2021

NICHD International Activities Catalog

Office of Global Health
Office of the Director

Eunice Kennedy Shriver National Institute of Child Health and Human Development

NICHD International Activities Catalog 2021

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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 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 (NGOs).

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 list international trainees and key publications.

Office of the Director (OD)

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

Mission

OGH seeks to improve health worldwide by providing leadership, coordination, and support toward realizing NICHD's mission to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all.

Major International Initiatives over the Past Year

COVID-19 Pandemic Research Response. Biomedical research continues to face challenges and disruptions caused by the COVID-19 pandemic around the globe. OGH has represented NICHD in ongoing interagency discussions on the U.S. government's COVID-19 response organized by the HHS Office of Global Affairs (OGA), the Fogarty International Center (FIC) at NIH, and the USAID Children in Adversity (APCCA) Interagency Working Group. While discussions continue on how best to address disrupted research and training activities in multiple countries, the Biden administration's renewed commitment to close collaborations between the United States and the World Health Organization (WHO) has helped facilitate joint work on global health research priorities. NICHD also provided input related to maternal and child health policy documents for the World Health Assembly held in May 2021.

NICHD Strategic Plan: The Wefting of Global Health. Although the implementation of the NICHD Strategic Plan has been delayed by the COVID-19 pandemic, OGH has contributed in two capacities to the identification of research priorities in the plan: 1) as co-chair for Research Theme 4A 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 implementation, OGH will seek to further improve real-time communications about global health priorities between the NICHD OD, including OGH, and other NICHD components, particularly on key global health research issues, science advances, and interagency activities.

NIH – Bill and Melinda Gates Foundation (BMGF) Collaboration. NIH has worked closely with BMGF during the COVID-19 pandemic to accelerate progress related to the development of diagnostic tests, vaccines, therapeutics, among other resources. NICHD co-chairs the NIH Maternal, Neonatal, and Child Health and the Contraceptive Research Working Groups, that 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 COVID-19, pregnancy outcomes, nutrition and growth, child neurodevelopment, neuroimaging, contraception development, among other areas.

NIH Common Fund: Data Science & Innovations in Africa Program (DS-I Africa). NICHD staff has been participating in the NIH Common Fund's DS-I Africa initiative to leverage data-science technologies and prior NIH investments to develop solutions to Africa's most pressing public health problems. This initiative has included participants from 18 African countries (top countries being Nigeria, South Africa, Uganda, Kenya, Ghana, Ethiopia), about one-half of whom come from academia as well as NGOs. Scientifically, the initiative included an emphasis on public health, particularly infectious diseases. Related NIH funding opportunities have

focused on four areas: an open data science platform and coordinating center; research hubs; research training programs; and ethical, legal, and social implications (ELSI) research. In 2021, NICHD will begin supporting two DS-I research grants. In addition, the DS-I Africa Data Scholar Program was established to promote data-science research in Africa.

FIC Global Health Program for Fellows and Scholars. NICHD participated for a second year in the Global Health Program for Fellows and Scholars. In the program, predoctoral (Scholars) and postdoctoral (Fellows) trainees, from the United States and from partnering institutions in low- and middle-income countries (LMICs), conduct a year of mentored research at an established U.S.-based or comparable LMIC-based academic institution. Each grant is led by a consortium of U.S. universities with strong global health research portfolios and their LMIC-based partner institutions. The program has trained more than 1,000 Fellows and Scholars at over 80 research sites in 27 LMICs, resulting in the publication of over 1,200 peer-reviewed papers. OGH and the NICHD Maternal and Pediatric Infectious Disease Branch organized an internal peer-review process for the selection of candidates working on HIV/AIDS research topics in line with the NICHD mission.

Global Alliance for Chronic Disease Initiative. The purpose of this initiative is to reduce the burden of chronic non-communicable diseases in LMICs, and in populations facing conditions of vulnerability in high-income countries, by building evidence to inform national and international policies. Interagency partners are working together to identify research priorities and to jointly administer a research grant program. NIH partners include NICHD, NHLBI, NIMH, NINDS, the National Cancer Institute (NCI), NIDA, the National Institute of Environmental Health Sciences (NIEHS), and the NIH Center for Scientific Review.

NICHD OGH Webinar on Global Child Injury. In July 2021, OGH organized a global health webinar featuring the research of Dr. Cinnamon Dixon, a pediatric emergency physician and former academic injury scientist in the NICHD Pediatric Trauma and Critical Illness Branch entitled, *Global Child Injury: Spotlight on Road Traffic Injury and Drowning*. Dr. Dixon shared data on these two leading global causes of child injury-related death—road traffic injury and drowning—and highlighted NIH activities, global initiatives, scientific achievements, and prevailing gaps.

NICHD OGH Panel on Implementation Science. In February 2021, OGH organized a panel discussion entitled, *The Role of Dissemination and Implementation Science to Strengthen Research in NICHD Populations*, which featured presentations by staff from the NICHD Pregnancy and Perinatology Branch, NCI, and the NIH Office of Behavioral and Social Science Research (OBSSR). The panel also included presentations from NICHD-funded researchers focused on Spreading the Integrated District Evidence-to-Action Program for Neonatal Mortality Reduction (IDEAs) in Mozambique and Addressing Obesity in Early Care and Education Settings in Los Angeles, California. The panel aimed to 1) provide 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.

NICHD Dissemination & Implementation Science (D&I) Workgroup. The purpose of the D&I Workgroup, led by OGH, is to plan and coordinate D&I activities (e.g., research and training) across NICHD and NIH, and in collaboration with external agencies. The workgroup acts as a forum for internal information exchange and as a catalyst for developing D&I initiatives at NICHD. Staff members representing several NICHD branches/programs are working with

OGH to advance this important area of science. Projected external and internal activities include seminars, trainings, workshops, and future funding announcements.

WHO Nurturing Care Framework. Since the start of the COVID-19 pandemic, the WHO has continued to assess its impact on children and their families around the globe, while also developing culturally responsive and evidence-based interventions. Over the past 4 years, OGH has represented NICHD on the WHO Nurturing Care Framework Planning and Implementation Working Group. The concept of "Nurturing Care" was coined in the 2016 *Lancet* series, "Advancing Early Childhood Development: From Evidence to Scale," to refer to a cluster of evidence-based interventions for enhancing health, nutrition, responsive caregiving, safety and security, and early learning. OGH participated in both the 2018 World Health Assembly launch of this WHO framework (which included over 200 participants) and subsequent technical consultations aimed at identifying research and implementation gap areas, developing plans for interagency implementation, and drafting guidelines for policymakers.

U.S. Government's Children in Adversity Initiative. 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 over the past year. The disruption of health services for children and families due to the COVID-19 outbreak, 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, and the increase in orphans due to the of caregivers were among the areas of interest. OGH has kept this working group apprised of trans-NIH research efforts on the COVID-19 outbreak most relevant for at-risk children and their families.

Trans-NIH Humanitarian Health Research Working Group. In November 2021, the working group hosted a virtual Global Forum on Humanitarian Health Research (GFH2R) together with interagency partners, including the International Development Research Centre (IDRC), the UK Medical Research Council (MRC), and the Wellcome Trust. The organization prioritizes the participation of early- to mid-career researchers from LMICs, encourages networking and mentoring, and creates a venue for open and inclusive discussions. The forum convened researchers and humanitarian organization experiences to promote collaboration around health research in humanitarian settings, and featured case study presentations related to the theme, *Research in the Context of Concurrent Crises*. OGH served on Meet-the-Expert panels at the meeting and provided overviews of NICHD-supported global health research.

Recent Achievements in International Health

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

Given the ongoing COVID-19 outbreak, some global health activities, such as visits to the NIH campus by foreign delegations, high-level U. S. government staff visits to NIH international research sites, and international travel to scientific conferences continue to be postponed, canceled, or occur virtually. Nonetheless, in collaboration with NICHD program staff, OGH has represented NICHD and prepared briefings for high-level global health leadership (e.g., HHS OGA, HHS Health Attaché in China, Norway Research Council), and provided input on relevant maternal and child health research for interagency documents (e.g., World Health Assembly, WHO Regional Meetings, Pan American Health Organization).

- **Coordination of Visits by Foreign Delegations:** Participated in the coordination of meetings and preparation of briefing materials for visits or virtual meetings with foreign delegations (e.g., congressional delegation site visits in India)
- **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/Webinar 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 page on the NICHD Insider and prepared the annual NICHD International Activities Catalog to facilitate information exchanges related to global health
- **Scientific Input for Interagency Global Health Documents:** Contributed to the writing of science and policy documents and requests for information from internal (e.g., NICHD, NIH, HHS) and external (e.g., USAID, WHO, United Nations Children's Fund [UNICEF]) sources that describe NICHD's mission and international activities

International Partnerships

OGH developed international partnerships through involvement with the following working groups.

Examples of Staff Membership on Global Health Committees/Working Groups

- NICHD Global Health Strategic Team: Drs. Vesna Kutlesic and Jenelle Walker
- NIH-BMGF Maternal, Neonatal, & Child Health Working Group: Dr. Vesna Kutlesic
- WHO Nurturing Care Framework Advisory Group: Dr. Vesna Kutlesic
- Children in Adversity Strategy Working Group: Drs. Vesna Kutlesic and Jenelle Walker
- Trans-NIH Global Health Research Working Group: Dr. Vesna Kutlesic
- Trans-NIH Promoting Equity in Global Health Working Group: Dr. Vesna Kutlesic
- Trans-NIH International Clinical Research Subcommittee: Dr. Vesna Kutlesic
- FIC International Representatives Working Group: Drs. Vesna Kutlesic and Jenelle Walker
- Fogarty International Interest Group: Drs. Vesna Kutlesic and Jenelle Walker
- NICHD Reproductive Health Working Group: Drs. Vesna Kutlesic and Jenelle Walker
- NICHD Maternal Health Coordinating Committee: Drs. Vesna Kutlesic and Jenelle Walker
- NICHD Male Health Working Group: Drs. Vesna Kutlesic and Jenelle Walker
- White House Gender Policy Council, Science & Technology Interagency Working Group: Dr. Vesna Kutlesic
- White House Gender Policy Council, Women and Girl's Education and Leadership Interagency Working Group: Dr. Jenelle Walker

- Global Nutrition Coordination Plan Technical Working Group: Dr. Jenelle Walker
- Trans-NIH D&I Working Group: Dr. Jenelle Walker
- NIH Global Health Interest Group: Dr. Jenelle Walker
- NICHD D&I Working Group: Drs. Jenelle Walker and Vesna Kutlesic
- STrategies to enRich Inclusion and achieVe Equity (STRIVE) Health Disparities Research Committee: Dr. Vesna Kutlesic
- STRIVE Scientific Workforce Committee: 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 progress 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 using 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 human 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 using a unique animal model (R01HD088558). The project takes advantage of a 5-decade, multigenerational study of baboons for 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 among 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 mother-child pairs in ADHD and control groups (5R01HD090051-04). This study will also characterize immune signatures of mothers during pregnancy and their children at birth, determine the association of these signatures with ADHD risk, and 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 are demonstrating which aspects of language development are 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 with 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 subcomponents of 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 using 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 women without HIV 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 condomless vaginal sex more or less frequently than women randomized to the IUD or LNG implant during trial follow-up by comparing vaginal PSA (a marker of recent semen exposure) between randomized contraceptive groups across multiple ECHO trial sites and then, 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 LNG implant during trial follow-up by evaluating the concordance of self-reported condom use or abstinence during trial follow-up with PSA detection for all groups, 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, a connection that is critical to the accurate interpretation of trial results. Policymakers, providers, and contraceptive users can use these findings to minimize the risk of both unwanted reproductive outcomes and HIV acquisition 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 evaluation of 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 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 four decades, the product consistently raised hemoglobin levels and increased 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 Women with HIV. Family planning options are essential for improving reproductive health, especially among women living with HIV. Prevention of unintended pregnancy decreases maternal and child mortality and reduces the risk of perinatal HIV transmission. Antiretroviral therapy (ART) is essential for reducing morbidity and mortality among individuals with HIV, in addition to preventing HIV transmission. It is of critical public health importance to safely combine hormonal contraceptives and ART. Millions of women with HIV 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 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 women with HIV. 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 women with HIV; and 3) advance the science of the drug-drug interaction field. The study seeks 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 women with HIV worldwide.

A Prospective Cohort of Malawian Women with HIV on EFV initiating the LNG Implant or the DPMA Injectable. Sub-Saharan Africa 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 sub-Saharan settings like Malawi because 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 the region, but 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 sub-Saharan Africa to consider policy recommendations against use of implants for women on EFV. This study compares the typical-use pregnancy rates of the LNG implant versus the DMPA injectable in a prospective cohort of 1,420 women with HIV on EFV (710 initiating the LNG implant and 710 initiating DMPA). Researchers will follow study participants and collect data 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

A Longitudinal Assessment of Cervical Inflammation and Immunity Associated with HIV-1 Disease, Hormonal Contraception, and Pregnancy. Hormonal contraception, particularly injectable DMPA, has been associated with increased HIV acquisition and higher levels of cervical regulated upon activation, normal T-cell expressed, and secreted (RANTES), which is also associated with HIV seroconversion. Longitudinal changes in cervical immunity associated with DMPA and combined oral contraceptives have not been studied. Cervical samples from 216 HIV seroconverters in Uganda and Zimbabwe with matched samples from 727 controls without HIV were collected at two quarterly visits, at two visits after HIV seroconversion, and at corresponding visits for controls without HIV. The study found longitudinal patterns of cervical immunity differed between HIV seroconverters, assessed both before and after HIV acquisition, and non-seroconverters. Furthermore, DMPA, combined oral contraceptive use, and pregnancy differentially affected the cervical immunoinflammatory mediators associated with HIV risk. (*AIDS Res Hum Retroviruses*, 2018: PMID: 30047279)

Effect of patient genetics on etonogestrel pharmacokinetics when combined with EFV or nevirapine (NVP) ART. Previous research demonstrated that etonogestrel concentrations were 82-percent lower in Ugandan women using etonogestrel contraceptive implants plus EFV-based ART compared with those not receiving ART. A secondary analysis of the genetic contribution to this previously observed drug-drug interaction examined single nucleotide polymorphisms (SNPs) in genes known to be involved in EFV, NVP, or etonogestrel metabolism in the same group of Ugandan women. Study results demonstrated the influence of pharmacogenetics on the extent of drug-drug interactions between etonogestrel and EFV- or NVP-based ART. EFV plus the etonogestrel contraceptive implant resulted in a detrimental drug-drug interaction irrespective of patient genetics, but was worsened in women possessing variant alleles for these *CYP2B6* SNPs. (*J Antimicrob Chemother,* 2019: PMID: 31299074)

A PK and pharmacogenetic evaluation of contraceptive implants and ART among women in Kenya and Uganda, 1995-2004. This study evaluated the PKs and pharmacogenetics of contraceptive implant progestin concentrations in women with HIV initiating EFV-containing or NVP-containing ART in Kenya and Uganda. Stored samples from women self-reporting implant use in the Partners Pre-Exposure Prophylaxis (PrEP) Study were analyzed. Concomitant use of

EFV significantly reduced LNV or etonogestrel concentrations by 61 percent and 49 percent, respectively, compared with no ART use. In addition, allelic variants in hepatic enzymes influence the extent of the observed drug interaction between progestins and EFV. (*AIDS,* 2019: PMID: 31306173)

Pharmacogenetic interactions between antiretroviral drugs and vaginally administered hormonal contraceptives. In the AIDS Clinical Trials Group (ACTG) study A5316, EFV lowered plasma concentrations of etonogestrel and ethinyl estradiol, given as a vaginal ring, while atazanavir/ritonavir increased etonogestrel and lowered ethinyl estradiol concentrations among study participants in Asia, South America, sub-Saharan Africa, and the United States. Compared to controls, EFV reduced median etonogestrel concentrations by at least 93 percent in *CYP2B6* slow metabolizers versus approximately 75 percent in normal and intermediate metabolizers. EFV reduced median ethinyl estradiol concentrations by 75 percent in *CYP2B6* slow metabolizers versus approximately 41 percent in normal and intermediate metabolizers. Slow metabolizer genotype worsens the PK interaction of EFV with hormonal contraceptives administered by vaginal ring. EFV dose reduction in *CYP2B6* slow metabolizers may reduce, but will likely not eliminate, this interaction. (*Pharmacogenet Genomics,* 2020: PMID: 32106141)

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

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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 related to the causes and prevention of structural birth defects, as well as research training in relevant academic and medical areas. Basic research is among the branch's high-priority areas, 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 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 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, birth defects consistently 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 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 and applies 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 that interfere with normal neural tube closure. Understanding the underlying biology of failed closure raises the possibility of developing effective intervention strategies for preventable NTDs, a prospect with broad implications for the 330,000 infants born with NTDs annually worldwide.

Multinational Collaborations

To obtain enough subjects for statistically significant study 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. Craniosynostosis and other skull abnormalities are among the most common human malformations and usually require surgical and medical interventions. 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. 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 for use in genotyping studies.

Japan, Sweden, and Hong Kong. Adolescent idiopathic scoliosis (AIS), a twisting condition of the spine, is the most common pediatric musculoskeletal disorder, affecting 3 percent of children worldwide. Children with AIS risk severe distortion, 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 of early diagnosis, prevention, and non-invasive biologic treatment. AIS is a complex genetic disease and, although genome-wide association studies (GWAS) of common non-coding variants have identified AIS-associated DNA variations/polymorphisms, the mechanistic basis of these associations remains to be defined. GWAS also require well-powered replication studies to validate the work being carried out; however, 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 associated with scoliosis as well as summary statistics (e.g., allele frequencies, odds ratios, P values, etc.) from the cohort. In this way, investigators can test these markers in each other's cohorts of scoliosis patients and controls to 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 further improve validation studies.

Canada, Spain, and China. X-chromosome inactivation (XCI) is a mechanism of dosage compensation that exemplifies epigenetic regulation during early mammalian development and serves as a model for understanding interactions between long noncoding RNA (lncRNA) and chromatin complexes. During XCI, the noncoding Xist RNA spreads along the X chromosome and targets Polycomb repressive complexes (PRC2) to active gene regions. In this project, the Principal Investigator (PI) seeks to understand the mechanisms underlying XCI and how functional interactions between PRC2 and lncRNA spread the silencing process through the X chromosome in a locus-specific manner for proper developmental regulation. A collaboration with Canadian researchers will examine the structural aspects of the interaction between Polycomb proteins (PRC2, EZH2) and their interacting RNA partners to determine whether there are allosteric changes or physical changes (e.g., cleavage of transcript by the ribozyme function). In addition, a collaboration with China will examine the role of Heterogeneous Nuclear RiboNucleoProtein K (HNRNPK) in the initiation and spreading of XCI and whether an associated phase transition, or a change from a liquid-soluble to less soluble semi-liquid state, could explain how Xist and Polycomb proteins can spread rapidly along the X chromosome. Finally, a collaboration with Spain will investigate the localization dynamics of PRC2, and how SirT7 mutations affect Xist and Polycomb spreading.

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 among investigators doing basic research with different animal models and with physician-scientists doing clinical or translational research has become paramount. Community databases are among the best ways to share data. Xenbase, the *Xenopus* model organism database, is one of the best available community databases 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. By ensuring that important data are available and easily accessible to guide further research projects without unnecessary duplication of effort, Xenbase provides an essential resource to the biomedical research community for understanding the molecular basis of development, health, and disease.

In the last year, echinoderm researchers in the United States and Canada launched a similar collaboration to improve the EchinoBase database. They are 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 research on 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.

Understanding short-stature syndromes, a family of structural birth defects, is also important to the mission of NICHD. The 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. Although some animals can regenerate their limbs after injury, humans cannot. In this grant, the PI proposed 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 it to the mouse digit stump after middle-phalanx amputation. A frog limb regeneration study conducted in China forms the basis of this collaboration. The activity involves parallel studies on the non-mammalian frog model to inform/benefit the NIH study of limb/digit regeneration in mammals.

Israel. A U.S.-based PI discovered a non-apoptotic developmental cell-death program that occurs in *C. elegans* linker cells. The morphology of a dying linker cell is characterized by lack of chromatin condensation, a crenellated nucleus, and swelling of cytoplasmic organelles. Remarkably, cell death with similar features, called linker cell-type death (LCD), also occurs in vertebrates and is characteristic of neuronal degeneration in polyglutamine diseases in humans. This grant is aimed at identifying signaling pathways involved in LCD and determining relevance to mammals. To conduct this work, the U.S.-based investigator will receive cell lines from University of Haifa, Israel, although all the work will be performed within United States.

Germany. Over the course its lifetime, an animal's cell-fate changes allow for normal development and growth as well as for 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 target mRNAs, control expression to affect specific cell-fate changes, and 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 tracking 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. These 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, as well as 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 researchers in the 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 of the organoid culture in a dish, avoiding the use of expensive and complex animals or human experiments.

New Zealand. Studies carried out in the University of Auckland branch of a U.S.-based PIs laboratory will obtain genetic data from *C. elegans* to study how changes in an animal's genome occur during its evolution. The work is also investigating how such changes allow it to develop from a fertilized egg into a normal animal without resulting in defective development.

Switzerland. Researchers are using different types of ribosomes within the embryo as a novel means of controlling expression of key developmental regulator genes. To understand this new level of gene regulation at a mechanistic level, 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.

The goal of another project with Swiss scientists is to understand how DNA is organized, what mediates this organization, and how this organization contributes to developmental gene expression. Given the coincidence of both structural organization and units of gene regulation, this project will systematically tease apart these contributing factors at a unified, developmentally important locus. This collaboration will test the contribution of three, structural protein (CCCTC-Binding Factor) binding sites to a long-range enhancer-promoter interaction at the Sonic hedgehog locus in embryonic mouse brain tissue. The Swiss collaborators will genetically engineer mouse embryonic stem cells with specific mutations of interest and use these cells to generate chimeric embryos. At appropriate times in development, these chimeric embryos will be fixed and shipped to the University of Pennsylvania, where collaborating U.S. investigators will conduct phenotypic and other downstream analyses.

United Kingdom. The goal of this project is to study mouse embryos engineered to carry precise mutations in a special category of regulators, called epigenetic regulators, which are essential for mammalian development, and determine which components are mutated in a variety of human diseases. This study aims to yield deep insights into the functions of epigenetic regulators in development and disease. The application was submitted in response to an NIH initiative requiring resulting data to be deposited in the European Molecular Biology Laboratory/European Bioinformatics Institute, which is supported by the NIH Knockout Mouse Phenotyping Program-2.

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. 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 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. Although women with OF often can be successfully treated with surgery, they may still not be reintegrated into their communities. GHDB currently supports a study 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, usually carried out by a member of the community or family, is conducted 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 more than 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 because there are still immigrant communities carrying out this procedure. As such, FGC remains both an international and domestic area of research interest.

GHDB is currently funding a study to measure the health and psychological impacts of FGC among West African immigrant females now living in New York City, as well as the knowledge, attitudes, and practices regarding FGC among healthcare providers who care 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 chronic sexual pain among Somali American women who have had FGC living in Minnesota. The overall goal is to gather information that may help mental health and medical professionals 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 related to 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 insights provided by studies of the normally functioning endometrium, as well as potential diagnostics for addressing atypical 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 2019 web spotlight.

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

- 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, 223*(5): 617-18. PMID: 32709301

2. Critchley H, et al. (2020). Menstruation: Science and Society. *AJOG, 223*(5): 624-64. PMID: 32707266

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 supporting a diverse portfolio of research projects, training programs, and research centers dedicated to promoting the well-being of individuals with intellectual and developmental disability (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 IDDs.

The mission of the IDDB is to support a program of research in IDD, including common and rare neuromuscular and neurodevelopmental disorders (NDDs), such as Down, Fragile X, and Rett syndromes, inborn errors of metabolism, autism spectrum disorders (ASDs), and conditions currently and soon-to-be detectable through newborn screening. 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 IDDs; 2) research on comorbid conditions of IDDs, 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 IDDs, including pre-symptomatic, adolescence to adulthood, middle adulthood to elderly, and causes of mortality; and 6) development and implementation of treatments for IDDs that impact clinical care and improve quality of life.

IDDs are not limited by geographic or national boundaries, though the factors that may lead or contribute to them, 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 IDDs in LMICs and 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 IDDs.

Major International Initiatives over the Past Year

Gene and Variant Curation. The branch supports 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 identifying many genomic variants with unknown significance, potentially leading to inappropriate medical interventions. In partnership with the Clinical Genome Resource (ClinGen), which is funded by the National Human Genome Research Institute, NICHD initiated a program that brings together international panels of experts to identify genes and genomic variants associated with the pathogenicity of conditions of high importance to the institute. Three expert curation panels that include international experts have been funded to study mitochondrial diseases, neonatal diabetes conditions, and brain malformation disorders. A new funding opportunity released in fiscal year 2020 expanded the program to other NIH institutes and centers, including NCI, National Eye Institute, NIMH, and NINDS. In fiscal year 2021, NICHD-awarded expert panels will include international experts from 15 different countries in total and will curate genes and variants related to immunodeficiency and infections in children (Drs. Ivan Chinn and Troy Torgerson);

severe structural anomalies and stillbirth (Dr. Ronald Wapner), and primary mitochondrial disorders (with NINDS, Drs. Marni Falk and Xiaowu Gai).

Down Syndrome. DS-Connect®: The Down Syndrome Registry is a secure online 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 5,300 registrants in the United States and abroad and has supported recruitment for over 60 research projects through its membership. International partners include Down Syndrome International, Trisomy 21 Research Society (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 version 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 is responsive to facilitate access on a wide variety of platforms. The DS-Connect® registry also includes a Medication Tracker, where participants enter information about medication and supplement use in people with Down syndrome, to help inform research and future clinical drug trials. Recently, the DS-Connect® website incorporated a search functionality specifically for NIH-supported clinical trials and studies in Down syndrome that are active and recruiting on ClinicalTrials.gov.

The trans-NIH INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) Project launched in 2018 to investigate conditions that affect individuals with Down syndrome and the general population, such as Alzheimer's disease/dementia, ASDs, cataracts, celiac disease, congenital heart disease, and diabetes. Its mission includes assembling a large study population of people with Down syndrome across the lifespan and promoting clinical trials to treat co-occurring conditions in Down syndrome; several studies include international populations from Europe and West Africa (additional details follow and are available in the Mobile Health section).

A collaboration, funded by the INCLUDE Project, between investigators in the United States and Canada is comparing longitudinal early brain development in infants and school-age children with Down syndrome, other developmental disabilities (ASDs and Fragile X syndrome), and typically developing infants and children. The study uses magnetic resonance imaging (MRI) to compare changes in brain structures, with the goal of eventually identifying therapeutic targets for interventions in individuals with Down syndrome. This effort builds on the Infant Brain Imaging Study (IBIS) project, which studies baby siblings of children diagnosed with ASD who are at high-risk for developing the condition themselves, to look for the earliest brain signatures and neuropsychological features of ASD. The project (PI: Dr. Kelly Botteron) includes a data coordinating center at the Montreal Neurological Institute in Canada.

Another project, known as the Alzheimer's Biomarkers Consortium-Down Syndrome (ABC-DS), is evaluating adults with Down syndrome via neuroimaging, neuropsychological testing, and blood- and spinal fluid-based biomarkers for manifestations of Alzheimer's disease, which is known to be increased in those with Down syndrome. This activity (PI: Dr. Benjamin Handen), co-funded by NICHD, National Institute on Aging, and the INCLUDE Project, has numerous recruitment sites throughout the United States and in the United Kingdom. A related study (PI: Dr. Michael Rafii) is investigating the adult Down syndrome population in France to create a trial-ready cohort for studying medications to prevent and/or treat Alzheimer's in this population.

Understanding the Long-Term Outcomes of In Utero Zika Virus Exposure. The extensive outbreak of Zika in Brazil and its devastating impacts on infants exposed in utero has left vulnerable families facing the long-term implications of raising a child with potentially severe and limiting disabilities. Longitudinal surveillance of affected infants and their families is urgently needed. A collaboration between the United States and Brazil supports 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 (PI: Dr. Don Bailey) has the potential to fill knowledge gaps about the developmental course of congenital Zika syndrome, the treatment needs of children, and support needs of family caregivers.

Recent Achievements in International Health

Brain Disorders in the Developing World: Research across the Lifespan Initiative. IDDB participates in this FIC-led initiative to enhance research to ameliorate IDDs in LMICs.

- A research collaboration between the United States and Guatemala will identify IDDs in children that result 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 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. The study will enroll a cohort of children from birth to 6 months of age who will use wearable sensors. A related multidisciplinary project will involve pediatric medicine, physical therapy, and biostatistics to build research capacity in Guatemala through a partnership between the University of Southern California and the Maya Health Alliance in Guatemala.
- Cyanide levels in cassava are known to lead to Konzo, a disease in which children exhibit neurodevelopmental delay. Konzo poses a serious public health threat in central and western Africa. A research collaboration between the Democratic Republic of Congo and the United States is evaluating the effectiveness of adding an early childhood developmental intervention, which better sensitizes mothers to children's development, to a proven treatment for Konzo. This study will determine whether the combination of these interventions leads to better neurocognitive outcomes in the children.
- A research collaboration between the United States and Uganda supports a clinical trial to evaluate the effectiveness of hydroxyurea for preventing 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.
- 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 IDDs that often go unrecognized because of difficulties in accessing medical services. This research collaboration with Sri Lanka is a proof-of-concept study to adapt mobile health technologies for transferring 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.
- A collaboration between investigators in the United States and India will use whole-exome sequencing (WES) technology to investigate genetic causes of inherited 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 research

capacity in India to address the needs of these children. This research collaboration will test and adapt tools for optimizing analysis and reanalysis of WES data to streamline variant identification, annotation, and interpretation by research scientists and medical professionals. These tools will then be used to build an integrative outreach portal for making de-identified population-specific genetic data publicly available. This data resource could allow other LMICs globally to adopt the lessons learned by this team and could facilitate the integration of genetic counseling into clinical practice.

- Epilepsy is a significant health problem in Uganda, but its frequent association with stigma and discrimination often leads to delays in accessing needed health care. A research collaboration between investigators in the United States and Uganda aims to reduce the public health burden and stigma around epilepsy among Ugandan adolescents. The project will use a multipronged approach, including deep clinical phenotyping to characterize disease severity and comorbidities and surveys to assess the magnitude and impact of stigma, in pursuit of a long-term goal of improving affected individuals' psychosocial and functional outcomes.
- A longstanding prospective cohort study is quantifying the progression of Fragile X-Associated Tremor Ataxia Syndrome (FXTAS), through repeated longitudinal assessment of biomarkers and clinical outcomes, to ascertain whether a correlation exists 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, research collaborators at La Trobe University in Melbourne, Australia, will recruit an independent validation sample of individuals to help increase the generalizability of clinical findings across multiple diverse populations.

Mobile Health: Technology and Outcomes in LMICs (mHealth). IDDB participates in this FIC-led initiative to encourage exploratory/developmental research applications on the development, validation, feasibility, and effectiveness of innovative mHealth interventions or tools that utilize new or emerging technology, platforms, systems, or analytics and that are specifically suited for LMICs.

A first-time collaboration between FIC and the INCLUDE Project will support a study of mHealth intervention tools that use facial recognition software to screen for syndromic congenital anomalies, with a focus on Down syndrome, and build a health outcomes data registry in the Democratic Republic of the Congo. These timely diagnoses will also enable screening for comorbidities, such as congenital heart defects and otitis media. Application of this research can improve the diagnostic rate of Down syndrome in individuals of African ancestry, as well as in diverse populations, including low-resource and underserved rural populations in the United States. This collaboration also adds FIC to the trans-NIH INCLUDE Project, further increasing NIH's investment in Down syndrome research internationally.

Rare Diseases Research. Many rare disorders 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 (NCATS). 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, Mitochondrial Diseases,

Developmental Synaptopathies, Phenylalanine-related disorders, Congenital Disorders of Glycosylation, and Brittle Bone 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 usually results in death during 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.

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

International Rare Diseases Research Consortium. Funders Constituent Committee Member: Dr. Melissa Parisi

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Maternal and Pediatric Infectious Disease Branch (MPIDB)

Scientific Scope

MPIDB supports domestic and international research and sponsors research training and career development programs related to the epidemiology, diagnosis, clinical manifestations, pathogenesis, transmission, treatment, and prevention of HIV acquisition 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 60 countries through grants, cooperative agreements, and contracts. For more information about the branch, please visit the MPIDB webpage and subscribe to our branch newsletter.

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. As the pandemic continued, MIS-C began to surface in children across the world as a rare but serious condition weeks after they had or were exposed to COVID-19. The severity of MIS-C disease in children followed trends like those of adults, with severity increasing in the presence of co-morbidities, such as obesity. World reports linked cases and deaths in children to a previous SARS-CoV-2 viral infection and to MIS-C, and most MIS-C related cases presented 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 cases and deaths, MPIDB/NICHD is leading a trans-NIH initiative to support the development of laboratory diagnostics integrated with digital health technologies and Artificial Intelligence (AI)-based algorithms to rapidly diagnose and characterize SARS-CoV-2 associated illness in children and to 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 the trans-NIH Rapid Acceleration of Diagnostics-Radical (RADx-rad) program to speed innovation in the development, commercialization, and implementation of technologies for COVID-19 testing and surveillance. NIH funded studies are enrolling children with diverse geographic, racial, and ethnic backgrounds across 30 U.S. states, Canada, the United Kingdom and South America.

MPIDB/NICHD also participates in NIH collaborations that build upon and further utilize existing infrastructures and contributes to calls for research proposals and projects to understand the effects of the virus among the branch's and the institute's populations of interest. 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 of infection 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.

FIC Global Health Program for Fellows and Scholars. As explained in the OGH section, NICHD participates in the FIC Global Health Program for Fellows and Scholars Program supporting predoctoral (Scholars) and postdoctoral (Fellows) trainees from the United States and from partner institutions in LMICs. The program provides 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. Several NICHD-selected candidates are working on HIV/AIDS research and on topics in line with the NICHD mission. Additional program and award information is available on the FIC Global Health Program for Fellows and Scholars webpage.

NIH Common Fund: DS-I Africa. As also explained in the OGH section, NICHD participates in the DS-I Africa Common Fund Initiative to leverage data science technologies and prior NIH investments to develop solutions for Africa's most pressing public health problems. NICHD, led by MPIDB, organized a Maternal and Child Health Panel in October 2020 on Innovative Data Science Approaches to Improve Maternal and Child Health; a recording of the panel is available at https://youtu.be/HhbzKtQig0g. MPIDB also contributed to the funding of a DS-I Research Hub.

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) in fiscal year 2018, in collaboration with the National Institute on Minority Health and Health Disparities (NIMHD) and the NIH OBSSR. These eight, large, cooperative agreements, which support research projects in South Africa, Kenya, Nigeria, Uganda, Zambia, Mozambique, and Brazil, are aimed at preventing HIV acquisition among at-risk youth and maintaining their status without HIV. 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 an 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*). NICHD currently funds 16 domestic sites, including Puerto Rico, and 10 international sites in five countries: Brazil, Kenya, Tanzania, Thailand, and Uganda. Through collaborations with the National Institute of Allergy and Infectious Diseases (NIAID), NIMH, Centers for Disease Control and Prevention (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 (IMPAACT) Network, ACTG, and the TB Trials Consortium.

International Epidemiologic Databases to Evaluate AIDS (IeDEA). IeDEA, co-funded by NIAID, NICHD, NIMH, NIDA, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and NCI, supports regional data centers in Africa, Asia, and North and South America to collect data on persons living with HIV who receive 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 projects, 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 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 and pregnant women without HIV that follows the infants born to them through the first year of life.

Reducing Stigma to Improve HIV/AIDS Prevention, Treatment, and Care in LMICs. In collaboration with FIC, NICHD, NIDA, NIMH, and NCI co-fund several research grants on interventions to reduce HIV-/AIDS-associated stigma and its impact on the prevention and treatment of HIV/AIDS and on the quality of life of people living with HIV/AIDS. These collaborative, exploratory studies seek to build the capacity for full research programs by improving the research environment and strengthening individual and institutional research capabilities of LMICs in the proposed research areas. The program has projects in the following countries: South Africa, Kenya, Tanzania, Ukraine, Botswana, Nepal, Thailand, India, Haiti, Dominican Republic, Vietnam, Guatemala, Senegal, Zambia, Uganda, and China.

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 items.

Emergency Awards: RADx-rad 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 early in the pandemic.

However, reports that followed 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, NCATS, and FIC). The initiative supports 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, to 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. For more information visit: NIH funds eight studies to uncover risk factors for COVID-19-related inflammatory syndrome in children.

Innovative Epidemiologic Approaches for Understanding Long-Term Health Outcomes of Populations Exposed to, but Without HIV, also called HIV-Exposed Uninfected (HEU) (RFA-HD-20-008). Utilizing a phased research approach (R61/R33), the purpose of this initiative was twofold: 1) demonstrate the capacity to enroll infants, children, adolescents, and young adults who are HEU in clinical studies; and 2) utilize innovative epidemiological approaches to assess overall health in the established 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 life-course questions about populations that are HEU and establishment and sustainability of a life-long evaluation model of in utero and postnatal HIV and antiretroviral (ARV) exposure. For more information on the five awarded projects check out the Science Highlights section of the Research for Reducing Health Disparities branch newsletter.

Utilizing Archived Data and Specimen Collections to Advance Maternal and Pediatric HIV/AIDS Research (RFA-HD-19-018, RFA-HD-20-020, and RFA-HD-21-030). Supporting research and data translation and sharing, this call for secondary analyses using archived HIV/AIDS data and specimen collections builds upon original research. Awardees 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 women living with HIV and without HIV, maternal and fetal physiologically based PK models of maternal/fetal antiviral drug disposition, Epstein-Barr virus viremia and malaria parasitemia in children living with HIV, and lipidome composition, immune activation, and subclinical vascular disease in adolescents living with perinatally acquired HIV. Data and specimens for these studies came from Kenya, Thailand, and Uganda.

Fogarty HIV Research Training Program for LMIC Institutions (D43 Clinical Trial Optional) (PAR-18-717 and PAR-19-283). FIC, in collaboration with other NIH institutes, including NICHD, encourages 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, mental health, microbiology and immunology, bioinformatics, drug resistance and pathogenesis, co-morbidities, and community-based research in women, children, and

adolescents. LMICs in which this research is being supported include Peru, Haiti, Ghana, Vietnam, Malawi, Kenya, Zimbabwe, Tanzania, 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 and continue 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 investigators in the United States, South Africa, and other African countries. 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 women living with HIV 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 to advance the effective use of evidence and help overcome implementation challenges related to prevention, screening, and treatment among adolescents living with HIV in sub-Saharan Africa. Grants were awarded to projects in the following 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. An AHISA-convened forum serves as a platform for collaboration among implementation scientists and other stakeholders focused on HIV in adolescents. The effort has also served as a foundational driver for development of the NICHD-funded PATC^{3}H initiative, described earlier. PATC^{3}H benefits from leveraging expertise and collaborations from AHISA investigators and has implemented eight successful ongoing research programs across sub-Saharan Africa and Brazil.

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 in 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.

Safety and Effectiveness of Triple ARV Drug Strategies for Prevention of Perinatal Transmission (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 perinatal HIV transmission 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; adverse pregnancy outcomes, 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 the

President's Emergency Plan for AIDS Relief (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 perinatal transmission and improvements to 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 to directly inform HIV prevention and care service-delivery programs for adolescents living with HIV and at-risk for HIV 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 to promote HIV testing.

HIV in Adolescents: Transitioning from Pediatric to the Adult Care Settings (RFA-HD-16-033). For individuals with HIV emerging as young adults, one of the most challenging obstacles to preventing poor health outcomes is the transition from pediatric to adult HIV care programs. Issued by MPIDB/NICHD in fiscal year 2016, this RFA funds four grants in multiple geographical locations (Kenya, Thailand, Malawi, South Africa, United States) that offer a range of approaches on transitioning youth living with HIV 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 is also a high-priority scientific research theme in the NICHD Strategic Plan.

Understanding and Addressing the Multilevel Influences on Uptake and Adherence to HIV Prevention Strategies among Adolescent Girls and Young Women (AGYW) in Sub-Saharan Africa (RFA-MH-17-550, RFA-MH-17-555, and RFA-MH-17-560). MPIDB/NICHD issued this RFA in 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 among AGYW in the region. 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, PrEP knowledge, and peer-networks. Investigators funded from this RFA have also participated in annual collaborative meetings with PATC^{3}H and AHISA.

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 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)

Selected Publications with International Collaborators

- Zash R, Holmes L, Diseko M, et al. (2019). Neural tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med. 381*: 827-40. PMID: 30037297 doi: 0.1056/NEJMc1807653.
- Paulson JN, Williams BL, Hehnly C, et al. (2020). Paenibacillus infection with frequent viral coinfection contributes to postinfectious hydrocephalus in Ugandan infants. *Sci Transl Med.12*(563):eaba0565. PMID: 32998967. doi: 10.1126/scitranslmed.aba0565.
- Stringer EM, Martinez E, Blette B, et al. (2021). Neurodevelopmental outcomes of children following in utero exposure to Zika in Nicaragua. *Clin Infect Dis Off Publ Infect Dis Soc Am*. *72*(5):e146-e153. PMID: 33515459. doi: 10.1093/cid/ciaa1833.
- Taiwo BO, Kuti KM, Kuhns LM, et al. (2021). Effect of text messaging plus peer navigation on viral suppression among youth with HIV in the iCARE Nigeria Pilot Study. *J Acquir Immune Defic Syndr 1999. 87*(4):1086-1092. PMID: 34153015. doi:10.1097/QAI.0000000000002694.
- Teasdale CA, Brittain K, Zerbe A, et al. (2021). Characteristics of adolescents aged 15-19 years living with vertically and horizontally acquired HIV in Nampula, Mozambique. *PloS One. 16*(4):e0250218. PMID: 33901229. doi:10.1371/journal.pone.0250218.
- Ssentongo P, Ssentongo AE, Ba DM, et al. (2021). Global, regional, and national epidemiology and prevalence of child stunting, wasting and underweight in low- and middle-income countries, 2006–2018. *Sci Rep*. *11*(1):5204. PMID: 33664313. doi:10.1038/s41598-021-84302-w.

Staff Membership on Global Health Committees/Working Groups

WHO Working group to develop PrEP implementation module for adolescents. Member: Dr. Bill Kapogiannis

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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, that include 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 its BPCA initiative activities, the OPPTB sponsors clinical trials of drugs and other therapeutic approaches (including devices) in 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. Additional clinical studies are underway in Botswana and South Africa. 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 U.S. Food and Drug Administration (FDA) 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 effort, including Canada, England, Japan, and France, among others. Plans for harmonization 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 to examine adverse pregnancy outcomes possibly associated with such exposure, including specific birth defects, preterm birth, small for gestational age, and stillbirth. This study includes the entire pregnant population of Ontario, Canada, with information linked to electronic health records.

A Clinical Trial of Praziquantel in Children with Schistosomiasis. This phase II PK/pharmacodynamic dose finding trial is investigating 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 be used to develop 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.

Surveillance and Treatment tO Prevent Fetal Atrioventricular Block Likely to Occur Quickly (STOP BLOQ). Anti-SSA/Ro-associated fetal complete (i.e., 3°) atrioventricular block (AVB), identified in the 2nd trimester in an otherwise normally developing heart, is fatal in one-fifth of cases, and those who survive require lifelong pacing. Nonetheless, reversal of incomplete block is possible but challenging to identify given only once weekly echocardiographic surveillance. This study comprises three steps: 1) screening anti-Ro-positive mothers for high-titer antibodies thought to confer greater risk of fetal AVB; 2) teaching mothers with high-titer anti-Ro to monitor fetal heart rates and rhythms at home and arrange immediate feedback on perceived abnormalities; and 3) treating fetuses whose mothers detect abnormal monitoring confirmed to be incomplete AVB by echocardiogram. The study aims to find out whether the level of anti-Ro/SSA can predict fetuses at greatest risk, if mothers can themselves identify reversible fetal cardiac injury by home monitoring, whether expeditious treatment of fetal incomplete AVB can restore normal rhythm, and if weekly echocardiographic testing is necessary to surveil for AVB. The STOP-BLOQ study is led by investigators at New York University and University of Colorado in collaboration with a consortium of centers across the United States along with the University of Alberta in Edmonton, Canada.

A Systems Pharmacology Approach to Predict the Effects of Pregnancy and Infectious Diseases on Transporter-mediated Drug Disposition. Both pregnancy and inflammation can alter drug PK processes, such as absorption, distribution, metabolism, and excretion. However, most published studies have focused on cytochrome P450-mediated drug disposition, leaving a knowledge gap on transporter-mediated drug disposition in pregnant women. The project addresses this significant knowledge gap using a physiologically based PK-modeling approach to predict the effect of pregnancy and cytokines on drug transporters. Researchers will build on the results to design safe and efficacious dosing regimens of drugs for pregnant women with HIV or other infectious diseases. This research is led by PIs at the University of Washington in collaboration with investigators at the University of Sao Paulo in Brazil and is co-funded by OPPTB and the NIH-São Paulo Research Foundation initiative (NOT-TW-16-001) via FIC.

Recent Achievements in International Health

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

- International Neonatal Consortia, Steering Committee. Member: Dr. Antonello Pileggi

- WHO and IMPAACT Network Workgroup on Study Design of New HIV-associated Drugs in Pregnant Women. Member: Dr. Zhaoxia Ren

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 nutritional promotion of 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, helps identify gaps and opportunities for scientific advancement, and supports research to understand 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—emphasizing the needs of reproductive-age women (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, such as 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 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 the aim of 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

Major Initiatives to Date

Since 2001, PGNB has served as a member of the WHO Technical Advisory Group and co-chair of the PEPFAR Technical Working Group on Food and Nutrition to develop the first (and only) set of guidelines for nutritional care of infants and children younger than 14 years with HIV. Building on that momentum and global input resulted in nutrition being included in the Office of AIDS Research planning process and culminated in the following efforts.

Iron and Malaria Project

- Initiated in 2007 and co-funded by a $9.3 million grant from the BMGF, the Iron and Malaria Project resulted in more than 90 peer-reviewed publications and several spin-off projects that continue today. These off-shoot projects include, most prominently, the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) Project, which has provided guidance to USAID, WHO, and the global community on factors influencing the impact of inflammation on the assessment of anemia and nutritional iron deficiency.
- In 2020, PGNB program staff were asked by USAID to chair the USAID Advancing Nutrition Anemia Task Force, which is developing resources to further our understanding of the ecology of anemia.

Nutritional Assessment: The Biomarkers of Nutrition for Development (BOND) Project

The BOND project, initiated in 2010, was a collaboration between PGNB, BMGF, and other agencies/organizations involved in global nutrition, particularly those focused on the development and deployment of nutritional assessment methodologies. BOND was designed to support basic/clinical research, clinicians, surveillance, program monitoring and assessment, and policy makers.

Nutrition and the "1000 Days"

- In 2012, the B-24 effort was initiated to support the Dietary Guidelines for Americans (DGA), which, until that time, excluded pregnant women and infants up to 2 years of age. B-24 was also designed to augment global efforts to develop evidence-based programs and policies targeting the "1000 Days" (i.e., pregnancy through age 2 years).
- Results of the systematic reviews conducted as part of the DGA in pregnancy/B-24 process highlighted a priority need related to the lack of understanding of facts affecting human milk composition. In 2021, the Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN) Project was initiated to address that priority need.

Intersection of Climate, Food Systems, Health, and Nutrition

- PGNB program staff initiated a series of symposia in partnership with the Agricultural Research Service (ARS) within the U.S. Department of Agriculture (USDA) to focus on various aspects of the intersection of climate/environmental change, food systems, health, and nutrition. This collaboration includes a recent effort involving the American

Society for Nutrition (ASN) and the Keystone Policy Center on Protein in a Changing Environment.

- Program staff also initiated and serves as co-chair with USDA/ARS of a new Research Interest Section at ASN focused on the intersection of climate, health, agriculture, and improving nutrition, which now has over 800 members representing the breadth of the domestic and international research community.

Global Nutrition Coordination Plans (GNCPs)

PGNB program staff have contributed to the development of GNCP 1.0 (2016 to 2021) and GNCP 2.0 (2021 to 2026). Although the GNCP is a voluntary effort without specific funding to support its activities, it aims to enhance the impact of and synergies among the programs funded and implemented by the U.S. government. It is, therefore, an initiative supported by U.S. government professionals committed to contributing to, strengthening, and harmonizing efforts to end malnutrition globally.

- The inception of GNCP 1.0 reflected recognition of the central importance of nutrition to saving lives and improving the prospects of future generations of children around the world, and of the potential to enhance U.S. government contributions to global efforts in pursuit of these ends. Its purpose was to strengthen the impact of the many diverse investments in global nutrition across the U.S. government through better communication, and to improve collaboration among government nutrition experts by linking research to program implementation.
- Drafting GNCP 2.0 began with a stocktaking exercise that involved interviews with 22 individuals from across the U.S. government who had participated in the drafting and/or implementation of GNCP 1.0 to learn what had worked well, identify key accomplishments and contributions, and characterize the changes recommended to strengthen both operations and outcomes. The vision, purpose, and priorities of GNCP 2.0 reflect the urgency of challenges to global nutrition as the COVID-19 pandemic threatens to reverse the gains made over the past decade. The coming years will provide multiple opportunities for the global community to convene and mobilize resources to support a full recovery of health, nutrition, and food systems in the countries hardest hit by the pandemic. The survival and well-being of countless children, mothers, and their families are at stake and, through them, promises of sustainable development and political stability are possible. Contributors to GNCP 2.0 hope that the coordinated efforts of the U.S. government will contribute to a response to meet the moment.

COVID-19

- PGNB initiated the COVID 19 Infant Feeding Research Interest Group (CIF-RIG) to address concerns and confusion resulting from the advent of the COVID-19 pandemic on safe and efficacious infant feeding practices.
- CIF-RIG leadership was asked to serve on the WHO COVID-19 Maternal, Newborn, Child, and Adolescent Research Network.

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

Previous Major International Initiatives

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 could delay or prevent the onset of T1DM in children with high genetic risk for the disease. The intervention consisted of being weaned from human milk to either standard cow milk-based infant formula, or a highly hydrolyzed casein-based formula. The rationale for TRIGR was that the intestines of infants prone to T1DM were more permeable to foreign proteins than the intestines of infants not susceptible to T1DM. By supplying amino acids instead of proteins, the exposure to foreign antigens was 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 enrolled reached their 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 years. 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 maternal glycemic state and 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 enrolled more than 25,000 pregnant women and administered oral glucose tolerance tests to them during their second trimesters. Other outcomes of interest were macrosomia of the infants, hyperinsulinemia in the cord blood of the infants, preeclampsia in the mothers, and infant hypoglycemia. An important finding of HAPO was that the rate of preeclampsia quintupled, from 3 percent to 15 percent, over the range of fasting plasma glucose noted earlier. The rates of operative delivery doubled from 13 percent to 26 percent over the same range of glycemia, despite the blinding. NICHD and NIDDK are collaborating on a follow-up study of the offspring of women in HAPO 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 years to 21 years of age and are being examined again at ages 12 years to 27 years. 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 efforts 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 on 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 also for 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. These agencies include the USDA, CDC, FDA, USAID, U.S. Department of Defense, WHO, UNICEF, World Food Programme, 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 during 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 (MODS) 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 among 1,000 8- to 16-year-old Syrian refugee children (and their primary caregivers) in Lebanon. By 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. A better understanding of how social, psychological, and biological factors contribute to the mental health of refugee children is important to better protecting war-affected children from the negative effects of political conflict and displacement and promoting 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, especially among school-age children. Each year in the United States, over 4,900 pedestrians are killed and another 207,000 are injured; 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, they regularly cross streets without supervision, and they struggle both with selecting where to cross and determining how to cross. Prior research has shown that they benefit from effective behavioral training in pedestrian behavior. The research, which addresses deficits in crossing skills, 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 activities 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 trauma experienced directly, such as beatings and the loss of a family member,

but also indirectly, such as 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. To appropriately focus interventions to mitigate harm to youth, policymakers need information on effects of both trauma and indirect exposure to conflict. 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. It uses 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 questions 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.

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 neither address the mental health problems of institutionalized children, nor 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.

Intergenerational Impact of Maternal Trauma History on Preschoolers’ Behavior and Health Outcomes: Assessing Links with Caregiving Sensitivity and DNA Methylation (1R01HD098153-01A1). This study builds 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. This study, conducted exclusively at the Peruvian research site, seeks to better understand maternal trauma history as a driver of behavioral health problems in 3-year-old children. Using a life-course theory approach within an intergenerational context, the researchers will test three models to determine whether the effect of maternal trauma: 1) Sensitive Period model, which depends on the timing of exposure; 2) Recency model, which posits the trauma is strongest when it is most proximal to the child outcome examined; or 3) Accumulation model, which suggests that trauma increases with the number of exposures. A primary study aim is to investigate how experience gets “under the skin” by examining associations between maternal trauma history and children’s salivary DNA methylation profiles. The team will also 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.

Biological and Environmental Factors Affecting Risk and Resilience Among Syrian Refugee Children (5R01HD099178-02). In recent years, evidence has been accumulating for the serious detrimental impact of childhood trauma exposure on child and adult physical and mental health. This evidence is mostly based on retrospective studies of traumatized adults. Prospective longitudinal studies in children are necessary to determine the impacts of trauma on neurobiological development. Because effects of trauma are not static and may oscillate based on environmental factors affecting neurobiology of traumatic stress, examining the longitudinal

course of trauma-related symptoms in children will help identify biological and environmental factors contributing to vulnerability and resilience. Toward that end, the investigators will leverage an existing cohort of Syrian and Iraqi refugee children ages 7 to 17 years and their parents who settled in the United States starting in 2016. Researchers will explore longitudinal changes in anxiety, depression, and posttraumatic stress disorder symptoms of post war-zone trauma in Syria, as well as resettlement, and the epigenetic, autonomic, and environmental correlates.

Pediatric Severe Traumatic Brain Injury (sTBI) in Latin America – A Randomized Trial Comparing Two Management Protocols (5R01HD106273-02). Children who survive sTBI live with profound impairments that alter their development and future possibilities. Worldwide, TBI is the leading cause of death and disability among children and adolescents. The primary focus of this scientific investigation is to conduct a high-quality randomized controlled trial addressing a critical TBI management issue: whether a protocol with information from intracranial pressure monitoring to direct treatment of children with sTBI improves outcomes versus an aggressive management protocol based on imaging and clinical examination alone. Study findings will inform U.S. and global clinical practice. This trial will be conducted in seven Latin American pediatric intensive care units where infrastructures and practice patterns are optimal for strong internal validity and resources represent trauma care in low-resource countries.

Training Leaders to Prevent and Reduce Domestic Violence in Their Communities: Experimental Evidence from Peru (1R01HD101581-01A1). Gender-based violence (GBV) affects one in three women in the world and has long-term welfare consequences for survivors and families and indirect costs to the health sector, the legal system, and the economy. Yet there has been little rigorous research on the efficacy of interventions that aim to reduce or prevent GBV. This project takes advantage of a long-standing partnership with the Peruvian Ministry of Women (MOW) to conduct an experimental evaluation randomized across 250 villages of Leaders in Action, the MOW's flagship GBV program, which trains local leaders on GBV and norms. The work experimentally assesses the impact of two main components: a household-based module, consisting of household visits by trained leaders; and a group-based module, with education sessions in small gender-segregated groups organized by trained facilitators. This study offers a unique opportunity to evaluate government programs to guide GBV programming, estimate cost effectiveness, and bring scientific evidence on GBV reduction and prevention to policy in Peru and worldwide.

iRise: Willingness of LMIC-based Health Workers to Respond to Public Health Emergencies and Disasters, an mHealth Intervention Study (5R21TW012210-02). Healthcare workers' willingness to report to work in pandemics and other public health emergencies and disasters is a foundational prerequisite for national, regional, and global health security amidst an ever-broadening array of natural and manmade emergent threats. Well-documented case reports and research point to significant and concerning gaps in response willingness toward public health emergencies and disasters, including among LMIC-based healthcare workers. Further, research to date in LMICs and other settings has highlighted healthcare workers' self-efficacy as a leading predictor of their willingness to respond during such crises. Higher levels of self-efficacy positively influenced motivation, willingness to respond and take action, and perseverance when challenges were encountered, including exhibiting teamwork, expressing sensitivity, managing politics, and handling pressure. This study aims to assess the feasibility of strengthening self-efficacy and response willingness toward public health emergencies, including pandemics, and disasters in emergency department clinical personnel in LMIC settings. Then, if feasible, the researchers will carry out a trial to confirm the effectiveness of the approach on outcomes in Karachi, Pakistan.

Development of an mHealth Personalized Physiologic Analytics Tool for Pediatric Patients with Sepsis (5R21TW012211-02). Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, encompasses a continuum that ranges from sepsis to severe sepsis, septic shock, MODS, and eventually death, if untreated. Sepsis is the leading cause of child mortality worldwide, with most of these deaths occurring in LMICs, yet few clinical tools have been developed for identifying, monitoring, or managing septic children in these settings. MHealth tools, wearable devices, and AI techniques have rapidly proliferated for a multitude of medical applications and could serve to bridge the gap in care of critically ill patients in LMIC settings. Furthermore, remote monitoring capabilities may also prove highly valuable in improving patient care and protecting the safety of healthcare workers during times of infectious disease outbreaks, such as COVID-19. This research—conducted in septic children admitted to the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh—will develop a context-appropriate mHealth tool linking continuous physiologic data obtained from a wearable device with a novel machine-learning approach, known as personalized physiologic analytics, run on a standard smartphone to provide clinicians with accurate assessments of sepsis severity and mortality risk.

Recent Achievements in International Health

N/A

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

- President's Task Force for Environmental Health and Safety Risks, Subcommittee on Climate, Emergencies, and Disasters. Co-Chair: Dr. Cinnamon Dixon
- Intra-NIH Disaster Interest Group. Co-Chair: Dr. Cinnamon Dixon
- National Academies of Science, Engineering, and Medicine Action Collaborative on Disaster Research. Co-Chair: Dr. Cinnamon Dixon
- HHS Assistant Secretary for Preparedness and Response Pediatric Surge Working Group. Co-Chair: Dr. Cinnamon Dixon

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.

In fiscal year 2021, PDB funded 48 grants involving international activities, 14 of which were new awards. Research involved more than 61 countries, most often India (11), Kenya (8); Nepal (7), South Africa (6), Uganda (6), Malawi (5), Bangladesh (4), and the United Kingdom (4).

Data Archiving

The branch uses the standard R01 Research Project Grant mechanism to support documenting, archiving, and disseminating 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 multi-country 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.

- **Integrated Global Health on Child Health and Development (R01 HD099182):** More than 90 LMICS in the Global South and Eastern Europe, including several countries in sub-Saharan Africa, Mozambique, Gambia, Ghana, Sudan, and Cuba
- **Integrated Public Use Microdata Series Demographic and Health Surveys (R01 HD069471):** Saharan African countries, Egypt, India, North Africa, the Middle East, and South Asia
- **Time Use Data for Health and Well Being (R01 HD053654):** North America: United States, Canada, Mexico; Northern, Western, and Southern Europe: Austria, Belgium, Finland, France, Germany, Italy, Netherlands, Spain, Basque Region of Spain, and the United Kingdom; Eastern Europe: Bulgaria, Czech Republic, Hungary, Poland, Serbia, and Slovenia; Asia: Pakistan, South Korea; Africa: South Africa; Middle East: Israel; and South America: Brazil
- **Integrated International Microdata for Population Dynamics and Health Research (R01 HD047283):** Bangladesh, China, Indonesia, Korea, Philippines, Thailand, Vietnam,

and other countries in Asia; France, Italy, Poland, Russia, Spain, Ukraine, United Kingdom, and other countries in Europe

Archiving and Documenting Child Health and Human Development Datasets

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

- **Archiving and Documenting Four Rounds of the Mekong Integrated Population-Registration Areas of Cambodia Project (R03 HD103861):** Cambodia (2008-2014)
- **Public Use Datasets for Reproductive Health Research (R03 HD100680):** Africa, South of the Sahara

Developing and Disseminating Methodology to Improve Global Population Research

PDB is at the forefront of supporting research on methodologies to project populations globally and to estimate mortality rates, disease prevalence, and demographic change in low-income countries and LMICs that lack adequate vital registration systems and health information systems.

- **Interdisciplinary Research Training Program for International Population Science (R25 HD101358):** Nepal
- **Projecting the Future of Early Life Mortality in the Developing World (K01 HD098313):** India
- **Workshop on Migration Data and Analysis (R25 HD094676):** United States, Europe, Africa
- **Global Age Patterns of Under-5 Mortality (R01 HD090082):** North America: United States, Costa Rica, Mexico; South America: Brazil, Colombia; Europe: Belgium, Denmark, England and Wales, Finland, France, Germany, Netherlands, Norway, Portugal, Sweden; East Asia: China, Japan; South Asia Bangladesh, India, Nepal, Sri Lanka; Southeast Asia: Philippines, Thailand; East Africa: Ethiopia, Kenya, Madagascar, Tanzania, Uganda; Southeast Africa: Malawi, Zimbabwe; Southern Africa: South Africa; West Africa: Burkina Faso, Côte d'Ivoire, Gambia, Guinea-Bissau, Senegal
- **Verbal Autopsy: Reimagining Data & Automated Cause Assignment (using ALPHA Network data) (R01 HD086227):** Kenya, Malawi, South Africa, Tanzania, Uganda, Zimbabwe

International Population Dynamics Research

PDB supports a robust research portfolio on international population dynamics 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. Most research projects supported by the PDB are investigator-initiated.

Child and Adolescent Health and Development, including Effects of Early Interventions on Outcomes in Later Life

- **Evaluation of Social Policies to Reduce Intimate Partner Violence and Improve Child Health in LMICs (K99 HD104896):** 24 LMICs, including India, South Africa
- **Synthesizing, Interpreting, and Extrapolating Interventions to Foster Human Development (R01 HD103666):** United States, Jamaica
- **A New Population-Scale Approach for the Study of Psychological Stress in the Transition to Adulthood (R21 HD104993):** Nepal
- **Long-Term Effects of an Intervention on Maternal Behavior, Child Health, and Community Influence (R01 HD102412):** Nigeria
- **Effects in Middle Childhood of Early Exposure to Water and Sanitation Interventions (R03 HD102468):** Bangladesh
- **Family Context, Socialization, and Children's Socio-Emotional Development (R01 HD101527):** Nepal
- **Social Networks and Child Malnutrition in a Resource-Limited Setting (R21 HD101268):** India
- **Kinship, Nuptiality, and Child Health Outcomes in a Low-Income Urban Area (R01 HD101613):** Kenya
- **Pathways and Mediators of Change in Early Childhood Development (R21 HD099488):** Kenya
- **Impact of Relationship Factors on Physical and Psychological Health and Wellbeing (R03 HD098706):** Nepal
- **Migration, Family Context, and Child Health (R03 HD098705):** Nepal
- **Effects of Age at Marriage and Education on Health of Mothers and Children (R01 HD095189):** Bangladesh
- **Intergenerational Impacts of Health Investments (R01 HD090118):** Kenya
- **India Human Development Survey (R01 HD041455):** India

Pregnancy and Pregnancy Outcomes

- **Improving Perinatal Outcomes Using Conditional and Targeted Transfers (R01 HD090231):** Nigeria, Malawi, India
- **Pregnancy Context and Health Outcomes (R01 HD095181):** Nepal
- **Biocultural Investigation of Maternal Adversity on Gene Expression and DNA Methylation in the Placenta (F30 HD097935):** Democratic Republic of the Congo
- **Family Dynamics, Maternal Stress, and the Biomarkers of Healthy Pregnancy (K01 HD103999):** India

Family Planning

- **Randomized Controlled Trial to Address Unintended Pregnancy Rates in Low Resource Settings (R01 HD101453):** Kenya

- **Reproductive Coercion and Related Risk Factors (F31 HD100019):** Niger
- **Development, Testing, and Health Effects of a Multilevel Family Planning Intervention (R21 HD098523):** Uganda
- **Enhancing Male Participation in Interventions to Prevent Unintended Pregnancy (R01 HD084453):** India

HIV/AIDS

- **Mobile WACh Empower: Mobile Solutions to Empower Reproductive Life Planning for Women Living with HIV (R01 HD104551):** Kenya
- **A Savings Intervention to Reduce Men's Engagement in HIV Risk Behaviors (R01 HD103563):** Kenya
- **The Effect of Migration on Sexual Risk Behaviors and HIV Incidence Among Non-Migrating Household Members: A Population-Based Study (F31 HD102287):** Uganda
- **Improving the Reproductive Health of Families (R01 HD094512):** Botswana
- **Structural and Social Transitions Among Adolescents in Rakai (R01 HD091003):** Uganda
- **Adverse Childhood Experiences and Adolescent HIV Risk: Causal Inferences from a High HIV Prevalence Context (R01 HD090988):** Malawi
- **Causal Pathways to Population Health Impact of HIV ART (R01 HD084233):** South Africa
- **HIV Risk and Access to Health Care Among Mobile Populations (R01 HD046886):** Mexico

Other Reproductive Health

- **Reproductive Outcomes and Schooling Expansion for Men in Ethiopia, Malawi, and Uganda (R03 HD103866):** Ethiopia, Malawi, Uganda
- **Policy Change and Women's Health (R01 HD095951):** United Kingdom, Canada

Natural Disasters, Population & Environment, and Spatial Demography

- **Longitudinal Study of Health Outcomes and Mitigating Factors in the Aftermath of the COVID Pandemic (R01 HD107420):** India
- **Health Decision-Making in the Aftermath of Disaster (R01 HD102382):** Mozambique
- **Environmental Change and Undernutrition among Women and Children (R03 HD101859):** 50 countries across Africa, Asia, and Latin America
- **Training for Health Professionals (R01 HD092655):** Tanzania
- **Migration, Urbanization, and Health in a Transition Setting (R01 HD083374):** South Africa
- **Longer Term Effects of a Natural Disaster on Health and Socio-Economic Status (R01 HD052762):** India, Indonesia

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

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Pregnancy and Perinatology Branch (PPB)

Scientific Scope

PPB aims to improve the health of women before, during, and after pregnancy; increase infant survival; and ensure the long-term health of mothers and their children. Specifically, the branch supports research to understand fetal development and improve ways to diagnose, treat, and prevent diseases in pregnant women and newborns.

As the focal point for NICHD extramural research and training in maternal-fetal medicine, neonatology, and related fields, branch staff also engage with and support investigators to identify knowledge gaps and opportunities for scientific advancement.

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 maternal and infant health outcomes of interest, 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 for local scientists to develop protocols, abstracts, manuscripts, and presentations and augmented local capabilities in information technology and data collection and management. 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 NICHD Global Network. As of 2021, NICHD has funded eight U.S. sites, each with an international partner institution, to conduct human subject research. A Data Coordinating Center has also been funded. More information is available at: https://globalnetwork.azurewebsites.net/. Current studies in the Global Network include the following.

Maternal Newborn Health Registry. This registry is a prospective, population-based study of pregnancies and outcomes at eight sites in seven LMICs, including the Democratic Republic of the Congo, Bangladesh, Guatemala, India, Kenya, Pakistan, and Zambia. With the addition of a new site in Bangladesh, it is anticipated that all pregnant women at participating sites are being registered and their outcomes tracked for 6 weeks post-delivery. The primary purpose of this observational study of approximately 60,000 women per year is to quantify and understand trends in pregnancy services and outcomes over time in defined, low-resource geographic clusters. The study goal is to provide population-based statistics on stillbirths and neonatal and maternal mortality that can help inform healthcare policy. Data from the registry also provide the mortality and morbidity outcomes for NICHD 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 NICHD Global Network launched an international study to track the prevalence and impact of COVID-19 infection during and after pregnancy. The year-long study will include about 2,000 pregnant

women in seven LMICs. The study will compare maternal, fetal, and neonatal outcomes among pregnant women infected with the virus to outcomes of non-infected pregnant women. Participants will receive antibody tests at delivery to track COVID-19 exposure. A subset of approximately 800 women will be tested during the antenatal period to determine trends of exposure over time. 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, conducted through the Global Network's Maternal Newborn Health Registry research partnership, includes participation from 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 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 NICHD Global Network's A-PLUS trial will enroll 34,000 pregnant women at eight research sites in Latin America, South Asia, and sub-Saharan Africa. 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; and 2) a single, oral dose of 2 g azithromycin given to women in labor will reduce neonatal death or sepsis. With the pilot study complete, researchers are actively recruiting participants to the main trial; enrollment should be completed by the third quarter of 2023.

Studies in Other Networks and Researcher-Initiated Activities

PregSource®: Crowdsourcing to Understand Pregnancy. Using a crowdsourcing approach with participants from around the globe, PregSource invites pregnant women to enter information directly about their pregnancies, throughout gestation, and about the health of their babies, throughout early infancy, via a confidential, secure website. The questionnaires capture data on nausea, mood, weight gain, labor, delivery, feeding, and early infancy. Once PregSource closes to new participants, the de-identified data will be made available to researchers through NICHD DASH. Although recruitment efforts focus on women in the United States, enrollment is open to women around the world. Learn more at: https://pregsource.nih.gov/.

Prenatal Alcohol in Sudden Infant Death Syndrome (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 SIDS and adverse pregnancy outcomes, such as stillbirth and fetal alcohol syndrome (FAS), and how they may be interrelated. Within the PASS Network, as part of the Safe Passage Study, enrollment was completed for 11,899 pregnant women from the U.S. Northern Plains (including American Indian Tribal communities) and the South African Cape Colored communities (from the Western Cape). This prospective longitudinal study is providing important information on the regulation of fetal and infant brain development, shedding light on the etiology and pathogenesis of stillbirth, SIDS, and FAS, and producing improved strategies to prevent or reduce risk for these disorders.

University of North Carolina Global Women's Health Fellowship. NICHD funds a T32 Institutional Research Training Award program to provide training in global women's health research with experienced research mentors from Malawi, Zambia, and the University of North Carolina, Chapel Hill. This program provides 2 years of dedicated research time abroad, during which obstetrician/gynecologist 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.

A Cohort Study of Preterm Delivery in Relation to Partner Abuse, Mood, and Anxiety (Peru). Previous studies have yet to rigorously evaluate the independent and joint effects of potent, highly relevant social and neuropsychological risk factors of preterm delivery among high-risk populations. To address these gaps, investigators are developing a prospective cohort of 6,000 Peruvian women to study the relationship between maternal history of childhood sexual abuse, prenatal and lifetime interpersonal violence, and 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 between preterm delivery risk and mood and anxiety disorders 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. Because previous research suggests a significant genetic component in the pathogenesis of AP, PPB-funded investigators are conducting a large multicenter epidemiologic study of AP in Lima, Peru. Using a self-matched case-crossover design, researchers will evaluate the acute effects of potential "triggers" of AP: 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. They will also study genetic variants that influence the pathogenesis of AP in 900 well-characterized mother-infant abruption case pairs and in 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 most early onset neonatal sepsis cases 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 UTIs 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. This work will also 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 women of reproductive age and children, who are more likely to be exposed to this pollution for longer periods of time. However, precise

mechanisms of adverse outcomes are unclear, and socioeconomic factors remain confounders, lending to the potential exposures. There has been an intensive effort to mitigate the negative effects of indoor air pollution, especially from burning fossil fuel for cooking purposes, a common practice 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. The approximately 10,000 women in the study will be prospectively evaluated to assess the speed of growth of their fetuses, while air pollution data in the region will be longitudinally assessed. Additional studies will be carried out in a subset of the participants 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 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 the PEARL study is an R01 to a researcher in Puerto Rico, with a subcontract to a consultant from University of Lund, Sweden. 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. 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. 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.

Cookstove-Related Achievements

- NICHD is partnering with NHLBI, NCI, NIEHS, the NIH Common Fund, and 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 for their 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 at six sites in the NICHD Global Network (described earlier), 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 Global Network sites—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.

Human Placenta Project (HPP)

HPP is aimed at developing tools and technologies to enable safe, non-invasive, real-time assessment of placental development and function across pregnancy. Multiple initiatives have been funded since the project's launch in 2014. Translation of technologies globally, especially in low-resource settings, remains 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 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 preventing adverse pregnancy outcomes. As initial steps in accomplishing this long-term goal, this study sought to determine which novel ultrasound tool was best at discriminating between pregnancies that would develop adverse outcomes and those that would not. To date, 620 pregnant women have been enrolled and received scans at 8 points across pregnancy, from 12 weeks to 37 weeks, plus deep phenotyping. Development of nomograms for the novel ultrasound tools is underway, as well as 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 (IUGR), 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 for use in routine clinical diagnosis. This study applies cutting-edge high-throughput lipidomic technologies to measure the lipidome in exosomes of placental origin in the circulation of pregnant mothers. To date, this work has shown that some lipid classes change markedly across gestation. Preeclamptic pregnancy profiles are revealing differences from control pregnancy profiles, and researchers are exploring these data 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: 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, that miRnome and DNA methylome correlate with placental function and health, and that these can be assessed non-invasively across gestation. Using miRNA sequencing, RNA sequencing, and DNA methylation arrays, researchers are creating molecular profiles in paired maternal blood and placental samples at multiple time points across gestation. To date, the investigators have obtained and are analyzing full miRnome datasets from 96 plasma and placenta samples from first and second trimester pregnancies.

- **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 adapts 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, researchers have optimized several aspects of the data pipeline and have completed validation of the ancestry verification approach.
- **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. As a result, researchers have a very limited understanding of how obesity and Western diet consumption affect placental metabolism, and a critical need remains 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, investigators have optimized several technical aspects of the approach in a 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 normally 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, the researchers have addressed several technical aspects of the MRI approaches, including management of motion artifacts. Ongoing fetal ECG studies will evaluate the utility of this approach for detecting pregnancy problems.
- **HD087177-01: Environmental Factors in Placental Pathology: A New Diagnostic Method Based on Umbilical Vessel Wave Mechanics.** Abnormal pulsatile flow in the umbilical cord arteries is an indicator that the downstream vessels are improperly formed. However, using this approach to detect placental abnormalities is not always accurate, particularly when abnormalities arise late in gestation. This study is developing a new method for obtaining more accurate diagnostic information from ultrasound data

based on the timing of pressure and blood-flow changes within the umbilical cord blood vessels. Researchers have validated the technology using experimental mice that mimic common and severe pregnancy complications, and they have begun to translate the non-invasive method to evaluate human pregnancies. They are developing criteria for detecting abnormal placental blood flow for comparison with established ultrasound criteria, as well as with standardized pathology assessment at birth. The widespread use and availability of ultrasound provides a clear path for clinical translation of the developed technology.

- **HD087209-01: Ultrasound Provides a Valuable Means for Evaluation of Placental Function but is Hindered by Variability Across Providers.** This study aims to develop automated measures using 3D-power Doppler ultrasound technologies that provide real-time, quantitative assessment of placental structural and vascular development. The same group or researchers previously achieved novel semi-automated methods for calculating placental volume, and new methods for measuring gross placental morphology (i.e., dimensions, surface area, etc.) and assessing the vasculature at the uteroplacental interface, including Fractional Moving Blood Volume. They have now developed the capability to fully automate the novel tools developed for measurement of placental volume into a real-time analytical package.
- **HD086323: Integrated Placental Imaging: Novel Methods for Probing Function and Metabolism.** Placental dysfunction is associated with a variety of pregnancy disorders. Using animal models of pregnancy complications, these studies will develop and validate robust, non-invasive imaging technologies for placental function assessment that will readily translate to human studies. The approach will apply state-of-the-art, non-invasive imaging modalities to compare and contrast transport functions, metabolism, and oxygen concentrations during placental development of control C57BL/6 pregnant mice with three mouse models of pregnancy pathology, which simulate hypoxia, IUGR, or preeclampsia. The preclinical studies for the direct measurement of placental oxygenation in the mouse models will inform proof-of-principle studies to determine oxygen transport and hemoglobin saturation in the human placenta in situ in control, uncomplicated pregnancies, and pregnancies with IUGR, between 32 and 37 weeks of gestation. In addition, phage display in preclinical mouse placental models, with validation in ex vivo human, term placentas from normal, IUGR, and preeclampsia pregnancies, will be used to identify novel peptide imaging targets that may serve as markers of pregnancy disorders, or that may offer a means for targeted drug delivery to the fetoplacental unit.

Recent Achievements in International Health

Neonatal Hypoglycemia and Long-Term Outcomes (R01HD091075-03). Hypoglycemia, or low blood sugar, occurs very commonly in newborn infants and, if severe, 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 level of hypoglycemia that causes brain injury. Researchers from Liggin’s Institute and University of Auckland, New Zealand, used a unique monitoring system (not available in the United States) to measure infants’ blood sugar each second, continuously, for as long as clinically needed. Using this monitoring device, researchers followed the course of glucose changes in the blood of 500 newborn infants. NICHD funded follow-up evaluations of these infants at ages 4 years to 5 years. Several papers from this work are providing 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, finding 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 at this age. Severe, recurrent, and clinically undetected episodes increased these risks. Work from this group continues to inform clinical decision-making by healthcare professionals globally.

Reducing Neonatal Infections and Infection-Related Infant Mortality (K23HD100594-01). Infections during the neonatal period are the major causes of infant mortality in LMICs around 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 versus 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 on these findings was published in *Nature Medicine* (PMID: 28813414).

Individual Patient Meta-Analysis of Oxygen Therapy in Preterm Infants. University of Alabama, Birmingham, with Subcontract to International Sites in 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 (Benefits of Oxygen Saturation Targeting [BOOST] II Australia, BOOST II New Zealand, BOOST II United Kingdom, and the Canadian Oxygen Trial) used the same intervention as SUPPORT as part of a planned prospective analysis. The groups 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 on 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 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. This study sought to determine the effect of parasitic infections in pregnant women in Kenya on 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. After testing mothers for malaria, filariasis, and schistosomiasis, researchers found that 64 percent 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 (defined as a rise in immune globulin levels in the blood) at 12, 18, and 24 months, compared to the offspring of women without malaria. Offspring of schistosomiasis-infected women also had lower levels of protective immune globulins compared to offspring of women without schistosomiasis. Similarly, diphtheria and Hib immune globulin levels declined at higher rates in children of malaria-infected mothers than in children of mothers without malaria. But the research also showed that, if mothers were treated for malaria and other parasitic infections, the immune responses in their respective offspring were restored. The findings indicate that healthcare providers need to aggressively test for and treat malaria, schistosomiasis, and other parasitic infections in women during

pregnancy because such treatment not only helps the mother, but also strengthens the immune responses of their offspring, preventing the latter from getting routine childhood illnesses.

Studies Utilizing International Collaboration

Hernia in Prematurity Study. This study, based at Vanderbilt Medical Center, with international sites in Canada and the Netherlands, is testing the most appropriate time to repair inguinal hernia in preterm infants. Infants randomized to one arm 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; a subset will also undergo an assessment of neurodevelopmental outcomes at age 2 years.

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. In addition to six U.S. sites, the University of Alberta, Canada, University College Cork, Ireland, and University of Ulm, Germany, are participating in this study. DCC, waiting to clamp the umbilical cord for 30 to 60 seconds after birth, provides the newborn with a significant autologous transfusion of blood from the placenta and is known to reduce IVH. DCC also reduces overall IVH (mainly lower grades 1 and 2) by 50 percent but has not reduced the incidence of severe IVH or death. This study will examine whether UCM is at least as good as or better than DCC in reducing bleeding in the brain or preventing death in preterm newborns. The investigators will study short- and long-term outcomes of infants delivered before 32 weeks of gestation who receive either UCM or DCC.

UCM 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. Among infants who need resuscitation, the currently recommended practice is to immediately clamp the umbilical cord—UCM and DCC are not recommended in these cases because of a lack of evidence. However, 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. In addition, several large studies from around the world found that infants needing resuscitation were more likely to develop conditions such as cerebral palsy, autism, and other developmental problems. MINVI will test whether infants in this situation benefit from UCM. The cord will be quickly milked four times before cutting, but this activity will not delay the resuscitation procedures. 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, the study has sites in 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 in Ghana (R01HD096277-01). The goal of this project is to improve health literacy and reduce preventable maternal and newborn morbidities and mortality in Ghana, with a focus on preparing for birth, identifying pregnancy 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 ages. Women will meet with the same group and the same provider over the course of their pregnancies for a 60-minute facilitated discussion in addition to their individual assessments. The team will recruit 845 women older than 15 years of age, at less than 24 weeks of gestation, during their first antenatal care visit at 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, 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 to reduce disparities in PCMHC by focusing on the role of healthcare provider stress and unconscious bias. In the K99 phase of this project, researchers will: 1) conduct secondary data analysis on existing data from about 1,000 women, 50 providers, and facility-levels 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 specific 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 effects of the intervention. The study will recruit 80 providers for the pilot and its evaluation. All study participants (i.e., healthcare 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 stress measurements in the R00 phase.

1. Afulani PA, Moyer CA. (2019). Accountability for respectful maternity care. *The Lancet*. *09; 394*(10210):1692-1693. PMID: 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. PMID: 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 is designed to foster the development of scientific knowledge needed to enhance the health, productivity, independence, and quality of life of persons with disabilities, 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 *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, establishing strategic direction for coordinated action, and strengthening health systems to provide rehabilitation. The overall objective of the partnership with NIH was to provide financial support to carry out the following activities:

- Compile a WHO package of interventions for rehabilitation
- Identify priority rehabilitation 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 level

These efforts are ongoing with an estimated completion date of December 2022.

Recent Achievements in International Health

N/A

International Partnerships

Designing Computer-Mediated Communication Supports to Improve Social Participation After Traumatic Brain Injury (TBI) (R01HD071089). Adults with TBI experience less social participation and more social isolation that peers without TBI. Computer-mediated communication and social media could potentially improve social participation for adults with TBI by providing alternate methods for involvement; however, individuals with TBI may not be able to fully utilize social media and computer-mediated communication if the platform is not accessible by individuals with cognitive disabilities. This project will develop software to aid individuals with TBI in using social media and computer-based communication. The investigators will test how individuals with TBI use and interact with the software, with the goal of improving social media use and computer-based communication in an adult population with TBI. Dr. Lyn Turkstra from McMaster University, Ontario, Canada, is an expert in communication after TBI and has developed clinical practice guidelines for the treatment of TBI. She and her lab will assist with the evaluation of the software and future developments to implement the software more broadly.

A Client-Based Outcome System for Individuals with Lower Limb Amputation (5 R01 HD065340-09). Individuals with lower limb loss or difference can have a wide range of functional capabilities depending on the degree of loss or difference, the use of prosthetic limbs, and the type of prosthetic limbs used. There are many validated measures to assess functional abilities in individuals with limb loss, but they may be time consuming, and they are not all well suited to the breadth of the population. The goal of this project is to develop a computer-based functional assessment for individuals with lower limb loss or limb difference that can adapt with the individual's responses to questions, thus, saving time and making the instrument better suited for clinical use. The project will begin by compiling a pool of 100 candidate questions or tasks that could be included in the final instrument. The project team will recruit 500 individuals with lower limb loss or difference, from many sites across the United States and one international site at the British Columbia Institute of Technology, to complete a subset of the candidate tasks. Once collected, this data will be used by researchers at the University of Washington to develop the new, computer-based, adaptive tool to assess functional ability for individuals with lower limb loss or limb difference.

A Longitudinal Population-Based Birth Cohort Study to Understand the Past, Present, and Future of Children and Youth with TBI (R03 HD104206-01). Some effects of pediatric TBI are evident immediately, but many effects can take years to become apparent because pediatric TBI disrupts brain development, as well as brain health. The CDC also has identified pediatric TBI as an area with insufficient data repositories. The goal of this research project is to ascertain the short- and long-term effects of pediatric TBI by producing a dataset covering over 4 million live births in Ontario, Canada, between 1992 and 2020. It would be the first such dataset in the United States or Canada and could greatly inform clinical decision making in both countries. This grant, awarded to the University Health Network in Ontario, Canada, will take advantage of unique healthcare datasets that are collected as part of the Canadian healthcare system, allowing researchers to understand the incidence of pediatric TBI, the long-term impacts on neural development, and health care utilization of individuals with TBI.

Calibrating Transcutaneous Spinal Stimulation for Spasticity, Pain, and Motor Function in Spinal Cord Injury (SCI) (R01 HD101812-01A1). SCI results in the loss of sensation and control of muscles below the level of the injury. In addition, individuals with SCI can experience uncontrolled muscle contractions, called spasticity, and severe pain that can greatly disrupt an individual's ability to participate in activities of daily living and to maintain employment. The goal of this study is use transcutaneous spinal stimulation to relieve spasticity and pain, while also restoring some motor function in individuals with SCI. Transcutaneous spinal stimulation involves placing an electrical device over the lower spine to stimulate nerves as they exit the spinal cord. Dr. Karen Minassian, a professor at the Medical University of Vienna, Center for Medical Physics and Biomedical Engineering, is a leading international expert in transcutaneous spinal stimulation and will assist with analysis and interpretation of results.

Multiscale Models of Proprioceptive Encoding to Reveal Mechanisms of Impaired Sensorimotor Control (R01 HD090642-06). Many neurological conditions, such as stroke, cerebral palsy, and Parkinson's disease, involve increased joint resistance to passive movements, including spasticity, rigidity, and dystonia. This project aims to understand how altered neural input to muscles drives hyper-resistance in joints for a variety of neurological conditions. The investigators will utilize computer models and animal experiments to study changes in different types of neural input and how those changes may lead to hyper-resistance in joints. These data will inform clinical exams and allow better understanding of neurological deficits at the patient level and better clinical care. The investigators will collaborate with Dr. Friedl De Groote, an expert in computer modeling of humans with cerebral palsy at Katholieke Universiteit Leuven in Belgium, to provide vital input allowing comparison of the computer models and experimental data from this study to the human condition. This expertise will increase the impact of the proposed work and provide an avenue for clinical translation in the future.

Quantifying the Energetic Cost of Support and Stabilization During Walking in Children with Cerebral Palsy (R21HD104112-01A1). Walking allows individuals to complete their daily activities and is a highly efficient metabolic activity. Individuals with cerebral palsy can require two times the energy to walk the same distance as someone without cerebral palsy. Although assistive technology, rehabilitation, and surgery can help individuals with cerebral palsy walk, these interventions have not made meaningful improvements in the energy efficiency of walking. As a result, people with cerebral palsy may tire faster and walk less. The goal of this project is to measure the energy required for a person with cerebral palsy to support their body weight and maintain balance while walking. The research team will use a special treadmill that can provide weight support and balance support to the walker to measure how much energy is used during regular walking versus while the treadmill is providing these supports. Dr. Max Donelan at Simon Fraser University in Canada, an expert in experimental measurement and computation analysis of energy expenditure, will participate with the research team by contributing to the design of experiments and the analysis of the results.

Lumbar Spine Muscle Degeneration Inhibits Rehabilitation-Induced Muscle Recovery (5R01HD088437). Low back pain is a common and complex condition that will affect most Americans at some point in their lives. Symptoms can be persistent and recurrent, and treatments may be ineffective. Previous research showed that muscle in the lower back is weakened and altered in low back pain, making these muscles a key target for rehabilitation. This study will characterize the structural, physiological, and adaptive potential of back muscles in response to exercise in patients with disc injury using MRI and gene expression profiles. A Swiss collaborator, Dr. Mazda Farshad of Balgrist University, is conducting a similar, but independent study, and will share data with Dr. Ward, PI of this project, to draw better

conclusions and potentially increase the impact of the work. Dr. Ward and Dr. Farshad intend to co-author a manuscript on the findings.

Perturbation Training for Enhancing Stability and Limb Support Control for Fall-Risk Reduction Among Stroke Survivors (5 R01 HD088543-04). Stroke survivors are at a greater risk of falls due to stroke-associated sensory and motor impairments, and these falls can lead to serious injuries, such as hip fracture, hospitalization, and death. The goal of this project is to develop a training program to prevent falls in stroke survivors. Many stroke survivors experience hemiparesis, in which the one side is more impacted while the opposite side of the body maintains more robust motor capabilities. In this study, researchers will train participants on using balance-recovery strategies to prevent falls. Participants will train on their non-paretic side first, and then get similar training on their paretic side. The project hypothesizes that bilateral training will improve outcomes overall and confirm the training program as effective in stroke rehabilitation. Dr. Joyce Fung of McGill University, Canada, an expert in sensorimotor control of posture and gait in stroke rehabilitation, will serve as a consultant on this project, providing insight for data analysis and contributing to publication of the results.

Dynamic Stability in the Anterior Cruciate Ligament (ACL)-Injured Knee (5R37HD037985-19). This study, a continuation of a prospective international cohort study of patients after acute unilateral ACL injury, will help influence care by answering important clinical questions regarding the role and impact of dynamic knee stability on patient outcomes. The project builds on a 10-year collaboration between the University of Delaware and Oslo University Hospital, Norway, where the practice pattern requires a substantial period of rehabilitation prior to reconstructive surgery. The inclusion of an international sample from the 10-year study provides an opportunity to test the conventional wisdom that drives surgical decision-making in the treatment of ACL rupture in the United States. In addition, 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 (5R01HD081120-05). Developmental disregard, a form of neglect that starts in infancy and impairs the ability to infer new and effective movements, contributes to neurodevelopmental trajectories in children with disabilities that rarely equal those of typically developing children. This project seeks to overcome this phenomenon in the early rehabilitation of children with cerebral palsy by showing that Constraint-Induced Movement Therapy (CIMT) at or before age 2 years can improve upper extremity sensory and motor function, thereby mitigating developmental disregard. Using a randomized controlled trial design with a waitlist control, the study will enroll children 12 months to 24 months of age with asymmetric cerebral palsy. The CIMT intervention combines 1 month of soft-constraint wear on the less affected arm (1/2-day sessions, electronically monitored), 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 treatment for children with cerebral palsy. Typically developing age-matched children will also be tested. The Centre Hospitalier Universitaire Vaudois, Switzerland, a collaborator, will assist with complex modeling of EEG data gathered in this project.

Neuroergonomic Assessment of Wheelchair Control in Real-World Environments with Both Healthy and Clinical Populations (1F30HD103527-01). Neuroergonomics is an emerging field that investigates the human brain in relation to behavioral performance in natural environments and everyday settings to expand our understanding of the neural mechanisms

underlying human perceptual, cognitive, and motor functioning, with a focus on real-world contexts. This study uses neuroergonimcs approaches to study wheelchair users, who are prone to a variety of serious short- and long-term injuries, sometimes even fatal, 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. Alison Cernich

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Division of Intramural Population Health Research (DIPHR)

Scientific Scope

With an ambitious, threefold mission consistent with the NIH intramural research program, DIPHR aims 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 division 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. Researchers aim to identify genetic and non-genetic determinants of 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 Asian phenotypes in gestational diabetes, and metabolic signatures in the conversion from gestational diabetes to postpartum abnormal glucose metabolism. The Growing Up Study will also examine the transgenerational impact of maternal glycemia during pregnancy on 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, this 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. In collaboration with Trinity College, Dublin, this study examines 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 (PACE) Consortium. This consortium, 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. This research showed that a 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, long-term health implications of gestational diabetes and genetic and non-genetic determinants for the progression from gestational diabetes to type 2 diabetes. PI: Dr. C. Zhang; co-investigators: Drs. J. Mills and E. Yeung
- 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
- PrePARED Consortium. Investigators: Drs. S. Mumford, E. Schisterman, and E. Yeung
- PACE Consortium. Investigators: Drs. S. Mumford, E. Schisterman, C. Zhang, and E. Yeung

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Staff Membership on Global Health Committees/Working Groups

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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 in pursuit of the NICHD 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 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. AGs are as follows:

- 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, and how does identifying cells' properties and location to give rise to tissues and organs?
- How are processes integrated during embryonic, fetal, and postnatal development?
- When these processes go awry and disease ensues, how may we intervene in this pathologic sequence to treat the disease?

Section on Clinical Neuroendocrinology (SCN)

PI: Karel Pacak, M.D., Ph.D., D.Sc.

AG: Developmental Endocrinology, Metabolism, Genetics, & 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

Endocrine Hypertension and PRESSOR: Pheochromocytoma and paraganglioma RESearch and Support ORganization. Representative: Dr. Karel Pacak

Point-of-Contact

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

PI: Joan Marini, M.D., Ph.D.

AG: Bone and Matrix Biology in Development and Disease

Scientific Scope

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

Major International Initiatives

The section's investigations of melorheostosis and recessive Osteogenesis Imperfecta (OI) types enhanced by bone tissue are conducted studied with collaborators in Austria at Osteology Institute, Austria, University of Pavia, Italy, and Israel.

Publications with International Collaborators

- Cabral, W.A., Fratzl-Zelman, N., Weis, M.A., Perosky, J.E., Alimasa, A., Harris, R., Kang, H., Makareeva, E., Barnes, A.M., Roschger, P., Leikin, S., Klaushofer, K., Forlino, A., Backlund, P., Eyre, D.R., Kozloff, K.M., and **Marini, J.M.** (2020). Substitution of murine type I collagen A1 3-hydroxylation site alters matrix structure but does not recapitulate OI bone dysplasia. *Matrix Biology. Aug; 90*:20-39. PMID: 32112888.
- Garibaldi, N., Contento, B.M., Babini, G., Morini, J., Siciliani, S., Biggiogera, M., Raspanti, M., **Marini, J.C.**, Rossi, A., Forlino, A., and Besio, R. (2021). Targeting cellular stress improves osteoblast homeostasis and matrix in murine models of OI. *Matrix Biology. Apr;98*:1-20. doi: 10.1016/j.matbio.2021.03.001. PMID: 33798677.
- Jovanovic, M., Guterman Ram, G., and **Marini, J.C.** (2021). OI: Mechanisms and signaling pathways connecting classical and rare OI types. *Endocrine Reviews* (Invited Review). *May 19*;bnab017. PMID: 34007986.

Recent Achievements in International Health

N/A

International Trainees

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

International Partnerships

Dr. Marini serves as chair of the Scientific Committee for the International OI Conference, with representation from 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)

PI: Leonid Margolis, Ph.D.

AG: 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 SARS CoV-2 infection; a collaborative project with Moscow University of Medicine and Dentistry, Moscow, Russia. PIs: Drs. Elena Vasilieva and Alexander Shpektor
- Morphological analysis of extracellular vesicles generated by cytomegalovirus (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: Dr. 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

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)

PI: Yun-Bo Shi, Ph.D.

AG: Cell Regulation and Development

Scientific Scope

SMM uses amphibian metamorphosis as its main model system to study the gene-regulatory mechanisms controlled by thyroid hormone (TH) receptor (TR), which establish the postembryonic developmental program in vertebrates. The laboratory recently showed that TR is both necessary and sufficient for *Xenopus* metamorphosis, by recruiting cofactors in a TH-dependent manner, and revealed the origin of TH-induced adult intestinal epithelial stem cells. The laboratory has also identified many TH target genes while 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 event 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 development during embryogenesis, as well as resorption during metamorphosis in the ornamented pygmy frog *Microhyla fissipes*, revealing conserved gene expression profiles between terrestrial and aquatic frog species.
- To investigate the function of endogenous genes during metamorphosis, SMM recently collaborated with scientists in Xi'an Jiaotong University School of Medicine. Using gene-editing technologies to knockout the endogenous SRC3, a coactivator for TR, in *Xenopus tropicalis*, researchers revealed an important role for this coactivator, which also functions as a histone acetyltransferase, in the formation and/or proliferation of adult intestinal stem cells during metamorphosis.
- The likely conservation of TH function in vertebrate development prompted SMM to conduct comparative studies on TH action in mice. Through collaboration with researchers at the University of Dundee in the United Kingdom, a conditional knockout mouse line was generated to investigate the role of a TH and amino-acid transporter that was previously shown to be induced by TH during frog intestinal metamorphosis. Analysis of the mouse knockout line indicated that the transporter facilitates nutrient signaling in mouse skeletal muscle, and that a total knockout leads to embryonic

lethality. Through a collaboration with researchers in Kanazawa University Graduate School, Japan, SMM then showed that the transporter also regulates osteoclastogenesis and bone homeostasis via the mTORC1 pathway.

- In collaboration with scientists at NCI/NIH, South-Central University for Nationalities, and Xi'an Jiaotong University School of Medicine, China, SMM recently showed that a heterozygous dominant negative-TRα mutation leads to stem-cell defects in the adult intestine of a mouse model that mimics human patients with resistance to TH from TR α mutations. This finding is consistent with a previous SMM finding on the role of TH in adult intestinal stem cell development in *Xenopus*. Furthermore, the lab has shown that intestinal epithelial-specific knockout of protein arginine methyltransferase 1, a coactivator for TR, leads to, surprisingly, increased cell proliferation in adult mouse adult intestinal crypt. This finding suggests an important role for the protein other than as a TR coactivator for this methyltransferase in regulating adult intestinal stem cell function.
- In addition, collaborations with Wuhan University and South-Central University for Nationalities have revealed that hepatitis B virus induces autophagy to increase viral replication by regulating NFkB signaling via the miR-192-3p-XIAP axis and that that placenta-specific protein 9 inhibits proliferation and stimulates motility of human bronchial epithelial cells.

Though some of these collaborations have formally concluded, continued data analysis resulted in the following publications.

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. 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.
3. 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.
4. Wang, S., Liu, L., Shi, Y.-B., Jiang, J. (2021) Gene Transcriptome profiling reveals gene regulation programs underlying tail development in the Ornamented Pygmy frog *Microhyla fissipes. Frontiers In Bioscience-Landmark.* in press.
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. Tanizaki, Y., Bao, L., Shi, B., and Shi, Y.-B. (2021) A role of endogenous histone acetyltransferase steroid hormone receptor coactivator (SRC) 3 in thyroid hormone signaling during *Xenopus* intestinal metamorphosis. *Thyroid.* 31:692-702. DOI: 10.1089/thy.2020.0410.
8. 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., and Hinoi, E. (2019). System L amino acid transporter LAT1 regulates osteoclastogenesis and bone homeostasis via the mTORC1 pathway. *Science Signaling. 12*:eaaw3921, 1-14.
9. Poncet, N., Gierliński, M., Melanie Febrer, M., Lipina, C., Halley, P.A., Shi, Y.-B., Yamaguchi, T.P., Taylor, P.M., and 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.
10. 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.
11. Xue, L., Bao, L., Roediger, J., Su, Y., Shi, B., and Shi, Y.-B. (2021) Protein arginine methyltransferase 1 regulates cell proliferation and differentiation in adult mouse adult intestine. *Cell & Bioscience.* 11: 113, 1-17. https://doi.org/10.1186/s13578-021-00627-z.
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. Wang, H.-X., Qin, X.-H., Shen, J., Liu, Q.-H., Shi, Y.-B., and Xue, L. (2021) Proteomic analysis reveals that placenta-specific protein 9 inhibits proliferation and stimulates motility of human bronchial epithelial cells. *Frontiers in Oncology-Molecular and Cellular Oncology.* 11:628480. doi: 10.3389/fonc.2021.628480.

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)

PI: Andres Buonanno, Ph.D.

AG: 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, which focused on understanding the cellular expression patterns 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 with cognitive deficits in persons diagnosed with schizophrenia. As part of her research, Dr. Erben helped 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 be specified to a single short exon. She 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. Last year, she defended her dissertation and received her Ph.D. from the University of Bonn.

SMN collaborated with Dr. Alon Shamir, who originally came from Ben Gurion University of the Negev in Israel to the section for training, and with Dr. Miguel Skirzewski, from the University of the Andes in Venezuela. 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. More recently, in collaboration with Dr. Skirzewski and Dr. Tim Bussey at the University of Western Ontario in Canada, SMN used 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 its collaboration with Dr. Tanveer Ahmad, presently at the Department of Biochemistry, University Grants Commission in New Delhi. This work investigates 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 the 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., and 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., and 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., and 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., and Buonanno A. (2020). Toxic and phenotypic effects of AAV-Cre transduced in 85esencephalic dopaminergic neurons (*in submission*).
8. Ahmad T., Guardia C.M., Vullhorst D., Karavanova I., Bonifacino J.S., and 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., and 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.
  Senior Scientist
  Wellstat Therapeutics
  Gaithersburg, Maryland
- Carmen M. Gonzalez, Ph.D.
  Department of Pathology and Experimental Therapy
  University of Barcelona, Spain
- Ryoichi Kimura, Ph.D.
  Assistant Professor
  Department of Physiology, Hyogo College of Medicine
  Nishinomiya, Japan
- Oh-Bin Kwon, Ph.D.
  Assistant Professor
  Molecular NeuroScience Lab
  Department of Life Science, POSTECH
  South Korea
- Elias Leiva-Salcedo
  Assistant Professor
  Facultad de Química y Biología, Universidad de Santiago
  Chile
- Marines Longart, Ph.D.
  Principal Investigator
  Center for Biosciences, Institute for Advanced Studies
  Caracas, Venezuela
- Joerg Neddens, Ph.D.
  Senior Scientist

Department of Histology
JSW Life Sciences, Austria

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

International Partnerships

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

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

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