric Growth and Nutrition Branch (PGNB)

Scientific Scope

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 Small Business Innovative Research and Small Business Technology Transfer 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 TRIGR 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. Auto-antibodies 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. Additional information and findings are available at https://www.trigr.org/.

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 to 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, hyperinsuinemia 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 versus 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.

Micronutrient Research. 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, 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

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Pediatric Trauma and Critical Illness Branch (PTCIB)

Scientific Scope

PTCIB was established as a result of the institute's re-organization 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

Biological Pathways of Risk and Resilience in Syrian Refugee Children (1R01HD083387-01A1). This study, conducted at St. George Hospital University Medical Center, investigates 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 deficits in crossing skills 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. This study is conducted at the University of Guelph, Canada.

Impact of Conflict on Mental Health and Risk Behaviors of Palestinian Youth (5R03HD094017-02). 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. 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.

Optimizing Prevention Approaches for Children Reintegrating from Orphanages in Azerbaijan (5R01HD099847-02). Due to the economic crisis following the collapse of the Soviet Union, Azerbaijan hosts a large population of "social orphans," children left by destitute parents in state-run institutions. Years of deprivation, separation from parents, and maltreatment in orphanages severely heighten the risk of mental health problems among institutionalized children. Current deinstitutionalization and family reunification initiatives provide basic case management services, but do not address the mental health problems of institutionalized children, and do not attend to the poverty-related factors that led to institutionalization in the first place. To prevent mental health problems among children from orphanages reunited with their biological or extended families in Azerbaijan, the proposed study will refine and test three evidence-based intervention approaches: 1) family strengthening intervention; 2) mental health screening and referral for treatment; and 3) economic empowerment in the form of Child Savings Accounts. Based on the formative research conducted by the study team in collaboration with a local Community Collaborative Board, the intervention components have been adapted to maximize fit into the cultural context of Azerbaijan. In the proposed study, the adapted interventions will be tested with 400 child-caregiver dyads in a trial using the Multiphase Optimization Strategy to compare different intervention components and identify the most optimal combination. The study will test effects of each intervention component on children's mental health outcomes (e.g., symptoms of depression, anxiety; disruptive behaviors; post-traumatic stress symptoms; and disturbances of attachment).

Intergenerational Impact of Maternal Trauma History on Preschoolers' Behavior and Health Outcomes: Assessing Links with Caregiving Sensitivity and DNA Methylation (1R01HD098153-01A1). This study will build on the work of the Pregnancy Outcomes, Maternal Infant Cohort Study (PrOMIS) at the Instituto National Materno Perinatal (INMP) in Lima, Perú. To date, PrOMIS has enrolled more than 5,000 pregnant patients at INMP with 4,400 live births. All the research will be performed at the Peruvian research site. This study seeks to better understand maternal trauma history as a driver of behavior health problems in 3-year-old children. The investigators will examine the impact of maternal trauma across four time periods: 1) maternal experience of pre-pregnancy abuse in childhood (when

mothers < 18 years); 2) maternal experience of pre-pregnancy abuse in adulthood; 3) maternal experience of abuse during pregnancy; and 4) maternal report of postnatal abuse (after childbirth to time of assessment) on their children's behavioral problems (internalizing and externalizing behaviors). Using a lifecourse theory approach within an intergenerational context, the researchers will test three models to determine whether the effect of maternal trauma: 1) depends on the timing of exposure (Sensitive Period model); or 2) is strongest when it is most proximal to the child outcome examined (Recency model); or 3) increases with the number of exposures (Accumulation model). A primary study aim is to investigate how "experience gets under the skin" by examining associations between maternal trauma history with children's salivary DNA methylation profiles. Finally, the team will test whether the effects of maternal trauma history on child health outcomes are mediated by children's salivary DNA methylation profiles and maternal caregiving sensitivity.

Recent Achievements in International Health

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

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Population Dynamics Branch (PDB)

Scientific Scope

PDB supports research, data collection, 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, pregnancy outcomes, mortality and morbidity (especially maternal, infant, child, adolescent, and young adult mortality and morbidity), migration, population distribution, population stratification (including disparities based on race, ethnicity, sex/gender, and age), 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 family planning, infertility, and STIs including HIV/AIDS. In population health, the branch supports research on how demographic, social, economic, institutional, geographic, and other factors influence human health, productivity, behavior, and development, with an emphasis on research using population-representative data and natural and policy experiments using methods addressing selection and other sources of bias. Research at multiple levels of analysis, involving interdisciplinary perspectives, incorporating social determinants of health, and elucidating mechanisms leading to health disparities are encouraged.

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 multi-time-period datasets are crucial for identifying trends and differentials in population health and demographic characteristics and understanding the causes and consequences of these changes. The datasets include the following.

- Integrated Public Use Microdata Series Demographic and Health Surveys (R01 HD069471); Boyle, Elizabeth H. (University of Minnesota): Africa South of the Sahara, Northern Africa, India
- Integrated Global Health on Child Health and Development (R01 HD099182); Boyle, Elizabeth H. (University of Minnesota): More than 90 LMICs in the Global South and Eastern Europe, including several countries in sub-Saharan Africa (SSA), Mozambique, Gambia, Ghana, Sudan, Cuba
- Time Use Data for Health and Well Being (R01 HD053654); Hofferth, Sandra L. (University of Maryland, College Park): South Africa, United Kingdom, Mexico

Archiving and Documenting Child Health and Human Development Datasets

PDB sponsored a program that promotes data sharing from projects supported by NICHD and that, if made widely available, would advance the scientific mission of NICHD. (See PAR-20-064: Archiving and Documenting Child Health and Human Development Datasets [R03].) Many PDB grants funded through this program will make available data from international health and development research projects.

- Documenting and Archiving the Annual Health Survey of Maternal and Child Outcomes (R03 HD098292); Coffey, Diane (University of Texas, Austin): India

- Archiving and Documenting Health and Human Development Datasets from the Impact of Microfinance on Health: Experimental Evidence from India (R03 HD094985); Pande, Rohini (Yale University): India
- Public Use Datasets for Reproductive Health Research (R03 HD100680); Frost, Jennifer J. (Guttmacher Institute): sub-Saharan Africa
- Archiving, Enhancing, and Expanding the Cross-National Equivalent File (R03 HD100924); Lillard, Dean (Ohio State University): Australia, United Kingdom, Mali, and Russia

Developing and Disseminating Methodology to Improve Global Population Research

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 and LMICs that lack adequate vital registration systems and health information systems.

- Projecting the Future of Early Life Mortality in the Developing World (K01 HD098313); Spears, Dean (University of Texas, Austin): India
- Verbal Autopsy: Reimagining Data & Automated Cause Assignment (using Analysing Longitudinal Population-based HIV/AIDS data on Africa Network data) (R01 HD086227); Clark, Samuel J. (Ohio State): South Africa, Zimbabwe, Kenya, Malawi, Tanzania, Uganda, India, Indonesia, United Kingdom
- Microsimulation of Obesity Policies (R01 HD087257); Sturm, Roland (Rand Corporation): Mexico
- Improving Statistical Methods for Small Area Estimates of Public Health Indicators and Demographic Characteristics (R01 HD092580); Waller, Lance A. (Emory University): France, United Kingdom
- Global Age Patterns of Under-Five Mortality (R01 HD090082); Guillot, Michel (University of Pennsylvania): sub-Saharan Africa, Bangladesh, France, United Kingdom
- Improving the Measurement of Adolescent and Adult Mortality in Low-Income Countries (R01 HD088516); Helleringer, Stephane (New York University): Guinea-Bissau, Malawi, Uganda, Bangladesh, United Kingdom
- Workshop on Migration Data and Analysis (R25 HD094676); Bloemraad, Irene (University of California Berkeley): Africa
- Interdisciplinary Research Training Program for International Population Science (R25 HD101358); Axinn, William G. (University of Michigan at Ann Arbor): Nepal

Supporting Offices of Research and Sponsored Programs

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 SSA, India, and LMICs in the Caribbean and South America are eligible to apply.

- CHAKA: Strengthening Research Support Structures in the Andean Region (G11 HD088113); Cabrera Matta, Ailin Rosario (Universidad Peruana Cayetano Heredia): Peru

- Strengthening Research Administration Infrastructure at Africa University, Zimbabwe (G11 HD088121); Mutseyekwa, Fadzai Naome Nyembesi (Africa University): Zimbabwe

International Population Dynamics Research

PDB supports a robust research portfolio on international population dynamics research covering topics such as reproductive health, the health of sexual and gender minority populations, effects of natural disasters, child health and development, maternal health, and family dynamics. Unlike most NICHD projects and networks, most research projects supported by the branch are investigator initiated.

Reproductive Health

- Biocultural Investigation of Maternal Adversity on Gene Expression and DNA Methylation in the Placenta (F30 HD097935); Hsiao, Chu (University of Florida): Democratic Republic of the Congo
- An Internet-Based Preconception Cohort Study in North America and Denmark (R01 HD086742); Wise, Lauren A. (Boston University Medical Campus): Denmark
- Improving Perinatal Outcomes Using Conditional and Targeted Transfers (R01 HD090231); Okeke, Edward N. (Rand Corporation): Nigeria, Malawi, India
- Pregnancy Context and Health Outcomes (R01 HD095181); Foster, Diana Greene (University of California, San Francisco): Nepal
- Reproductive Coercion and Related Risk Factors (F31 HD100019); Boyce, Sabrina Christine (University of California Berkeley): Niger
- Preventing Intimate Partner Violence and Reproductive Coercion Among Underserved Adolescents (K23 HD084756); Servin, Argentina Elisa Noelle (University of California, San Diego): sub-Saharan Africa, Mexico
- The Effect of Migration on Sexual Risk Behaviors and HIV Incidence Among Non-Migrating Household Members: A Population-Based Study (F31 HD102287); Young, Ruth (Johns Hopkins University): Uganda
- HIV Risk and Access to Health Care Among Mobile Populations (R01 HD046886); Martinez-Donate, Ana P. (Drexel University): Mexico
- Integrating Counseling to Transform HIV Family Planning Services (R01 HD090981); Wagner, Glenn John (Rand Corporation): Uganda
- Contraceptive Side Effects, Method Dissatisfaction, and Early Discontinuation (F31 HD097841); Rothschild, Claire Watt (University of Washington): Kenya
- Development, Testing, and Health Effects of a Multilevel Family Planning Intervention (R21 HD098523); Sileo, Katelyn Mary (University of Texas San Antonio): Uganda
- Enhancing Male Participation in Interventions to Prevent Unintended Pregnancy (R01 HD084453); Raj, Anita (University of California, San Diego): India
- Prospective Determinants of Unintended Pregnancy and Its Health Consequences (R03 HD097360); Yeatman, Sara (University of Colorado Denver): Malawi
- Interpregnancy Interval and Pregnancy Outcomes (R03 HD099241); Klebanoff, Mark A. (Research Institute Nationwide Children's Hospital): Sweden, Canada

- Trends in the Stratification of Premarital Childbirth (R03 HD099449); Stoebenau, Kirsten (University of Maryland, College Park): sub-Saharan Africa
- Determining Longitudinal Trends and Risk Factors for Adolescent Reproductive Health (R03 HD102740); Frank, Reanne (Ohio State): Denmark
- Improving the Reproductive Health of Families (R01 HD094512); St Lawrence, Janet S. (Portland State): Botswana

Maternal Health and Child Health and Development

- Trends, Predictors, and Consequences of Child Undernutrition (F30 HD091975); Soni, Apurv (University of Massachusetts Medical School, Worcester): Africa, India
- Understanding the Role of Gender Inequality and Food Insecurity on Maternal and Child Health (K01 HD086281); Diamond-Smith, Nadia Griffi (University of California, San Francisco): Nepal
- India Human Development Survey (R01 HD041455); Desai, Sonalde B. (University of Maryland, College Park): India
- Intergenerational Impacts of Health Investments (R01 HD090118); Miguel, Edward Andrew (University of California Berkeley): Kenya
- Effects of Age at Marriage and Education on Health of Mothers and Children (R01 HD095189); Field, Erica M. (Duke University): Bangladesh
- Policy Change and Women's Health (R01 HD095951); Margerison, Claire E. (Michigan State): United Kingdom, Canada
- Kinship, Nuptiality and Child Health Outcomes in a Low-Income Urban Area (R01 HD101613); Madhavan, Sangeetha (University of Maryland, College Park): Kenya
- Early Childhood Health Among Latinos/as (R03 HD092644); Crosnoe, Robert L. (University of Texas, Austin): Mexico
- Father Involvement Interventions and Child Mental Health (R03 HD096184); Rossin-Slater, Maya (Stanford University): Denmark, Sweden
- Foundational Cognitive Skills in Developing Countries: Early-Life Nutritional, Climatic, and Policy Determinants and Impacts on Adolescent Education, Socio-Emotional Competencies, and Risky Behaviors (R21 HD097576); Behrman, Jere R. (University of Pennsylvania): Africa, India, United Kingdom, Peru
- Household Income at Birth and Preschool Child Health (R03 HD097425); Majid, Muhammad Farhan (University of Georgia): Indonesia
- Migration, Family Context, and Child Health (R03 HD098705); Treleaven, Emily (University of Michigan at Ann Arbor): Nepal
- Male Absence Due to Migration and the Health of Left-Behind Wives in India (R03 HD098377); Lei, Lei (Rutgers, The State University of New Jersey): India, France
- Effects in Middle Childhood of Early Exposure to Water and Sanitation Interventions (R03 HD102468); Fernald, Lia C. H. (University of California Berkeley): Bangladesh

- The Impact of Ebola Infection on Demographic and Social Outcomes in Sierra Leone (R21 HD098504); Anglewicz, Philip Anthony (Johns Hopkins University): Guinea
- Pathways and Mediators of Change in Early Childhood Development (R21 HD099488); Lopez Garcia, Italo (Rand Corporation): Kenya
- Intervention to Improve Developmental and Health Outcomes for Female Adolescents (R21 HD099508); Sensoy Bahar, Ozge (Washington University): sub-Saharan Africa
- Social Networks and Child Malnutrition in a Resource-Limited Setting (R21 HD101268); Mohanan, Manoj (Duke University): India

Population-Environment Interactions and Natural Disasters

- Longer Term Effects of a Natural Disaster on Health and Socio-Economic Status (R01 HD052762); Frankenberg, Elizabeth A. (University of North Carolina Chapel Hill): India, Indonesia
- Surviving an Epidemic: Families and Well-Being, Malawi 1998-2020 (R01 HD087391); Kohler, Hans-Peter (University of Pennsylvania): Southern Africa, Malawi
- Structural and Social Transitions Among Adolescents in Rakai (SSTAR) (R01 HD091003); Santelli, John S. (Columbia University Health Sciences): Uganda
- Training for Health Professionals (R01 HD092655); Rosser, B. R. Simon (University of Minnesota): Tanzania
- Demographic Responses to Natural Resource Changes (R03 HD095014); Curtis, Katherine J. (University of Wisconsin-Madison): Mexico
- Environmental Change and Undernutrition among Women and Children (R03 HD101859); Gray, Clark (University of North Carolina Chapel Hill): 50 countries across Africa, Asia, and Latin America
- Population Dynamics in Africa: Selected Outcomes and Causes (R03 HD098357); Gray, Clark (University of North Carolina Chapel Hill): Botswana, Burkina Faso, Kenya, Uganda

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

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Pregnancy and Perinatology Branch (PPB)

Scientific Scope

The scientific scope 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

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

The NICHD 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. These collaborations have led to improvements in 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. The Network has also 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, healthcare systems, and independent funding, while also providing opportunities for other NIH institutes and funders to collaborate with the Global Network. As of 2018, NICHD has funded eight U.S. sites, each with an international partner institution, to conduct human subjects 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 healthcare 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 1 million mother-baby dyads.

Maternal Newborn Health Registry – Supplemental COVID 19 Trial. The Global Network launched an international study to track the prevalence and impact of COVID-19 infection during and after pregnancy. The year-long study, set to launch the summer of 2020, will include about 2,000 pregnant women in seven LMICs. The study aims to compare maternal, fetal, and neonatal outcomes among pregnant women infected with the virus with outcomes of non-infected pregnant women. Participants will be given antibody tests at delivery to track COVID-19 exposure. Researchers also will document fetal and neonatal outcomes, such as preterm birth, fetal growth restriction, stillbirth, neonatal mortality, and congenital anomalies. A follow-up study aims to determine the effect of maternal COVID-19

infection on infant neurodevelopment outcomes, such as cerebral palsy, developmental delays, and hearing and vision abnormalities. The study will be conducted through the Global Network's Maternal Newborn Health Registry research partnership. Participating countries are Guatemala, Bangladesh, India, Pakistan, Kenya, Democratic Republic of Congo, and Zambia. Through a follow-up questionnaire, researchers also hope to assess knowledge and attitudes about the COVID-19 infection among pregnant women, safety and protective practices, and prenatal care.

Azithromycin-Prevention in Labor Use Study (A-PLUS): Prevention of maternal and neonatal death/infections with a single oral dose of azithromycin in women in labor. The A-PLUS trial will assess the effect of a single oral dose of azithromycin given to women in labor for the prevention of maternal and neonatal deaths and infection. The trial will enroll 34,000 pregnant women at eight research sites in Latin America, South Asia, and SSA. The trial includes two primary hypotheses: 1) a single, oral dose of 2 g azithromycin given to women in labor will reduce maternal death or sepsis; 2) a single, oral dose of 2 g azithromycin given to women in labor will reduce neonatal death or sepsis. To date, a pilot study has been completed and the main trial is set to launch in late 2020.

Studies in Other Networks and Researcher-Initiated Activities

PregSource®: Crowdsourcing to Understand Pregnancy. Using a crowdsourcing approach, PregSource asks women to enter information directly about their pregnancies, throughout gestation, and the health of their babies into early infancy via a confidential, secure website. The questionnaires capture data on nausea, mood, weight gain, labor, delivery, feeding, and early infancy. In the future, the de-identified data from PregSource will become available to researchers. While it is targeting women in the United States, women around the world are welcome to join. As of July 2020, 1,822 participants have joined, and 153 of them were from outside the United States. Learn more at: https://pregsource.nih.gov/.

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 the PASS Network. 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 percent 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, during which trainees 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:

- Provides a sustained training opportunity for obstetrician/gynecologists pursuing academic careers in global women's health
- Allows trainees to complete degree requirements for a master-of-science degree in clinical research, providing the necessary theoretical framework for later practical training
- Leverages 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
- Introduces 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 Post-Traumatic Stress Disorder). 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 percent to 2 percent of all pregnancies. Results from previous studies suggest a significant genetic component in the pathogenesis of AP. 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 900 well-characterized 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 Infections and Adverse Perinatal Outcomes (Bangladesh). Maternal genitourinary infections, particularly bacterial vaginosis and urinary tract infections (UTIs) 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 genitourinary 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 of 8,134 pregnant mothers from that district. Findings will enhance understanding of the burden of abnormal vaginal flora and UTIs, and the impact of a screening-treatment program on perinatal outcomes, and will help inform public health recommendations for screening and treatment of maternal genitourinary 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 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 determine 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 system 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. These limitations mean 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 and, 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 the Liggins 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 (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 an NICHD-funded 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 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 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 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 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. The findings are important: providers need 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, released 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, the fetus in utero, and the infant, either 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 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 Umbilical Cord Milking (UCM) 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 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 who 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 participating. The specific aims of this trial are to: 1) 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; 2) 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; and 3) compare the outcomes of premature newborns <32 weeks gestational age delivered by caesarean section.

Umbilical Cord Milking in Non-Vigorous Infants (MINVI) (R01HD096023). At birth, it is critical that an infant begins breathing quickly, switching 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 but will not delay the resuscitation procedures. Currently, 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 found 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. In addition to eight U.S. sites, 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 of 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 healthcare 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 women 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 of age 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.

1. Afulani PA, Moyer CA. (2019). Accountability for respectful maternity care. *The Lancet*. 09; 394(10210):1692-1693. https://pubmed.ncbi.nlm.nih.gov/31604661/
2. Afulani PA, Kelly AM, Buback L, Asunka J, Kirumbi L, Lyndon A. (2020). Providers' perceptions of disrespect and abuse during childbirth: a mixed-methods study in Kenya. *Health Policy Plan*. Jun 1;35(5):577-586 2020. https://pubmed.ncbi.nlm.nih.gov/32154878/

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Points-of-Contact

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National Center for Medical Rehabilitation Research (NCMRR)

Scientific Scope

NCMRR aims 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

In January 2017, the WHO launched the *Rehabilitation 2030: A Call for Action* to raise the profile of rehabilitation as a health strategy relevant to the whole population, across the lifespan and across the continuum of care. The Rehabilitation 2030 initiative highlights the need to strengthen health systems to better provide rehabilitation, and calls for coordinated and collaborative global action on several fronts, including improving leadership and governance, service provision, financing, human resources, data collection and research capacity for rehabilitation. NIH was a major contributor to this effort.

In line with this initiative, the WHO rehabilitation program launched several activities aimed at building technical capacity in countries, establishing strategic direction for coordinated action, and strengthening the health system to provide rehabilitation. The overall objective of the partnership with NIH was to provide financial support to carry out the following activities:

- WHO Package of Interventions for Rehabilitation
- Rehabilitation priority interventions in primary care
- Establish a research agenda for rehabilitation
- Financially support and co-host the second global Rehabilitation 2030 meeting
- Define assessment approaches for rehabilitation at the clinical, facility, and systems levels

This effort is ongoing with an estimated completion date of June 2021.

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, and all of these variations 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 starts in infancy, impairing 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, thereby mitigating developmental disregard. To accomplish this goal, 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 one 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 (the 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. 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.

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 and the University of Sao Paulo in Brazil, 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.

MRI and Machine Learning to Improve Early Prognosis and Clinical Management after SCI. The purpose of this research project is to use early MRI measures of spinal cord damage as objective biomarkers to improve the prediction of walking recovery and specific motor return of individuals following SCI. This research will provide patients with a quantified sense of expectations regarding their chances of walking recovery, and will help guide the healthcare team on the best options for clinical management and rehabilitation (i.e., focusing on neuroplasticity and restoration of walking versus compensatory strategies). Ultimately, this research aims to improve the lives and wellbeing of those suffering from SCI. The research team will use previously collected data on 250 SCI subjects from the U.S. SCI Model System at the Craig Hospital. They will identify possible biomarkers that associate with clinical outcomes by using artificial intelligence techniques to evaluate radiographic images. The researchers are collaborating with the University of Sydney, Australia, to help analyze some of these outcome measures.

Neuroergonomic Assessment of Wheelchair Control in Real-World Environments with both Healthy and Clinical Populations. Neuroergonomics is an emerging field that investigates the human brain in

relation to behavioral performance in natural environments and everyday settings, with the goal of expanding our understanding of the neural mechanisms that underlie human perceptual, cognitive, and motor functioning with a focus on real-world contexts. In this study, neuroergonimcs approaches will be used to study wheelchair users. Wheelchair users are prone to a variety of serious, sometimes even fatal, short- and long-term injuries related to the operation of their chair. Researchers from Drexel University are working with researchers from Oxford Brookes University to analyze data previously collected in the United Kingdom. This work will provide a new framework to understand human-machine interactions.

Staff Membership on Global Health Committees/Working Groups

Priority Package of Interventions Working Group, Rehabilitation 2030, Rehabilitation & Disability Component, WHO. Representative: Dr. Theresa Hayes Cruz

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Division of Intramural Population Health Research (DIPHR)

Scientific Scope

DIPHR has an ambitious threefold mission consistent with the NIH intramural research program to:

- Design and conduct original and collaborative public health research consistent with NICHD'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

The DIPHR designs research responsive to critical data gaps to advance 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 also 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. The data have been edited and the analysis is beginning.

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. Several key study papers were published.

Developmental Origins of Health and Disease. In collaboration with investigators in National University of Singapore, the Growing Up in Singapore Towards Healthy Outcomes Study aims to evaluate the Asian phenotypes of gestational diabetes and 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 United Kingdom, 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.

Preconception Period analysis of Risks and Exposures Influencing Health and Development (PrePARED) Consortium. This study is a collaboration with investigators across the United States, Canada, Australia, Denmark, China, and India to investigate the effects of preconception exposures on fertility and miscarriage, pregnancy-related conditions, perinatal and child health, and adult health outcomes.

Pregnancy and Childhood Epigenetics Consortium. This study, led by NIEHS, is an international collaboration of investigators using DNA methylation data to investigate the epigenetics of perinatal and pediatric exposures and outcomes.

Recent Achievements in International Health

Genetic variants and risk of progression from gestational diabetes to type 2 diabetes. Genetic risk score and its potential interactions with dietary patterns played a role on the risk of developing type 2 diabetes following pregnancies complicated by gestational diabetes. Learn more at https://www.nichd.nih.gov/newsroom/news/021320-gestational-diabetes.

International Partnerships

- NTDs: Biochemistry related to birth defects and GWAS with Trinity College in Dublin, Ireland. PI: 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: Drs. E. Schisterman, J. Mills, E. Yeung, 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
- In collaboration with investigators at SSI, NICHD investigators are working to investigate pyloric stenosis genetics and are conducting GWAS. Co-investigator: Dr. J. Mills
- PrePARED Consortium. Investigators: Drs. S. Mumford, E. Schisterman, E. Yeung
- International consortium project on pregnancy exposures and newborn DNA methylation. Investigators: Drs. S. Mumford, E. Schisterman, C. Zhang, E. Yeung
- In collaboration with investigators at the Brighton and Sussex Medical School, United Kingdom; Armauer Hansen Research Institute, Ethiopia; NHGRI; and Institute of Translational Genomics, Helmholtz Zentrum München, Germany, NICHD investigators are conducting GWAS to understand the genetic basis of podoconiosis. Investigator: Dr. F. Tekola-Ayele

Epidemiology Branch Investigators Involved in International Activities

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Staff Membership on Global Health Committees/Working Groups

DIPHR memberships and working groups include the International COVID-19 Pregnancy Consortium and the Global Network for COVID-19 focused research in pregnancy. Dr. E. Schisterman

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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 60 tenured and tenure-track investigators, organized into 12 affinity groups (AGs), and approximately 250 postbaccalaureate, clinical, and postdoctoral fellows and graduate students.

Each of the 12 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
- Bone and Matrix Biology in Development and Disease
- Cell and Structural Biology
- Cell Regulation and Development
- Developmental Endocrinology, Metabolism, Genetics, & Endocrine Oncology
- Genetics and Epigenetics of Development
- Genomics and Basic Mechanisms of Growth and Development
- Maternal-Fetal Medicine, and Translational Imaging
- Molecular Medicine
- Neurosciences
- Physical Biology and Medicine
- Reproductive Endocrinology and Infertility and Pediatric and Adolescent Gynecology

DIR research addresses several fundamental questions, including:

- 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)

Principal Investigator: Karel Pacak, M.D., Ph.D., D.Sc.

Affinity Group: Developmental Endocrinology, Metabolism, Genetics, and Endocrine Oncology

Scientific Scope

SCN's major scientific focus is on endocrine tumors.

Major International Initiatives

Dr. Pacak is a member of the International Advisory Panel of the Czech Government Board for Science, Technology, and Innovation, 2017 to the Present.

Recent Achievements in International Health

N/A

International Trainees

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

SCN working group participation includes: Endocrine Hypertension and PRESSOR: Pheochromocytoma Research and Support Organization

Point-of-Contact

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Section on Endocrinology and Genetics (SEGEN)

Principal Investigator: Constantine A. Stratakis, M.D., M. (Med) Sci

Affinity Group: Developmental Endocrinology, Metabolism, Genetics, and Endocrine Oncology

Scientific Scope

SEGEN focuses on understanding the genetic and molecular mechanisms leading to disorders that affect the adrenal cortex, with an 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 (INSERM), 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, United Kingdom
- Amanda C. Swart: Department of Biochemistry, Stellenbosch University, Stellenbosch, South Africa

- Amit Tirosh: Neuroendocrine Tumors Service, Division of Endocrinology, Diabetes and Metabolism, The Chaim Sheba Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Selected Publications with International Collaborators in the Past Five Years

1. Tirosh A, Hamimi A, Faucz F, Aharon-Hananel G, Zavras PD, Bonella B, Auerbach A, Gillis D, Lyssikatos C, Belyavskaya E, Stratakis CA, Gharib AM. Liver findings in patients with Carney complex, germline *PRKAR1A* pathogenic variants, and link to cardiac myxomas. *Endocr Relat Cancer*, *2020, Jun;27*(6):355-360.
2. Tirosh A, RaviPrakash H, Papadakis GZ, Tatsi C, Belyavskaya E, Charalampos L, Lodish MB, Bagci U, Stratakis CA. Computerized analysis of brain MRI parameter dynamics in young patients with Cushing syndrome: a case-control study. *J Clin Endocrinol Metab*, *2020 May 1*;*105*(5):e2069-77.
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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.

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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 because of this research.

International Trainees

- 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

- 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 with:

- Dr. Albert Beckers and others in 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

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Section on Heritable Disorders of Bone and Extracellular Matrix (SHDBEM)

Principal Investigator: Joan Marini, Ph.D., M.D.

Affinity Group: Bone and Matrix Biology in Development and Disease

Scientific Scope

SHDBEM's scientific focus is on causative genes for heritable bone disorders, using patient cells and mouse models to understand the mechanism, and applying this information for novel therapies.

Major International Initiatives

Investigations of melorheostosis and recessive Osteogenesis Imperfecta (OI) types enhanced by bone tissue studied with collaborators in Austria at Osteology Institute, Bangkok, Switzerland, and Israel.

Publications with International Collaborators

1. Kang H, Jha S, Deng Z, Fratzl-Zelman N, Cabral WA, Ivovic A, Meylan F, Hanson EP, Lange E, Katz J, Roschger P, Klaushofer K, Cowen EW, Siegel RM, Marini, JC, Bhattacharyya T. (2018). Somatic activating mutations in *MAP2K1* cause melorheostosis. *Nature Commun 9*(1):1390. PMID: 296433386.
2. Besio R, Iula G, Garibaldi N, Lina C, Sabbioneda S, Biggiogera M, Marin JC, Rossi A, Forlino A. (2018). 4-PBA ameliorates cellular homeostasis in fibroblasts from osteogenesis imperfecta patients by enhancing autophagy and stimulating protein secretion. *BBA 1864*(5 Pt A):1642-1652. doi: 10.1016/j.bbadis.2018.02.002.
3. Fratzl-Zelman N, Rochger P, Kang H, Jha S, Roschger A, Blouin S, Deng Z, Cabral WA, Ivovic A, Katz J, Siegel RM, Klaushofer K, Fratzl P, Bhattacharyya T, Marini JC. (2019). Melorheostotic bone lesions caused by somatic mutations in *MAP2K1* have deteriorated microarchitecture and periosteal reaction. *J Bone Miner Res. 34*:833-895. PMID: 30667555.
4. Kang H, Jha S, Ivovic A, Fratzl-Zelman N, Deng Z, Mitra A, Cabral WA, Hanson EP, Lange E, Cowen EW, Katz J, Roschger P, Klaushofer K, Dale RK, Siegel RM, Bhattacharyya T, and Marini JC. (2020) *SMAD3* somatic activating mutations cause melorheostosis with an endosteal radiographic pattern by upregulating the TGFb/SMAD pathway. *J Exp Med May 4; 217*(5) e:20191499. PMID: 32232430.

Recent Achievements in International Health

N/A

International Trainees

SHDBEM hosts international trainees are from Israel, Korea, and the United Kingdom.

International Partnerships

Dr. Marini serves as Chair of Scientific Committee for International OI Conference, committee representing the United States, Canada, and Europe.

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

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Section on Intercellular Interactions (SII)

Principal Investigator: Leonid Margolis, Ph.D.

Affinity Group: Maternal-Fetal Medicine, Imaging, and Behavioral Determinants

Scientific Scope

SII aims to identify the basic mechanisms of cell interactions under normal and pathological conditions.

Major International Initiatives

- Development of ex vivo models of atherosclerotic plaques: Thrombosis in SARC CoV-2 infection. 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. Virology and Pathogenesis Department Galicia Sur Health Research Institute, Spain (PI: Dr. Eva Povedra)
- Investigation of the role of *Lactobacillus*-generated 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 (PI: Prof. D. Mikeladze)

Publications with International Collaborators

N/A

Recent Achievements in International Health

N/A

International Trainees

- Dr. Rogers Palomino
  University of Bologna, Italy
- Mr. Paolo Costantini
  University of Bologna, Italy
- Mr. Vincenzo Mercurio
  University of Milan, Italy

International Partnerships

SII's international partnership falls within the framework of the Office of AIDS Research Intramural-to-Russia Program.

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

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Section on Molecular Morphogenesis (SMM)

Principal Investigator: Yun-Bo Shi, Ph.D.

Affinity Group: Cell Regulation and Development

Scientific Scope

SMM studies the gene-regulatory mechanisms, controlled by thyroid hormone (TH) receptor (TR), that establish the postembryonic developmental program in vertebrates, using amphibian metamorphosis as the main model system. The laboratory recently showed that TR 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 has been investigating their regulation and function during larval organ degeneration and adult organ development.

Major International Initiatives

SMM has collaborated with laboratories in several different countries. The following collaborations have resulted in publications within the last five years.

The work of SMM on intestinal remodeling during TH-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. Because intestinal maturation in frog metamorphosis resembles that of 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 preterm 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, SMM recently discovered a unique role of TR β in regulating notochord resorption during *Xenopus* metamorphosis. The team analyzed the expression program underlying tail resorption during metamorphosis in 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, SMM recently collaborated with scientists in the 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. This work led to novel discoveries on the functions of TH receptor alpha and a histone methyltransferase.

Through collaboration with researchers at the University of Dundee in the United Kingdom, a conditional knockout mouse line has been generated to investigate the role of a transporter for TH and amino acids that was 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, and that total knockout leads to embryonic lethality. Through a collaboration with

researchers in Kanazawa University Graduate School, Japan, we have also shown that the transporter also regulates osteoclastogenesis and bone homeostasis via the mTORC1 pathway.

The likely conservation of TH function in vertebrate development prompted us to investigate the role of TH in mouse intestinal development. In a collaboration with scientists at NCI, NIH, and Xi'an Jiaotong University School of Medicine, China, we have recently shown that in a mouse model mimicking human patients with resistance to TH due to TRα mutations, a heterozygous dominant negative TRα mutation leads to stem cell defects in the adult intestine. This finding is 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.

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 some of the collaborations formally concluded earlier, continued data analysis resulted in recent publications listed below.

Publications with International Collaborators

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. Nakajima, K., Tanizaki, Y., Luu, N., Zhang, H., and Shi, Y.-B. (2020). Comprehensive RNA-seq analysis of notochord-specific genes induced during *Xenopus tropicalis* tail resorption. *General and Comparative Endocrinology*. *287*:113349, 1-9. doi: 10.1016/j.ygcen.2019.113349.
7. 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.

8. 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.
9. 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). System L amino acid transporter LAT1 regulates osteoclastogenesis and bone homeostasis via the mTORC1 pathway. *Science Signaling*, *12*:eaaw3921, 1-14.
10. Poncet, N., Gierliński, M., Melanie Febrer, M., Lipina, C., Halley, P.A., Shi, Y.-B., Yamaguchi, T.P., Taylor, P.M., Storey, K.G. (2020). Wnt promotes amino acid transporter *Slc7a5* to constrain the integrated stress response during mouse embryogenesis. *EMBO Reports*. *21*: e48469, 1-20.
11. 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.
12. Shibata, Y., Bao, L., Fu, L., Shi, B., and Shi, Y.-B. (2019). Functional studies of transcriptional cofactors via microinjection-mediated gene editing in *Xenopus*. In: C. Liu and Y. Du. (Eds.) *Microinjection. Methods in Molecular Biology*. 1874:507-524; Humana Press, New York, NY; https://doi.org/10.1007/978-1-4939-8831-0_29.
13. Bao, L., Shi, B., and Shi, Y.-B. (2020). Viewpoint: Intestinal homeostasis: A communication between life and death. *Cell & Bioscience*. *10*:66, 1-3.
14. 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.
15. 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

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Section on Molecular Neurobiology (SMN)

Principal Investigator: Andres Buonanno, Ph.D.

Affinity Group: Cell and Structural Biology

Scientific Scope

The SMN aims to elucidate how Neuregulins (NRG1, NRG2 and NRG3) and their receptor ErbB4, signaling molecules 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. To achieve these aims, researchers are using multidisciplinary approaches that include: optogenetics, fiber-photometry, electrophysiology, neurochemistry, intersectional genetics, neuronal pathway tracing, and molecular/cellular and touch-screen behavioral techniques. The 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 that affect behaviors and cognitive functions altered in psychiatric and neurodegenerative disorders.

Major International Initiatives

SMN participated in the following three major international initiatives.

Through a collaborative agreement with Dr. Andreas Zimmer at the University of Bonn in Germany, Ms. Larissa Erben joined the SMN as a graduate student to work on her dissertation project. Last year, Dr. Erben defended and received her Ph.D. from the University of Bonn. Her project focused on understanding the cellular expression pattern and functional roles of distinct ErbB4 splice variants in the brain. This is work is significant because specific ErbB4 splice variants (i.e., ErbB4 Cyt-1) are associated with the maturation of the prefrontal cortex during juvenile development and cognitive deficits in persons diagnosed with schizophrenia. As part of her research, Dr. Erben helped to establish a novel highly sensitive fluorescent in situ hybridization approach (i.e., Basescope) that allows detection and quantification of RNA splice variants at a single-cell level that can differ by a single short exon. Dr. Erben then went on to investigate how deletion of the ErbB4 Cyt-1 exon (26 base pairs), targeted by loxP/Cre recombination, affects development and behaviors of Cyt-1knockout mice.

SMN collaborated with Dr. Alon Shamir and Dr. Miguel Skirzewski, who originally came to the section for training from Ben Gurion University of the Negev in Israel, and the University of the Andes in Venezuela, respectively. Work with Dr. Shamir focused on how modulation of ErbB4 receptor activity regulates numerous behaviors in rodents with relevance to schizophrenia and the potential role of dopamine. Work with Dr. Skirzewski originally used neurochemical techniques to measure changes in dopamine levels in NRG2 and ErbB4 knockout mice. Our more recent collaboration with Dr. Skirzewski and Dr. Tim Bussey at the University of Western Ontario in Canada, uses cutting-edge techniques, such as optogenetics, fiber photometry, and touchscreen-based behavioral paradigms, to investigate the roles of the NRG/ErbB4 and dopamine signaling pathways in regulating distinct cognitive domains.

The SMN continued our collaboration with Dr. Tanveer Ahmad, presently at the Department of Biochemistry, University Grants Commission in New Delhi, to investigate how NRG3 initially is proteolytically processed by BACE-1 in the Golgi apparatus and, subsequently, packaged and transported to axons, where it accumulates at excitatory glutamatergic terminals that synapse onto

ErbB4-expressing inhibitory GABAergic interneurons. These findings are important because NRG3-ErbB4 interactions regulate glutamatergic excitatory inputs that drive GABAergic interneuron firing and, consequently, the synchrony of local neuronal networks that is essential for information processing.

Publications with Recent International Collaborators

1. 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.
2. 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.
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. (2018). ErbB4 signaling in dopaminergic axonal projections increases extracellular dopamine levels and regulates spatial/working memory behaviors. *Mol Psychiatry. 23*, 2227-2237.
4. Erben L., He M.X., Laeremans A., Park E., Buonanno A. (2018). A novel ultrasensitive in situ hybridization approach to detect short sequences and splice variants with cellular resolution. *Mol Neurobiol. 55*,6169-6181. doi: 10.1007/s12035-017-0834-6.
5. Erben L., Buonanno A. (2019). Detection and quantification of multiple RNA sequences using emerging ultrasensitive fluorescent in situ hybridization techniques. *Curr Protoc Neurosci. 87*(1):e63. doi: 10.1002.
6. Skirzewski M., Cronin M.E., Murphy R., Fobbs W., Kravitz A., Buonanno A. (2020). *ErbB4* null mice display altered mesocorticolimbic and nigrostriatal dopamine levels, as well as deficits in cognitive and motivational behaviors. *eNeuro*. 0395-19.2020. doi: 10.1523/ENEURO.0395-19.2020.
7. Erben L., Welday J.P., Murphy R., Buonanno A. (2020). Toxic and phenotypic effects of AAV-Cre transduced in mesenchephalic dopaminergic neurons (*in submission*).
8. Ahmad T., Guardia C.M., Vullhorst D., Karavanova I., Bonifacino J.S., Buonanno A. (2020). Trafficking mechanisms underlying presynaptic NRG3 accumulation in central neurons (*in preparation*).
9. Erben L., Cronin M.E., Welday J.P., Murphy R., Skirzewski M., Karavanova I., Vullhorst D., Carroll S.L., Buonanno A. (2020). Developmental, neurochemical, and behavioral analyses of *ErbB4 Cyt-1* knockout mice (*in preparation*).

Recent Achievements in International Health

SMN works on basic science projects with a potential for translational research.

International Trainees

- 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.
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  Head of Research Laboratory
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- Miguel Skirzewski, Ph.D.
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- Raluca Yonescu, Ph.D.
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International Partnerships

- Universidad de los Andes, Merida, Venezuela. Memorandum of Understanding (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

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Section on Nutrient Control of Gene Expression (SNCGE)

Principal Investigator: Alan Hinnebusch, Ph.D.

Affinity Group: Cell Regulation and Development

Scientific Scope

SNCGE focuses on the mechanism of protein synthesis initiation in budding yeast provided the foundation for a collaboration with researchers at the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, England, on high-resolution cryo-electron microscopy of reconstituted preinitiation complexes. This work revealed 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.

Recent collaborative work with researchers at the University of Prague, Czech Republic, and the John Curtin School of Medical Research, The Australian National University, Canberra, Australia, led to the development of human TCP-seq, capable of capturing footprints of small (40S) subunits throughout the translatome; and also yeast and human selective TCP-seq (Sel-TCP-seq), enabling selection of 40Ss associated with immuno-targeted initiation factors.

The latter demonstrated that factors eIF2 and eIF3 travel along mRNA leaders with scanning 40Ss, and that a proportion of eIF3 lingers on following initiation during the initial elongation cycles. Sel-TCP-seq also identified multiple initiating 48S conformational intermediates, provided novel insights into *ATF4* and *GCN4* mRNA translational control, and demonstrated co-translational assembly of initiation factor complexes.

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. 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. 2017 18*:2651-2663.

3. 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. 2017, 6*: e31250.
4. 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. 2018 71*:761-774.
5. 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.
6. 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]
7. Wagner S, Herrmannová A, Hronová V, Gunišová S, Sen ND, Hannan RD, Hinnebusch AG, Shirokikh NE, Preiss T, Valášek LS. Selective Translation Complex profiling reveals staged initiation and co-translational assembly of initiation factor complexes. *Mol Cell. 2020 Jun 25*:S1097-2765(20)30389-0. doi: 10.1016/j.molcel.2020.06.004. [Online 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

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Section on Protein Biosynthesis (SPB)

Principal Investigator: Thomas Dever, Ph.D.

Affinity Group: Cell Regulation and Development

Scientific Scope

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 genetics 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 Germany identified additional mutations in the translation factor eIF2gamma that cause MEHMO syndrome. These studies broaden the limited genetic spectrum and underscore the clinically variable expressivity of MEHMO syndrome. Studies of these mutations in yeast models revealed that the mutations impair protein synthesis and relax the stringency of translation start site selection. Additional studies in collaboration with other scientists in Germany revealed that the translation and neuronal differentiation defects observed in inducted pluripotent stem cells derived from a patient with MEHMO syndrome could be rescued by the drug ISRIB, offering the possibility of therapeutic intervention for MEHMO syndrome.

Publications with International Collaborators

1. Kotzaeridou U, Young-Baird SK, Suckow V, Thornburg AG, Wagner M, Harting I, Christ S, Strom T, Dever TE, Kalscheuer VM. Novel pathogenic *EIF2S3* missense variants causing clinically variable MEHMO syndrome with impaired eIF2gamma translational function, and literature review. *Clinical Genetics. In press*, DOI: 10.1111/cge.13831. PMID: 32799315.
2. Young-Baird SK, Lourenco MB, Elder MK, Klann E, Liebau S, Dever TE. Suppression of MEHMO syndrome mutation in *eIF2* by small molecule ISRIB. *Mol Cell. 2020 77*:875-886. PMID: 31836389.

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

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