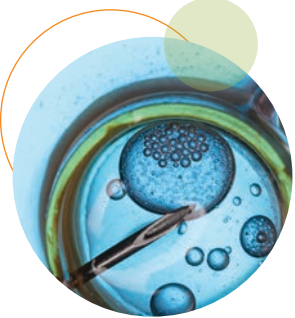NIH — Eunice Kennedy Shriver National Institute of Child Health and Human Development

NICHD | Global Health Catalog

Office of Global Health • Office of the Director

2023

NICHD Global Health
Activities Catalog 2023

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

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Overview

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

NICHD has supported research around the globe since the institute was first established and has a strong commitment to continued global health research collaborations. In 2009, a panel representing the Consortium of Universities for Global Health, with input from NICHD and several other National Institutes of Health (NIH) institutes, centers, and offices (ICOs), published in the *Lancet* an updated definition for "global health." The definition reads:

> Global health is an area for study, research and practice that places a priority on improving health and achieving equity in health for all people worldwide. Global health emphasizes transnational health issues, determinants and solutions; involves many disciplines within and beyond the health sciences and promotes interdisciplinary collaboration; and is a synthesis of population-based prevention with individual-level clinical care. (PMID: 19493564)

Within the context of this definition, the NICHD Global Health Catalog includes extramural and intramural research (e.g., basic science) with international collaborators.

The NICHD Office of Global Health (OGH) resides within the Office of the Director (OD) and supports global health activities across the institute. OGH works in close collaboration with NICHD divisions and offices, as well as with other NIH ICOs 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 health 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 domestic 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, representatives of global health and non-governmental organizations, and other groups.

The NICHD Global Health Catalog, prepared by OGH, provides an annual reporting of global health activities across the NICHD grouped by office, division, and center (for details on the institute's structure, review [NICHD's Organizational Chart](#)). Activities include the scientific scope of each component, current research initiatives and achievements, global health collaborative partnerships, staff membership on global health committees and working groups, and points-of-contact. Some intramural entries also list global health trainees and key global health 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 of leading research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all.

Major Global Health Initiatives over the Past Year

NIH collaboration with the [Bill and Melinda Gates Foundation (BMGF)](#). For the past 10 years, NIH OD has overseen an NIH-wide global health collaboration with BMGF that includes 14 scientific working groups. The NICHD Director co-chairs the NIH Maternal, Neonatal, and Child Health (MNCH) Working Group, which consists of the Pregnancy Outcomes, Growth and Nutrition, and Neurodevelopment Subgroups. OGH serves in the coordinating role for this NICHD-BMGF collaboration. These NICHD-led working groups also include representation from BMGF, the National Institute of Mental Health (NIMH), the National Institute of Drug Abuse (NIDA), the National Institute of Neurological Disorders and Stroke (NINDS), the National Heart, Lung, and Blood Institute (NHLBI), and the NIH Environmental Influences on Child Health Outcomes Program, among others. The primary aim of this working group is to identify mutual MNCH research priorities and activities in the areas of pregnancy outcomes, nutrition and growth, child neurodevelopment, neuroimaging, contraception development, and other areas.

Joint U.S.-Canada Workshop on COVID-19 in Children. Following an HHS-level U.S.-Canada Dialogue on the COVID-19 pandemic held in January 2022, NICHD has had a series of scientific consultations related to maternal and child research and the COVID-19 pandemic with the Institute of Human Development, Child and Youth Health (IHDCYH) within of the Canadian Institutes of Health Research (CIHR). On October 25, 2023, OGH organized a joint workshop with IHDCYH on *[Understanding the Impact of the COVID-19 Pandemic and Promoting Health Equity among Children, Adolescents, and Families in Canada and the United States.](#)* This workshop included researchers and community members with lived experiences who reported on the social determinants of health and the impact of the COVID-19 pandemic on children and adolescents in diverse underserved communities (e.g., Indigenous, Black/African American, Individuals with Disabilities) in Canada and the United States.

NICHD Dissemination & Implementation Science (D&I) Workgroup. The NICHD D&I Workgroup, led by OGH, plans and coordinates [D&I activities across NICHD,](#) across NIH, and in collaboration with external agencies. Staff members representing several NICHD branches/programs work with OGH to advance this important area of science. In June 2023, group members organized an NICHD Science Friday presentation with Dr. Michele Decker, from Johns Hopkins University, who spoke on *[Women's Health and Safety: Dissemination and Implementation Strategies for Domestic and Global Impact](#)*. An NICHD-specific D&I training opportunity is also under development.

NICHD Planning Group: Multiple Burdens of Malnutrition Among Children and Adolescents in Low- and Middle-Income Countries (LMICs). In 2023, several follow up activities built upon research priorities and gaps identified at the October 2022 NICHD global health conference, *[Socio-ecological Factors and the Double Burden of Malnutrition Among Children and Adolescents in LMICs](#)*. In April 2023, highlights from this NICHD conference were reported by OGH in a briefing document prepared for the NIH Obesity Research Task Force Meeting on *Weight Bias and Stigma: Research and Lived Experience*. Also in April 2023, a joint NICHD and Fogarty International Center (FIC) panel presentation on *Climate Change and Malnutrition* was organized at the annual conference of the Consortium of Universities in Global Health. A peer-reviewed journal publication related to this NICHD conference is also under development.

NIH Working Group: [Promoting Equity in Global Health Research](#). FIC established this NIH-wide working group to identify approaches for promoting equity in global health research. OGH represents NICHD on this working group and served as a co-author for an NIH Request for Information and for the subsequent [report](#) that was published in June 2023. Next steps include organizing and implementing NIH-wide working groups to address identified priority areas including: 1) equitable partnerships and community engagement; 2) building grants applications and management capacity; 3) data sharing, management, and scientific capacity; 4) funding opportunities, mechanisms, and applications; and 5) peer review.

NIH Working Group: [Global Health Reciprocal Innovation (GHRI)](#). Reciprocal innovation, defined as the bi-directional and iterative exchange of a technology, methodology, or process between at least two countries, one LMIC and one high-income country (HIC), is a newly developed term to address common health challenges and provide mutual benefit. In October 2022, FIC, together with several NIH ICOs including NICHD's OGH, organized an international workshop that

featured examples of NIH-supported research with demonstrated reciprocal innovation between foreign countries and the United States. As a follow-up activity, OGH participated in an NIH GHRI writing group that prepared an executive summary and organized a group of NIH researchers to prepare a journal supplement, which was accepted by the *British Medical Journal* for publication.

Global Alliance for Chronic Disease (GACD) Initiative. Since 2007, the GACD has brought together major international research funding agencies specifically to address the growing burden of noncommunicable diseases (NCDs) in LMICs and vulnerable populations in HICs. In 2023, the GACD team received an NIH Director's Award in recognition of the initiative's research and capacity-building achievements since its inception. Several NIH ICOs participated, including OGH and Pediatric Growth and Nutrition Branch (PGNB) staff from NICHD. Other NIH partners include NHLBI, NIMH, NINDS, the National Cancer Institute (NCI), NIDA, the National Institute of Environmental Health Sciences, and the NIH Center for Scientific Review. NICHD is currently supporting two grants from a related research funding announcement, PAR-22-132: Implementation Research to Reduce NCD Burden in LMICs and Tribal Nations During Critical Life Stages and Key Transition Periods.

U.S. Government Children in Adversity Initiative. During the COVID-19 pandemic, this USAID-led interagency working group for the implementation of the Children in Adversity Initiative focused on the impact of the pandemic on vulnerable children and families in LMICs. Areas of interest included 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 the number of orphans due to the absence of caregivers. OGH informs this working group of NIH-wide research efforts on the COVID-19 outbreak that are most relevant for at-risk children and their families.

NIH Global Health Program for Fellows and Scholars. NICHD staff have participated in peer review of research applications for this program during the last three years. 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 Maternal and Pediatric Infectious Disease Branch (MPIDB) organized an internal peer-review process for the selection of candidates working on HIV/AIDS research topics in line with the NICHD mission. Applicants from several African countries (i.e., Malawi, Democratic Republic of Congo [DRC], Ghana, Nigeria, Tanzania, Botswana, and South Africa) proposed HIV/AIDS research projects in the areas of maternal dietary patterns and gestational diabetes, COVID-

19 in children, micronutrient status in children, HIV stigma in childbirth, and vaginal health. All seven candidates were recommended for funding to NICHD leadership.

[**NIH Common Fund: Data Science & Innovations in Africa Program (DS-I Africa)**](#). NICHD staff has participated in the DS-I Africa initiative since its creation to leverage data-science technologies and prior NIH investments to develop solutions for Africa's most pressing public health problems. This NIH Common Fund initiative has included participants from 18 African countries (most active being Nigeria, South Africa, Uganda, Kenya, Ghana, Ethiopia), about one-half of which work in academia, as well as non-governmental organizations (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 research. NICHD is currently funding DS-I Africa research grants on health topics within the NICHD mission.

[**World Health Organization (WHO) Nurturing Care Framework**](#). Over the past six years, OGH has represented NICHD on the Planning and Implementation Working Group for this framework initiative. The concept of "Nurturing Care" was coined in the 2016 *Lancet* series, *Advancing Early Childhood Development: From Evidence to Scale*, in reference 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 (with more than 200 participants) and subsequent technical consultations aimed at identifying research and implementation gap areas, developing plans for interagency implementation, and drafting guidelines for policymakers.

Recent Achievements in Global Health

- **Organizing and Participating in High Level Interagency Global Health Meetings:** OGH has represented NICHD and prepared briefings for meetings with high-level global health leadership including with HHS Office of Global Affairs (OGA) leadership and HHS Health Attachés in Brazil, China, India, Mexico, and South Africa. OGH has also participated in the U.S.-Finland Joint Committee Meeting, the trans-NIH meeting with the President and delegation from the Cuban Academy of Sciences, WHO representative in Africa, among others. OGH also participated in the USAID-led study tour with a Serbian delegation focused on the federal COVID-19 multisectoral response.

- **Planning of International Site Visits by Senior NICHD, NIH, HHS, and Congressional Leadership:** OGH has prepared briefing materials for NIH leadership for international research site visits in Poland, Peru, and Mozambique.

- **Public Law 109-95 Congressional Report Data Call:** OGH contributes to the NIH report on research projects studying the health and developmental outcomes of orphans and vulnerable children for the annual PL 109-95 report to Congress. OGH also prepared an NIH Congressional Briefing for Senators Blunt, Coons, and Fitzpatrick on the Global Child Thrive Act.

- **OGH Brown Bag/Webinar Series:** Organized talks on global health and diverse scientific topics in line with the NICHD mission.

- **Dissemination of NICHD Global Health Information:** Prepared communication materials, including the annual NICHD Global Health Catalog, to facilitate information exchanges related to NICHD global health research.

- **Scientific Input for Interagency Global Health Documents:** Provided input to HHS OGA and other international agencies on relevant maternal and child health research for interagency documents (e.g., World Health Assembly, WHO Regional Meetings, Pan American Health Organization, U.N. General Assembly Health Side-Meetings).

Global Health Partnerships

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

Staff Membership on Global Health Committees/Working Groups

- NIH-BMGF MNCH Working Group: Drs. Vesna Kutlesic and Jenelle Walker

- IHDCYH/CIHR-NICHD COVID-19 in Children in Canada and U.S. Planning Team. Drs. Vesna Kutlesic and Jenelle Walker

- NICHD D&I Working Group: Drs. Jenelle Walker and Vesna Kutlesic

- NIH D&I Working Group: Dr. Jenelle Walker

- NIH Promoting Equity in Global Health Working Group: Dr. Vesna Kutlesic

- WHO Nurturing Care Framework Advisory Group: Dr. Vesna Kutlesic

- USAID Advancing Protection and Care for Children in Adversity Strategy Working Group: Drs. Vesna Kutlesic and Jenelle Walker

- FIC International Representatives Working Group: Drs. Vesna Kutlesic and Jenelle Walker

- FIC International Interest Group: Drs. Vesna Kutlesic and Jenelle Walker

- NICHD Reproductive Health Working Group: Drs. Jenelle Walker and Vesna Kutlesic

- NICHD Maternal Health Coordinating Committee: Drs. Jenelle Walker and Vesna Kutlesic

- Global Nutrition Coordination Plan Technical Working Group: Dr. Jenelle Walker

- NIH Global Health Interest Group: Dr. Jenelle Walker

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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, typical and atypical development in childhood, reproductive health, and population dynamics across the lifespan. While NICHD's Division of Intramural Research 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 arise from or are differentially affected by genetic and environmental risk/protective factors 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). The branch uses these findings to inform translational prevention, intervention, and health promotion studies designed to enhance the lives of children and adolescents.

Major Global Health Initiatives over the Past Year

Parenting Across Cultures ([HD054805](#) and [HD075875](#)). 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 youth behavior and development from childhood through early adulthood. Participants are currently in their early 20s, and the study will examine young adult adjustment, including risk and protective factors, predictors of parent-young-adult relationships across cultures, and the impact of COVID-related disruptions on adjustment or maladjustment. Another study, set in Pakistan, is evaluating the impact of an intervention for maternal depression on child socio-emotional, cognitive, and physical outcomes during middle childhood, and whether improved parenting mediates child outcomes.

Adolescent Behavior ([HD087485-05](#)). In Mauritius, CDBB funds a study on omega-3 supplementation and adolescent behavior. This study hypothesizes that this supplementation will reduce externalizing behavior, such as aggressive and antisocial behavior, which predispose teens not just to later adult violence, but also to a wide array of adult psychiatric disorders. The adult outcomes can result in an economic and social burden on society, as well as reduced quality of life for both victims and perpetrators. Reducing the overall level of externalizing behaviors in

the general population can therefore reduce these adult adverse public health outcomes, with considerable savings to society.

Integrated Early Childhood Development (ECD) Interventions ([HD090045](#), [HD094803](#), [HD094830](#), [HD094803](#), [HD094830](#)). 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 are known 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.

A branch-supported multisensory development initiative, which established a network of 13 research labs, including the University of Western Ontario in London, Canada, will administer the first two protocols to assess individual differences in attention, social, and language functioning skills in infants and toddlers. The aggregate database resulting from these efforts will provide the first characterization of the how these fundamental skills develop typically in children, and will serve as a basis for identifying atypical development, inform early interventions, and provide a new model for collaborative research.

Additionally, the branch supports Play and Learning Across a Year (PLAY) to catalyze discovery about behavioral development in infancy. PLAY focuses on the critical period from 12 to 24 months of age when infants show remarkable advances in language, object interaction, locomotion, and emotion regulation. PLAY leverages the joint expertise of 63 "launch group" researchers, including teams at three Canadian universities: University of Toronto and University of Waterloo in Ontario, and Mount Allison University in Sackville, New Brunswick. Together, PLAY researchers collect, transcribe, code, and share a video corpus of infant and mother naturalistic activities in the home that test behavioral, developmental, and environmental cascades.

Pediatric Health Promotion Interventions ([HD110844](), [HD090984](), [HD090051]()).
The branch is currently funding research on a community-based digital outreach and educational intervention, called "Chanjo Kwa Wakati" (timely vaccination), being implemented across 40 health facilities in two predominantly rural regions of Tanzania. The intervention is geared toward mothers who have recently given birth and comprises a combination of in-person community health worker outreach and low-cost digital strategies. It utilizes an effectiveness–implementation hybrid design, which means that researchers are not only studying whether the intervention works, but they are also collecting information on key elements of implementation that will allow quick scale-up of the intervention if it is found to be effective. Study findings also have the potential to inform strategies for improving vaccination equity among children living in rural and underserved communities in the United States.

The branch also funds a longitudinal follow-up study of HIV risk and treatment among orphaned and separated children in five LMICs: Cambodia, Ethiopia, India, Kenya; orphaned and separated children are at especially high risk of contracting HIV. The study aims to identify predictors of HIV-risk behaviors, HIV testing, and engagement in HIV care as these children transition into young adulthood. The study will also evaluate the differing acceptability of these interventions by location and gender, which may be useful in future design and implementation of policies and interventions that address HIV risk and treatment engagement among this population.

Additionally, CDBB supports research on the relationships between infection, fever, immunity, and Attention Deficit-Hyperactivity Disorder (ADHD) in a population-based pregnancy/birth cohort. This study analyzes prospective data on pre- and postnatal infections, fever, and comorbid immune disorders, as well as the influence of medications and diet; examines biological specimens from mothers and infants to establish evidence of immune and inflammatory responses; and tests for exposure to specific pathogens in mothers during pregnancy and at birth. By identifying risk factors and biomarkers, these analyses will facilitate early diagnosis, intervention and, potentially, prevention of ADHD. This study has performance sites in the United States as well as at the Norwegian Institute of Public Health in Oslo, Norway.

Child Cognition ([HD094054]() and [HD096363]()). Examining physical activity behaviors that positively influence brain health, cognition, and academic performance in preadolescent children is important for improving school performance, maximizing overall health, and improving the function of individuals as they progress through

the human lifespan. A CDBB-funded study is examining a biological mechanism that may mediate the beneficial effect of a single bout of exercise on brain function, cognition, and academic achievement of preadolescent children. This study takes place, in part, at the University of Ottawa in Ontario, Canada.

Spatial awareness is a significant predictor of success in math and science that is understudied and rarely addressed in formal education. The branch is supporting a study evaluating spatial awareness in infants and young children—in the United States and Israel—in the context of native orthography and parental input. In addition to exploring spatial cognition from a cultural perspective, researchers are testing a parent-led intervention designed to increase the number of parent-child interactions that involve spatial associations. Through these examinations, this study has the potential to uncover factors that contribute to development of children's spatial awareness, as well as means of increasing it.

Bilingualism ([HD111637](#), [HD096144](#), [HD095912](#)). CDBB supports an observational study in Taiwan to uncover how Chinese-English bilingualism influences literacy development in neurotypical children and in children with dyslexia. Results from this research will advance our understanding of children's emerging neural architecture for learning to read in linguistically diverse learners with and without dyslexia.

The branch also supports research into monolingual and bilingual reading comprehension among middle and high school students through a study with performance sites in the United States and at Lancaster University, United Kingdom. This project investigates the changing structure of reading comprehension in monolingual and Spanish-English bilingual students, as well as cognitive and linguistic predictors of reading comprehension in 8th and 10th grade.

Additionally, in collaboration with Concordia University and McGill University in Montreal, Quebec, Canada, and multiple U.S. universities, the branch supports research on the effects of everyday language-switching on bilingual infants and toddlers. The study investigates how young bilinguals navigate and learn from dynamic exposure to multiple languages. Findings could have transformative implications for parents, educators, and clinicians who strive to support dual-language proficiency and minimize the risk of language delays.

Cross-Linguistic Studies of Literacy and Language Development ([HD108937](#), [HD051698](#), [HD103358](#), [HD108300](#)). The branch, with collaborators in Germany, recently began funding a project that investigates the role of temporal prediction

and attention in language processing. The goal of this research is to inform the development of effective therapies for language disorders. Additionally, the branch funds TalkBank, an integrated database of transcripts and language samples. An important tool for the language-science community, TalkBank supports integrated and harmonious analyses of patterns across different language domains, opening new avenues for interdisciplinary research in communication development and disorders.

CDBB supports a longitudinal study to examine mechanisms underlying math and reading development, with performance sites in the United States as well as at the University of Western Ontario in Canada. This study compares typical and atypical developmental trajectories of reading and math skills, from kindergarten to 3rd grade, to identify shared mechanisms underlying development of these skills. The goal of this work is to identify a set of predictors, in kindergarten, for math and reading outcomes after formal instruction.

Additionally, the branch supports research to develop a model to predict adolescent reading comprehension abilities in monolingual English speakers and Spanish-English bilingual speakers. This project expands existing understanding of reading comprehension to older children, and could improve curriculum design and educational interventions. The effort has performance sites in the United States and at Lancaster University, United Kingdom.

Recent Achievements in Global Health

Low-Level Lead Exposure in Early Childhood and Parental Education on Adolescent IQ and Working Memory: A Cohort Study. Continued childhood exposure to low levels of environmental lead in China and globally warrants examination of their impacts. This work demonstrated that even relatively low-level lead exposure in early childhood significantly influences adolescent neurocognitive functioning. Furthermore, co-existing variables related to social determinants of health, measured in this study as parental education, have a combined impact on neurocognition. These results highlighted which children are at greater risk for neurocognitive deficits and demonstrated the need to examine these exposures within the broader socio-ecological environment, as these factors work in tandem to influence longer term neurocognitive outcomes. (*Journal of Exposure Science & Environmental Epidemiology*, 2022, PMID: [35750750](#))

Predicting Child Aggression: The Role of Parent and Child Endorsement of Reactive Aggression. This study examined the unique predictive effects of parent and child endorsement of reactive aggression at age 8, on child aggression at age 9,

in 1,456 children from 13 cultural groups in 9 nations. Results revealed that greater parent endorsement of reactive aggression at age 8 predicted greater child endorsement of aggression at age 9. In addition, greater parent endorsement of reactive aggression at age 8 uniquely predicted greater aggression at age 9 in girls, and greater child endorsement of reactive aggression at age 8 uniquely predicted greater aggression at age 9 in boys. All three of these associations emerged across cultures. (*Aggressive Behavior*, 2023, PMID: 36565473)

The Day-in-the-Life (DIL) Method for Assessing Infant Caregiving in Rural Pakistan. The DIL was designed as a semi-structured interview in which mothers describe their child's day from their perspective. Using regression analyses of the Patient Health Questionnaire-9 (PHQ-9) measure, researchers explored the correlation between the DIL and maternal depression symptoms. The findings indicated that, although instrumental caregiving was mostly provided by the mother alone, others in the household tended to contribute more to infant social interactions, and there was more support from others when the mother was less able to provide care. Depression symptoms were higher among women who experienced less contribution from family members when the mother was less able to provide care. The DIL can be deployed to measure infant caregiving activities and associations with maternal mental health. This method is promising for researchers interested in disentangling the contribution of multiple family members toward child caregiving and its impacts on maternal and child health. (*Family Relations*, 2023, PMID: 37346745)

Global Health Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

NIH-BMGF MNCH Working Group, Neurodevelopment Subgroup: Dr. Virginia Salo

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Contraception Research Branch (CRB)

Scientific Scope

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

Major Global Health Initiatives over the Past Year

Understanding the Impact of Lower Dose Depot Medroxyprogesterone Acetate (DMPA) on Female Genital Tract Microbiome and Immunology (HD096937-05 and HD096937-04S1). DMPA, under the brand name Depo-Provera®, is the most widely used injectable contraceptive worldwide, and is associated with increased HIV acquisition in multiple observational studies. This study leverages three randomized trials to conduct timely, innovative, and cost-efficient evaluation of the impact of multiple contraceptives—the levonorgestrel (LNG) implant 150-IM, the copper Intrauterine Device (IUD), Sayana® Press injection, and novel low-dose DMPA formulations—on the female genital tract microbial and immune environments. The 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 a 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.

This grant also received an administrative supplement (*Expansion of Microbiome and Immune Mediator Analysis to Include HIV Acquisition in a Case-Control Study*) to expand its original specific aims to include HIV acquisition as a clinical endpoint. This case-control analysis involved measuring nine immune mediators.

Clinical Trial with the LNG Intrauterine System to Measure Changes in Hemoglobin and Serum Ferritin Among Anemic Women in Kenya (HD100497-04). 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, and 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 this project 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 works 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 (HD085887-05). 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. Because 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 understand how 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 (LARC), 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 1 year reduced LNG plasma concentrations by approximately 50 percent compared to women not on ART. Importantly, the study group of women on EFV-based ART plus the LNG implant had a 15-percent unintended pregnancy rate, 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 inform 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:

- Identify strategies to overcome the drug-drug interaction between LNG and EFV- based ART

- Advance contraceptive therapeutic options for women with HIV

- Advance the science of the drug-drug interaction field

By establishing an evidence-based approach to safely combining LNG implants with ART regimens across the continuum of HIV care, this collaborative study can 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 (HD088279-05). Sub-Saharan Africa has high rates of unintended pregnancy, maternal mortality, and perinatally acquired 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. However, DMPA injectable is the most used contraceptive in the region, even though it requires repeat injections every 3 months, and has 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 interactions between the two drugs, leading 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 effort with 240 women in a 2:1 nested case-control study from the cohort will determine if higher EFV concentrations are associated with LNG implant contraceptive failure. They will also evaluate the effect of switching ARTs on LNG, MPA, sex hormone-binding globulin concentrations, and HIV viral load among a subset of 50 women; they will also measure of viral suppression, adherence, and ART resistance before and after changing from one ART to another among a subset of up to 1,000 women.

Implementation and Evaluation of a Large-Scale Postpartum Family Planning (PPFP) Program in Rwanda (HD101600-03). To address the high unmet need for PPFP options in Rwanda, this project uses an implementation science framework determine whether the C4 intervention—involving Couples/clients, Clinic providers, Champions, and Community health workers—can cost-effectively and sustainably be adapted to large-scale implementation. Working closely with the Rwandan Ministry of Health, a small-scale pilot study of LARC uptake measured significant increases among postpartum women (2,687 percent for PP IUD, 172 percent for PP

implant). Among providers and clients, PPFP feasibility and acceptability were high, and side-effects were rare. These LARCs are highly effective and, for breastfeeding women in the early postpartum period, LARCs are the only reversible methods that may be used safely. A critical goal of the program is to create an adaptable and sustainable framework appropriate for Rwandan government facilities; therefore, the Ministry of Health and other local stakeholders have been engaged from the outset. During the project period, the investigators expect to deliver C4 PPFP counseling to over 21,000 women/couples. Implementation of C4 is expected to dramatically reduce unintended pregnancy and abortion, allow better birth spacing, and improve maternal and newborn health.

This year, the project added a Type 2 effectiveness implementation hybrid study in Kigali to evaluate the effectiveness of different demand-creation strategies, making it the first study to rigorously evaluate PPFP demand creation strategies, cost-effectiveness, and sustainability of services delivered at-scale. Like many countries and because it is the most densely populated country in continental Africa, Rwanda is committed to reducing unmet PPFP needs and increasing LARC use. C4 could dramatically reduce maternal-child morbidity and mortality in Rwanda. Moreover, C4 is a potentially replicable and sustainable model that could be expanded to countries across the region. This study aligns with the NICHD high-priority areas of research on contraception use and improving the health of women before, during, and after pregnancy.

Recent Achievements in Global Health

In Vitro Assessment of the Potential for Dolutegravir to Affect Hepatic Clearance of LNG (HD085887-05). LNG is a commonly used hormonal contraceptive that is known to undergo drug-drug interactions with some antiretrovirals (ARVs), but the potential interaction between dolutegravir and LNG has not been examined. This situation is unusual because the WHO recommended that all countries adopt dolutegravir-based ART as the preferred regimen for individuals living with HIV. This work evaluated LNG metabolism, mediated by cytochrome P450 (CYP), and quantified the effects of dolutegravir on LNG apparent intrinsic clearance and CYP gene expression. The results of this in vitro study suggest that dolutegravir may potentially increase hepatic clearance of LNG via induction of both CYP3A and non-CYP3A enzymes. Therefore, further clinical studies may be needed to fully understand the observed in vitro dolutegravir-LNG drug-drug interaction to benefit patients who might be receiving these two medications. (*HIV Med*, 2021, PMID: 34328253)

Pharmacokinetics of LNG and Etonogestrel Contraceptive Implants Over 48 Weeks with Rilpivirine- or Darunavir-Based ART (HD085887-05). There is a paucity of PK data for progestin-releasing subdermal contraceptive implants when used with either rilpivirine- or darunavir/ritonavir-based ART. The branch funded work to characterize PK data in two separate, parallel, three-group, non-randomized, PK studies conducted concurrently at the Infectious Diseases Institute, Makerere University, Kampala, Uganda. These studies evaluated use of either etonogestrel or LNG in women receiving ART (either rilpivirine- or darunavir-based) compared with women without HIV (control group) over 48 weeks. At week 24, progestin concentrations were similar between the rilpivirine and control groups, but progestin exposure was higher in the darunavir groups compared with the control group. These results remained consistent through week 48. Although no differences in etonogestrel-related adverse events were observed, both ART groups experienced more menstrual abnormalities versus the control group with levonorgestrel. For the rilpivirine-based ART, progestin concentrations were not altered. In the ART groups, those receiving ritonavir-boosted darunavir regimens had higher progestin concentrations, but no implant-related serious adverse events were observed. The findings confirm that for those on either rilpivirine- or darunavir/ritonavir-based ART, both progestin-releasing implants are appropriate contraceptive options. (*J Antimicrob Chemother*, 2022, PMID: 36059130).

Genital Inflammatory Status and the Innate Immune Response to Contraceptive Initiation (HD096937). Previously obtained data on the effects of contraceptives on female genital tract immune mediators have been inconsistent, possibly because contraceptive initiation influences immune mediator changes, especially in those with pre-existing conditions. In the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial, 161 South African women were randomized to injectable intramuscular DMPA (DMPA-IM), copper IUD, or LNG implant. While copper IUD and LNG implant initiation were associated with increased inflammatory cytokines, no changes were observed following DMPA-IM initiation. However, if stratified by their baseline inflammatory profiles, women with low baseline inflammation experienced a significant increase in inflammatory cytokines, but those with a high baseline inflammatory profile experienced no change or decreases in inflammatory cytokines. Thus, the immune profile before contraceptive initiation can modify the effect of contraceptives on the innate immune response of the female genital tract. (*Am J Reprod Immunol*, 2022, PMID: 35394678)

Differences in Condomless Vaginal Sex Among Women Randomized to Intramuscular Depot Medroxyprogesterone Acetate Injections, a Copper Intrauterine Device or a LNG Implant in the ECHO Trial (HD095708-02). The ECHO trial found no difference in HIV acquisition risk between women receiving DMPA-IM, a copper IUD, or the LNG implant. In a subset of ECHO participants (n=458), the frequency of condomless sex was evaluated, using the objective measure of prostate specific antigen (PSA) detection in vaginal swabs. In an unadjusted model, PSA was detected less frequently in the DMPA-IM (16 percent) group, compared to the copper IUD (21 percent) and LNG implant (24 percent) groups, although these results were not statistically significant. However, there were significant differences in PSA detection between the DMPA-IM and LNG implant groups in the adjusted model, suggesting that the frequency of condomless sex may be influenced by contraceptive method. Further, inconsistencies between self-reported sexual behavior and detectable PSA may be useful for the design of future HIV prevention studies. (*AIDS Behav*, 2023, PMID: 36357806)

Effect of Double-Dose LNG Subdermal Implant in Women Taking EFV-Based ART: The DoubLNG PK Study (HD085887-05). This study sought to determine pharmacokinetically if a double-dose of LNG implants was enough to overcome the drug–drug interaction with EFV-based ART using a nonrandomized, open-label, parallel-group, longitudinal pharmacokinetic study among Ugandan women ages 18 to 45 years. For women with a doubled dose of 2 implants (n=27), the measure of systemic drug release was 34-percent lower versus the standard dose of LNG (n=19). Also, the percentage of participants with LNG concentrations at the benchmark of ≥300 pg/mL was not statistically different between groups at week 24. Therefore, a double-dose of the LNG implant ("DoubLNG") did not completely overcome the drug–drug interaction with EFV, and women using ART containing EFV had evidence of ovulatory activity with LNG implants. Thus, women using contraceptive implants may need to consider alternative ART that does not have known drug–drug interactions, such as dolutegravir. (*Contraception*, 2023, PMID: 36787829)

Global Health Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

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Developmental Biology and Congenital Anomalies Branch (DBCAB)

Scientific Scope

DBCAB (formerly the Developmental Biology and Structural Variation Branch [DBSVB]) supports basic, clinical, and translational research on normal and abnormal development relating to the causes and prevention of structural congenital anomalies (formerly called birth defects), as well as research training in relevant academic and medical areas. The branch focuses on basic research, primarily using a variety of animal models, to elucidate the biochemical, molecular biologic, genetic, biophysical, and cellular mechanisms of embryonic development. DBCAB supports both basic and translational aspects of structural congenital anomalies research by supporting and fostering collaborations among basic developmental biologists studying developmental mechanisms at all embryonic stages and the causes of congenital anomalies in model organisms. Additionally, the branch supports biophysicists studying physical/biomechanical aspects of development and clinicians studying the causes and intervention strategies for congenital anomalies in humans.

In addition to an emphasis on structural congenital anomalies and transdisciplinary research, [DBCAB 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 congenital anomalies 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 DBCAB actively promotes the collaboration of basic and clinical scientists through the [NICHD's Birth Defects Initiative](#) and encourages interactions between NIH institutes with shared interests in congenital anomalies research by providing leadership for the [Gabriella Miller Kids First Pediatric Research Program](#).

Major Global Health Initiatives over the Past Year

Multinational Collaborations

Canada, Spain, and China ([HD097665-11](#)). 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 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 PI seeks to understand the mechanisms underlying XCI and how functional interactions between PRC2 and long noncoding RNA (lncRNA) spread the silencing process through the X chromosome in a locus-specific manner for proper developmental regulation. A collaboration with Canadian researchers is examining 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 is examining the role of HNRNPK (heterogeneous nuclear ribonucleoprotein K) 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 is investigating the localization dynamics of PRC2 and how SirT7 mutations affect Xist and Polycomb spreading.

Canada and United Kingdom ([HD110059-01A1](#)). Supravalvular aortic stenosis (SVAS) is a developmental genetic disease characterized by accumulation of excess smooth muscle cells which narrows the aorta, reducing blood flow and putting a heightened load on the heart. The project aims to study the epigenetic regulation of SVAS, utilizing mouse models and human cells, to provide the foundation for developing novel therapeutic approaches for SVAS and other vascular diseases. De-identified human induced pluripotent stem cells (iPSCs) derived from unaffected control individuals and patients with congenital cardiovascular disorders, including SVAS and Williams-Beuren syndrome, were obtained from a Canadian collaborator. For the proposed experiments, these cells were differentiated in vitro into cells that resemble smooth muscle cells, and the collaborator provided key input into the proposed gene expression studies utilizing this unique iPSC resource. Further support of the planned work will come in the form of key reagents provided by researchers in the United Kingdom that will drive overexpression of constitutively

active Smad2 and Smad3, allowing investigation of the TGFb signaling pathway in elastin biology.

Single Country Collaborations

Canada (HD064556-13, HD095831-04, HD112607-01). The wide use of animal models to elucidate the causes of human disease generates a great deal of genomic data. In recent years, the need to share these data between investigators doing basic research with different animal models and physician-scientists doing clinical or translational research has become paramount. One of the best ways to share data is through community databases. Xenbase, the Xenopus model organism database, is one of the best available 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 and provides access and tools for data analysis, serving as a resource to the international research community, and ensuring that important data are available and accessible to guide further research projects without unnecessary duplication of effort. In serving this function, Xenbase provides an essential resource to the biomedical research community for understanding the molecular basis of development, health, and disease.

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

In addition to database development, another DBCAB-Canadian collaboration is in progress, focusing on mechanical signaling as a critical driver of embryonic cell fate. For example, tensile forces can be transmitted between nuclear and cytoplasmic compartments via the lamin meshwork below the nuclear membrane. However, the mechanisms that link nuclear mechanics to chromatin regulation and early mammalian fates are not fully understood. This project is investigating the role of

mechanical forces transmitted though the nuclear membrane cytoskeleton in the regulation of transcriptional programs in the early embryo, with an emphasis on the development of the trophectoderm. To accomplish the project aims, the PI is utilizing four mouse lines engineered to express labeled proteins that will sense nuclear membrane tension via a fluorescence resonance energy transfer signal detected using fluorescence lifetime imaging (FILM). These mice are a unique resource and will be obtained from a Canadian collaborator with extensive expertise in applying a range of biophysical strategies to developmental biology questions, including measurement of nuclear physical viscoelasticity and mechanotransduction. In addition, the collaborator will provide guidance on troubleshooting and the interpretation of results from the FILM experiments.

France ([HD105946-01](#)). Determining how neurons are assembled into functional circuits will provide insight into developmental disorders of the nervous system and may suggest therapeutic approaches to promote nerve regeneration. To navigate to their correct targets, axons must modulate their responses to extracellular cues, and regulated intracellular protein trafficking plays a pivotal role in this process. For example, commissural axons cross the midline, despite the presence of repellant ligands, to establish connections essential for coordinated motor behavior. In Drosophila, the endosomal protein Commissureless (Comm) prevents commissural axons from prematurely responding to the repellant Slit, by inhibiting surface expression of the Slit receptor Roundabout1 (Robo1). In mammals, Robo receptors are also negatively regulated in commissural axons prior to midline crossing, but the mechanisms are unknown. Unlike Slit and Robo, Comm is not conserved in vertebrates. However, preliminary data indicate that the vertebrate Nedd-4 interacting proteins (Ndfip1 and Ndfip2) can act analogously to Comm for regulation of trafficking and stability of human Robo receptors in vitro; loss of Ndfip1or Ndfip2 function in vivo in mice results in increased expression of Robo receptors and defects in axon guidance. This work, in collaboration with investigators in France, examines the hypothesis that Ndfip proteins control axon guidance in the developing brain and spinal cord by recruiting Robo receptors to endosomes and triggering their degradation through interactions with Nedd-4 E3 ubiquitin ligases.

Germany ([HD095797-05](#), [HD091921-04](#)). DBCAB originally awarded a grant to a PI at the University of California Santa Barbara (UCSB), who moved to Dresden University of Technology, Germany, in 2023. This investigator's interdisciplinary training in biology and physics allowed him to develop several novel technologies unique to his laboratory; no other UCSB investigators had similar expertise to complete the funded project. Therefore, NICHD Council approved transfer of the

grant to Dresden University of Technology for the remaining 1.5 years of the project to allow the PI to complete the work.

The project investigates the mechanics (such as the mechanical forces and material properties) involved in sculpting tissues and organs into their 3D functional morphologies, using zebrafish embryos as a model system. Two novel microdroplet-based techniques developed by the PI will be used to measure tissue material properties and mechanical stresses involved in the elongation of the vertebrate body axis during embryonic development. This work tests the hypothesis that transitions between fluid-like and solid-like states allow tissues to flow, enabling tissue remodeling and morphogenesis, while also providing mechanical integrity to developmentally older anterior structures, thereby guiding the nearly unidirectional tissue elongation of the body axis. In addition, this study tests the role of functional proteins that determine physical properties of cells (e.g., actin, non-muscle myosin II and N-cadherin) in the control of the solid-like and fluid-like tissue states. This research will provide new insights on potential diagnostic tools for diseases affecting the formation of the body axis, such as scoliosis, and inform bioengineering applications aimed at engineering tissues and organs.

In another collaboration with German investigators, researchers aim to define the molecular mechanisms by which developmentally important RNA-binding proteins select their target mRNAs and control their expression to affect specific cell-fate decisions, and to understand how defects in these processes contribute to cell dysfunction and organismal disease. Branch-funded U.S. investigators, in collaboration with colleagues in Germany, are functionally manipulating one such essential RNA-binding protein in frog embryos and identifying the cellular and molecular consequences. Together, they have discovered a critical role for this protein in controlling the events of left-right patterning in vertebrate embryos. Their results also provide new insights into the critical, but poorly understood, regulation of organ position within developing organisms.

Israel ([5F32GM145036-02](#)). A branch-funded 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 (linker cell-type death [LCD]) also occurs in vertebrates, and is characteristic of neuronal degeneration in polyglutamine diseases in the human. This work hopes to identify signaling pathways involved in LCD and determine relevance to mammals using cell lines from University of Haifa, Israel. Although no funds are going to the University of

Haifa, and all the work will be performed within United States, the collaboration is critical to advancing this line of research.

Italy (HD102614-02). Congenital anomalies are a leading cause of morbidity and mortality worldwide, accounting for the deaths of 330,000 newborns every year. Among these anomalies, brain malformations seem to be the most common and represent a major cause of death and lifelong disability. In most cases, the cause of the brain malformation remains uncertain, due to the complexity and the multigenic origin of these anomalies. Genes that encode transcription factors and epigenetic regulators have become potential causal candidates given the central role of these proteins in integrating signaling cascades and orchestrating multiple biological processes. Deficiency in their function may disturb entire transcriptional programs, involving several genes and molecular pathways. U.S. researchers, working with collaborators in Italy, are combining mouse genetics and epigenomic approaches to uncover the role of PRDM15, a previously unsuspected, disease-associated epigenetic regulator, in congenital brain malformations. When the investigators functionally characterized PRDM15 downstream effectors (e.g., NOTCH and WNT/PCP pathways) in patients with brain malformations (i.e., holoprosencephaly and microcephaly), they found mutations in underappreciated genes. PRDM15 is, thus far, and uncharacterized critical regulator of embryonic development, meaning knowledge of the downstream regulated pathways will be useful to the field of regenerative medicine and could have diagnostic and clinical implications for patients with holoprosencephaly and microcephaly. Given the multigenic origins of brain malformations, targeted sequencing of PRDM15 and its key downstream targets could be added to routine genetic testing in at-risk families, including those carrying other holoprosencephaly-causing mutations (e.g., SHH, ZIC2, TGIF).

New Zealand (HD108921-01). Complex morphogenetic processes, often requiring various combinations of cell migration, proliferation, invasion, and fate acquisition, are required for proper organismal development. The coordination of these processes must be tightly regulated, as dysregulation of these processes can lead to developmental disorders and disease states. One U.S.-based PI, in collaboration with colleagues at the University of Otago in Dunedin, New Zealand, turned to zebrafish as a model system to study these processes. In zebrafish, morphogenesis of midline tissue structures, such as the notochord, floor plate, and hypochord, drive axis elongation of the developing embryo, and structural tissues are derived from a population of progenitors, known as midline progenitor cells (MPCs), which reside in the tailbud. MPCs undergo a morphogenetic process called Convergent Extension (CE), in which adjacent MPCs migrate and intercalate between one

another, to give rise to the notochord. MPCs rely on local signaling cues, such as Wnt and Notch, to adopt a notochord, floor plate, or hypochord fate. These signaling pathways are known to regulate morphogenetic cell behaviors, but growing evidence suggests that the cell cycle can also modulate cell behaviors; however, the mechanisms by which cell cycle state dictates cell behavior and cell fate during tailbud morphogenesis remain unclear. The study addressed this gap in knowledge and seeks to elucidate the relationship between cell cycle state and cell fate/morphogenesis during development within this context as a model.

United Kingdom. Researchers have engineered a group of mutant mouse embryos to carry precise mutations in a special category of regulators, called epigenetic regulators, which are essential for mammalian development. Mutations in components of this machinery are implicated 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, submitted in response to an NIH initiative, is required to submit its data generated to the European Molecular Biology Laboratory (EMBL)/European Bioinformatics Institute (EBI-UK), supported by the [NIH Knockout Mouse Phenotyping Program-2 (KOMP2)](). Coordination of data submission does not involve payment for any foreign collaborators, and the use of foreign resources is restricted to databased managed by EBI staff. The PI anticipates that this coordination could lead to co-authored publications in the future.

Recent Achievements in Global Health

N/A

Global Health 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 supports research and research training programs to enhance 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 male and female fertility.

Major Global Health Initiatives over the Past Year

Artificial Intelligence (AI) and Assisted Reproduction Technology (ART) (HD104969). Almost 2 percent of babies in the United States are born from ART each year. To avoid high-risk twin (or higher multiple) pregnancies that could jeopardize the pregnant person or the pregnancy, choosing the single "best" embryo to implant is critical in ART success. To date, however, there is little to no scientific rationale to guide the decision. FIB supports research to create a clinical decision-support system that will improve embryo selection in ART. Scientists in the United States and Israel are developing deep learning models for embryo quality based on visual parameters, to be matched with patients' electronic health records. The goal is to develop computational models that score embryos on their viability so that ART clinicians can use a validated, data-driven process to choose embryos with the best chance of implantation and viable pregnancy.

Polycystic Ovary Syndrome (PCOS) in Diverse Populations (HD100812). Up to 15 percent of U.S. women have PCOS and experience infertility, obesity, and diabetes associated with the syndrome. Current diagnostic criteria vary because they are based on the presence of particular symptoms, rather than on an understanding of the underlying disease mechanisms. Although current hypotheses suggest that many genes contribute to PCOS, it is believed that women with certain constellations of reproductive and metabolic phenotypes, which result from variations in PCOS-related genes, actually have a PCOS subtype. An FIB-funded study involving researchers from the United States, the United Kingdom, the Netherlands, and Korea is testing this hypothesis to determine whether African American, Hispanic, and East Asian women have a distinct subtype of PCOS.

Health of Children Born From In Vitro Fertilization (HD112081). Since the birth of the first child from in vitro fertilization (IVF) in 1978, more than 10 million babies have been born from this technology. Research shows that IVF-conceived pregnancies and resulting children have a greater risk for a range of adverse outcomes. The United Kingdom tracks individuals treated with, and children

conceived through IVF, as far back as 1991, with linkages to other national health databases. While the United States has more annual IVF cycles and births, and greater racial and ethnic diversity than the United Kingdom, U.S. IVF databases are far from comprehensive. An FIB-funded study led by a team of U.S. and United Kingdom scientists will evaluate the growth and health of children of more than 458,000 children born from IVF, from conception through childhood in the United States, and from conception through adulthood in the United Kingdom. Outcomes include incidences of congenital anomalies and cancer in the children, with analysis of epigenetic contributors, and the effects of different IVF protocols on child size at birth, height and weight across development, and acute and chronic illness or mortality. The results will provide a thorough assessment of child health after conception by IVF.

Global Health Collaborations in Fertility and Infertility Research ([HD092499-04](#), [HD106968-01A1](#), [HD109721](#), [HD100812](#), [HD108809](#)). In the past year, FIB-funded investigators collaborated with scientists from Argentina, Chile, Italy, Japan, Korea, Mexico, Netherlands, Sweden, and the United Kingdom to advance research related to the branch mission.

Collaborators provided key animal models (such as Crispr mice), patient cohorts (such as genetically diverse women with PCOS), and technical expertise (such as cDNA electroporation into sperm cells, measurement of sperm movement in 3D, and single mouse embryo RNA-seq).

Recent Achievements in Global Health

N/A

Global Health Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

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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, PCOS, pelvic floor disorders, and gynecologic pain syndromes. Global health activities include support of research on obstetric fistula and female genital mutilation.

Major Global Health Initiatives over the Past Year

Obstetric Fistula (OF) (HD106002-02, HD086232-05, HD108236-01). OF is a debilitating injury resulting from obstructed labor that leads to 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 successful surgical treatment is often available, women with OF may not be reintegrated into their communities even after treatment. GHDB currently supports several studies regarding risks and therapies for OF in sub-Saharan African communities. These include the following:

- *Addressing critical gaps in knowledge on risk of adverse outcomes following OF repair.* This longitudinal cohort study of 800 women who received OF repair at one of nine Ugandan facilities hopes to identify predictors of post-repair fistula breakdown and recurrence, identify predictors and characteristics of post-repair incontinence, and engage key stakeholders in a theory-guided iterative process, eventually developing a roadmap of intervention strategies likely to be feasible and acceptable within this setting.

- *Assessing the long-term mental health and physical sequelae of OF surgery.* This study follows women who have had surgery for OF to determine predictors of reintegration success after surgical repair in a Ugandan population. A novel post-surgical reintegration intervention for these women and their households, will follow this work, with subsequent pilot testing for feasibility, acceptability, and impact on reintegration success.

- *Quantifying the effectiveness of a non-surgical insertable vaginal cup to manage OF urinary incontinence.* This work will also examine user and implementer acceptability, as well as quantify fistula management cost at two care centers in Ghana. The researchers hope the cup provides an acceptable non-surgical option for therapeutically managing fistula-related

urinary incontinence in those faced with substantial multilevel barriers to surgical repair.

Female Genital Cutting (FGC) ([HD091685-05](#)). FGC (a.k.a., female circumcision or female genital mutilation) is a cultural/religious/social practice that involves removal of 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, may be conducted on young girls up to age 15 years and can result in obstructed labor, chronic vulvar/vestibular pain, urination problems, and sexual dysfunction, as well as death from unclean practices. The WHO estimates that more than 125 million girls and women alive today have undergone this procedure. Recent immigration patterns have contributed to a large increase in the number of U.S. girls and women who have undergone FGC. Because there are still immigrant communities carrying out this procedure, it may be performed either abroad or domestically, making FGC both an international and domestic area of research interest for the branch.

One GHDB-funded study is investigating factors that contribute to an increased risk of chronic sexual pain among Somali American women living in Minnesota who have had FGC. The effort will gather information that may help mental health and medical professionals provide culturally sensitive and empirically informed health care for these women.

Vulvodynia ([HD099533-02](#)). Although some therapies can help relieve symptoms of vulvodynia—defined as chronic pain or discomfort of the vulva—condition can have some serious effects on women's reproductive health and day-to-day life. GHDB-funded researchers are conducting a case-control study of women within the Swedish National Registry who have a specific vulvodynia diagnosis. This natural history study capitalizes on the 15-year birth cohort that meticulously tracks health data for all females born in Sweden. To further our understanding of the pathogenic mechanisms underlying vulvodynia in women aged 15 to 35 years, researchers aim to assess the effects of: 1) maternal and neonatal events and antibiotic use; 2) immune-specific conditions from infancy up to onset of vulvodynia; and 3) diagnosed psychiatric conditions on the risk of vulvodynia development.

Recent Achievements in Global Health

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- El Ayadi AM, Nalubwama H, Miller S, Mitchell A, Korn AP, Chen CCG, Byamugisha J, Painter C, Obore S, Barageine JK. Women's sexual activity and experiences following female genital fistula surgery. *J Sex Med. 2023 Apr 27*;20(5):633-644. doi: 10.1093/jsxmed/qdad010. PMID: 36892111; PMCID: PMC10149378.

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Global Health 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 disabilities (IDDs). 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 branch 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, Attention Deficit/Hyperactivity Disorder (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 Global Health Initiatives over the Past Year

Gene and Variant Curation ([HD112205-01](#) and [HD108087-01A1](#)). 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 funding opportunity in 2017 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. In 2020, four other NIH ICs joined NICHD in funding these gene and variant curation expert panels (NCI, National Eye Institute [NEI], NIMH, and NINDS). To date, 17 expert panels have received NIH funding. In fiscal year 2023, NICHD-funded expert panels included international experts spanning six different countries to curate genes and variants involved in congenital forms of monogenic diabetes and variants involved in urea cycle disorders. NICHD reissued this funding opportunity in 2023 in partnership with six other NIH ICs: NCI, National Center for Advancing Translational Sciences (NCATS), NEI, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute on Deafness and Other Communication Disorders, and NINDS.

Down Syndrome (DS). 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 DS 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® registry has attracted over 5,905 registrants in the United States and abroad and has supported recruitment for over 100 research projects through its membership. International partners include Down Syndrome International, Trisomy 21 Research Society, 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 worldwide. The DS-Connect website is also fully responsive to facilitate access on a wide variety of platforms. The registry includes a Medication Tracker, which allows participants to enter information about medication and supplement use in people with DS to help inform research and future clinical drug trials. The website recently incorporated functionality enabling users to more easily search for NIH-supported

active and recruiting clinical research on DS. Currently, the registry is incorporating culturally appropriate images and inclusive language to encourage participation from families of diverse backgrounds.

The INCLUDE Project ([5R01HD088125-05](#) and [5R01HD109307-02](#)). The NIH-wide [INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) Project](#) launched in 2018 to investigate conditions that affect individuals with DS 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 DS across the lifespan and promoting clinical trials to treat co-occurring conditions in DS; several studies include international populations from Europe and West Africa, including:

- 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 DS, other developmental disabilities (ASDs and Fragile X syndrome), and in 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 DS. This effort builds on the Infant Brain Imaging Study project, which studies younger 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 includes a data coordinating center at the Montreal Neurological Institute in Canada.

- Another collaboration, funded by the INCLUDE Project, between investigators in the United States and Zambia seeks to identify and characterize rural Zambian children and youth who have developmental disabilities (DD), including epilepsy, intellectual disability, vision and hearing problems, and genomic syndromes, such as DS. The researchers plan to recruit 2,000 children and matched siblings (3 to 18 years old) who have DD and to utilize assessments of cognitive ability, academic achievement, and adaptive behavior, as well as neural, sensory, and physiological indicators. Investigators will also access medical records and conduct neurophysiological assessments (Electroencephalogram [EEG]/Brain-evoked Related Potentials [ERP] and Functional Near-Infrared Spectroscopy [fNIRS]) and genotyping to deeply characterize these children. Through interviews and focus groups, they will also collect qualitative data from parents and

important community stakeholders to obtain information about locally held beliefs about DD, as well as the potential etiology of DD. The prevalence of DS is also not well ascertained in sub-Saharan African population. This study has the potential to fill a knowledge gap about the prevalence and etiology of different types of DD among children and youth in rural Zambia and identify barriers to services.

Alzheimer's and DS ([5U19AG068054-04](#) and [5R33AG066543-04](#)). Another project, known as the [Alzheimer's Biomarkers Consortium-Down](#) [Syndrome (ABC-DS)](#), is evaluating adults with DS 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 DS. This activity, 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 is recruiting a trial-ready cohort of adults with DS in France to study medications that prevent and/or treat Alzheimer's in this population.

Sex Differences ([HD100298-04](#)). Humans exhibit substantial variation in age-dependent sex differences across a variety of disorders and other domains (e.g., motor, language, and social skills). A collaboration between researchers in United States and at the University of Oxford, United Kingdom, is examining how gonadal hormones and X and Y chromosomes impact sex differences in homologous neural structures in mice and humans. These findings can improve our understanding of the trajectory of sex differences within the context of age, including timing of sensitivity to the impact of hormones and sex chromosome dose. Similarly, by providing data on commonalities between mice and humans, these findings can guide translational mouse studies at a level not possible in humans, aimed at understanding human sex differences in morphology and disease disparity. For instance:

- Employing a novel sex chromosome trisomy mouse model to examine the effects of gonadal status and sex chromosome complement on the emergence of sex differences

- Using a single-cell RNAseq to determine sex differences in gene expression patterns and genetic pathways

- Applying high-throughput and bioinformatic approaches to analyze large amounts of data

- Generating a 4-D map of brain development, focused on sexually dimorphic brain regions and nuclei, to uniquely benefit fields dependent upon accurate developmental brain maps, not just those examining sex differences

Inborn Errors of Metabolism (HD105934-02). A U.S.-India research collaboration proposes to develop synthetic enzymes for the treatment of inborn errors of metabolism associated with branched-chain amino acids (BCAAs), such as maple syrup urine disease and isovaleric acidemia. Under the current standard of care, which is difficult to adhere to and requires close monitoring to avoid crises, the quality of life of patients remains poor. Successful engineering of high-activity ammonia-lyase enzymes able to reduce high systemic concentrations of the BCAAs in patients would be a major advance in the management of these diseases.

Autism Spectrum Disorders (ASDs). The branch supports multiple studies (including HD107528-02 and HD098883-05) on aspects of ASD risk in collaboration with different global institutions, including:

- A research collaboration between the United States and University of Haifa, Israel, will examine the association of prescription and over-the-counter medication use during pregnancy with risk of ASD in offspring. The research group in Israel will provide a data resource—with information on pharmacological exposures, psychiatric, and medical history, and demographic and familial relations data—on this population-based epidemiological cohort from health registers in Israel. The study will examine, in detail, how exposures to medications in pregnancy modify the offspring's risk for ASD.

- The substantial variability in the presentation of ASD is a key barrier in early diagnosis and in developing and evaluating effective treatments for the disorder. A research collaboration between United States and University of British Columbia, Canada, plans to utilize a multimodal approach to examine whether and how the co-occurrence of anxiety and ADHD in children with ASD contributes to behavioral, cognitive, and neurophysiological outcomes. Dr. Kerns at the University of British Columbia created an adapted version of the Anxiety Disorders Interview Schedule (ADIS)/Autism Spectrum Addendum (ASA). He also has a strong record of conducting research on anxiety in ASD as a remotely located coinvestigator or consultant and, specifically, in training and conducting quality assurance checks of diagnosticians using the ADIS/ASA at other research sites.

- This research collaboration between the United States, Aarhus Universitet, Denmark, and Karolinska Institutet, Sweden, will use large national registry datasets from Demark and Sweden to examine the relationship between maternal cardiometabolic conditions (CMCs) during pregnancy and the risk of ASDs in the offspring. By leveraging data on over 1.5 million pregnancies (about 25,000 with ASD offspring), the Autism Risk and maternal Cardiometabolic Health (ARCH) Study hopes to determine the role of maternal CMCs and related familial and genetic factors in ASD etiology. Research groups in Denmark and Sweden will provide information on multigeneration familial relations, psychiatric and medical histories, and demographic and other data for these population-based epidemiological cohorts.

Succinic Semialdehyde Dehydrogenase Deficiency (SSADHD) Disorder (HD091142-01A1): A Research Collaboration. Children's Hospital, Germany, is studying the natural history of the SSADHD disorder, a rare heritable disorder of GABA metabolism. To characterize the course of the disease, researchers will perform comprehensive yearly assessments of biochemical, neurophysiological, and clinical biomarkers for 5 years. In addition, the researchers will develop a blood-spot GABA assay for future screenings. This work is highly significant because it could improve our understanding of the prognostic value of neurophysiological and biochemical markers of the disease. A validated GABA assay suitable for high-throughput newborn screening platforms could eliminate barriers to early detection and facilitate the establishment of disease prognosis and the assessment of the efficacy of novel therapeutics.

Folic Acid Supplementation (HD107489-02). There is growing evidence that excessive folic acid can produce negative outcomes with respect to fetal brain development and a possible association with ASDs. A research collaboration between the United States and University College London, United Kingdom, is exploring the consequences of excess folic acid supplementation, with and without vitamin B12 deficiency, on neurodevelopmental and behavioral outcomes. This work will also correlate these changes with DNA methylation patterns and with the expression of key folate enzymes and of folate and vitamin B12 status indicators. Efforts to explore any connections between folic acid and ASDs more directly, in a preclinical model, are of important mechanistic and translational significance.

Also, due to mandatory food fortification with folic acid and increased use of multivitamin supplements, certain groups in the U.S. population and worldwide

consume more folate than may be optimal to support health, adding to the study's timeliness and importance.

Hypoxic Ischemic (HI) Insult/Injury ([HD074593-11](#)). A collaboration between U.S. researcher and investigators at the University of Eastern Finland is developing novel in vivo MRI methods to examine tissue microstructure and neuronal activity in the progression of HI insult/injury, and the effects of therapeutic hypothermia, in a neonatal mouse model. Hypothermia is the standard of care for newborns with neonatal HI issues; its protective mechanisms are not clearly understood, but are assumed to include reduction in cell swelling, inflammation, and vasogenic edema, and possible delay of the pseudo-normalization process. The team is examining the sensitivity of novel diffusion-MRI (dMRI) techniques to identify tissue microstructural changes caused by HI injury. Preliminary results suggest that the proposed techniques can more sensitively detect mild brain injuries than conventional dMRI techniques, while being less susceptible to confounding pseudo-normalization than conventional dMRI signals. The researchers plan to optimize the imaging protocols to detect key structural changes after neonatal HI insult.

Noonan Syndrome ([5R01HD108684-02](#)). Noonan syndrome is a rare genetic disorder that can affect brain and physical development and cause neurodevelopmental disorders. A research collaboration between researchers in the United States and Rome, Italy, aims to assess the effects of mutations in three distinct genetic subtypes (RAF1, PTPN11, and SOS1) of Noonan syndrome on striatal and brain structure/ connectivity and on attentional abilities using brain imaging approaches and psychological testing in children/adolescents. Researchers propose using Noonan syndrome (1:2000) as a human model system to provide critical data on the effects of Ras/mitogen-activated protein kinase genetic alterations on the human brain and systems-level biology.

Understanding the Long-Term Outcomes of In Utero Zika Virus Exposure ([HD093572-05](#)). The extensive outbreak of Zika in Brazil during 2015 and 2016 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. 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 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 Global Health

Brain Disorders in the Developing World: Research Across the Lifespan Initiative (HD096521-01A1, HD096559-05, HD093570-04, HD106277-03, HD102975-03, HD036071-24A1). IDDB participates in this FIC-led initiative to enhance research to ameliorate IDDs in LMICs:

- A U.S.-Guatemalan research collaboration will identify IDDs in children that result from stunting, in which growth and development processes are hindered. The study includes a cohort of at-risk children, birth to 6 months of age, who will use wearable sensors. Researchers will use measurements from these sensors to determine the relationship between earliest spontaneous limb movements and developmental outcomes at 12 months of age. The researchers hope to determine whether wearable sensor assessment is more accurate than current clinical assessments at predicting developmental outcomes in at-risk infants. A related multidisciplinary project—involving pediatric medicine, physical therapy, and biostatistics—will help build research capacity through a partnership between the University of Southern California and the Maya Health Alliance in Guatemala.

- A research collaboration between U.S. and Ugandan investigators supports a clinical trial to evaluate the effectiveness of hydroxyurea for preventing cognitive defects in Ugandan children with sickle cell vasculopathy. The trial builds on findings from an NICHD-funded pilot study, which found that children in Uganda were particularly vulnerable to brain injury due to the combination of sickle cell disease, anemia, malnutrition, and infection.

- A collaboration between investigators in the United States and India will use whole-exome sequencing (WES) technology to investigate genetic causes of inherited NDDs, which occur with high incidence among children in LMICs. This research collaboration will test and adapt tools to optimize analysis and reanalysis of WES data, thereby streamlining variant identification, annotation, and interpretation by research scientists and medical professionals, while also building research capacity in India. The researchers will then use these tools to build an integrative outreach portal through which de-identified population-specific genetic data will be publicly available. This data resource could allow other LMICs to adopt the lessons learned by this team and could facilitate the integration of genetic counseling into global clinical practice.

- Epilepsy is a significant health problem in Uganda, but its associated stigma and discrimination often lead to delays in accessing needed health care. A 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 is using a multipronged approach, including deep clinical phenotyping to characterize disease severity and comorbidities, and surveys to assess the magnitude and impact of stigma, with a long-term goal of improving affected individuals' psychosocial and functional outcomes.

- African individuals are severely underrepresented in genetic studies of NDDs, including IDDs, ASDs, and attention disorders. A collaboration between researchers at Harvard University, University of Oxford, and the Kenya Medical Research Institute, Kenya, will conduct phenotypic characterization and collect biological samples from children (ages 2 to 17 years) and adults with NDDs residing in Kilifi and Mombasa counties in Kenya for genetic studies. The NeuroDev Kenya data set will be the first large-scale data collection of its kind, providing an unprecedented opportunity to study the etiology of NDDs in East Africa, and creating a valuable international research resource.

- Existence of a correlation between the size of the *FMR1* CGG repeat and the rate of clinical progression of Fragile X-Associated Tremor Ataxia Syndrome (FXTAS) manifestations is currently a critical unanswered question in FXTAS and *FMR1* research. A longstanding prospective cohort study is quantifying the progression of FXTAS, through recurrent long-term assessment of biomarkers and clinical outcomes, to address this question. Although the largest portion of participants are in the United States, research collaborators at La Trobe University in Melbourne, Australia, is also recruiting an independent validation sample to help increase the generalizability of clinical findings across multiple, diverse populations.

Mobile Health (mHealth): Technology and Outcomes in LMICs (HD102988-01A1). IDDB participates in this FIC-led initiative to encourage exploratory and developmental research applications on the development, validation, feasibility, and effectiveness of innovative mHealth interventions or tools that are specifically suited for LMICs and that utilize new or emerging technology, platforms, systems, or analytics.

A first-time collaboration between FIC and the INCLUDE Project will support a study in the DRC on mHealth intervention tools that use facial recognition software to screen for syndromic congenital anomalies, with a focus on DS. This partnership between Institut National de Recherche Biomédicale, a DRC national research institute, and Children's National Hospital in Washington, D.C., will create the infrastructure of a Birth Defects Registry, allowing for future surveillance and intervention programs in low-resource settings. 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 DS 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 NIH-wide INCLUDE Project, further increasing NIH's investment in DS research internationally.

DS-I Africa. IDDB is funding a data science collaboration as part of NIH Common Fund's [Harnessing Data Science for Health Discovery and Innovation in Africa (DS-I Africa) program](). The project between researchers at South Africa (WITS Health Consortium) and DRC (Center for Human Genetics) will use clinical information, genetic data, and DNA resources from the [Deciphering Developmental Disorders (DDD)-Africa study]() to increase diagnostic yield and make new discoveries about the causes of NDDs in African people. This work will further increase health data science capacity in Africa and create an ecosystem that can provide local solutions for rare diseases, such as NDDs, in Africa.

Rare Diseases Research ([HD070855-10]()). 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 within 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.

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 during childhood with early onset diabetes, optic nerve atrophy, and deafness, and that is usually fatal during early to

mid-adulthood. With the identification of the causative gene, investigators have discovered a broader range of phenotypes. Through a partnership with investigators in the United Kingdom, the research team hopes to increase the number of children enrolled in the study to better understand the neuropathophysiology of this disorder and identify potential targets for brain-specific interventions.

Global Health 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 people. 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, hepatitis, sexually transmitted infections (STIs), 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-related projects in 70 countries through a wide variety of grant programs. For more information about the branch, please visit the [MPIDB webpage](#) and [subscribe to our branch newsletter](#).

Major Global Health Initiatives over the Past Year

Study of Tecovirimat for Human Monkeypox Virus (STOMP) ([NCT05534984](#)). To address the 2022 monkeypox (mpox) outbreak, HHS and NIH initiated STOMP, a randomized, placebo-controlled, double-blinded trial of the safety and efficacy of tecovirimat (TPOXX) for the treatment of human mpox. This international multicenter, Phase 3 clinical trial is being conducted in Brazil, Mexico, Peru, and South Africa, in addition to the mainland United States and Puerto Rico through the [AIDS Clinical Trials Group](#) [(ACTG)](#) and [International Maternal Pediatric Adolescent AIDS Clinical Trials](#) [(IMPAACT) Network,](#) in which NICHD supports several participating sites. STOMP randomizes participants with mpox to either tecovirimat or placebo to compare clinical efficacy (time to clinical resolution of skin and visible mucosal lesions). It will also evaluate the safety profile of tecovirimat in children younger than 18 years of age and determine PK in pregnant women and in children younger than age 18 years. It is one of the first studies of tecovirimat to date that includes pregnant women or children.

[Multisystem Inflammatory Syndrome in Children (MIS-C)](HD105593-03S2).
Early in the pandemic, it seemed that children were less likely than adults to get SARS-CoV-2 and, if infected, most had only mild to moderate illness. As the pandemic continued, MIS-C began to surface as a rare but serious condition in children across the world. The severity of MIS-C followed trends similar to adults, with severity increasing in the presence of comorbidities, such as obesity. World reports linked MIS-C cases and deaths to a previous SARS-CoV-2 viral infection, and most MIS-C cases presented in school-age children. MIS-C is now characterized as rare childhood condition linked to COVID-19 infection with a spectrum of inflammatory processes, including features like Kawasaki disease, specific to children. Given the rise in child cases and deaths, MPIDB/NICHD leads an NIH-wide initiative to support the development of laboratory diagnostics integrated with digital health technologies and AI-based algorithms to rapidly diagnose and characterize SARS-CoV-2 associated illness in children, including MIS-C, and to predict disease severity. This initiative, called [Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIds)](#), is part of the NIH-wide [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 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 populations of interest. Areas of research supported by NICHD relevant 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 this FIC-funded program to support predoctoral (Scholars) and postdoctoral (Fellows) trainees from the United States and from partner institutions in LMICs by providing a year of mentored research at an established U.S.-based or comparable academic institution in an LMIC. Several NICHD-selected candidates, including one new fellow as of 2023, are working on HIV/AIDS research and on topics aligned 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 previous sections, NICHD participates in the DS-I Africa Initiative, led by the NIH Common Fund, to leverage data science technologies and prior NIH investments to develop solutions for Africa's most pressing public health problems. In October 2020, NICHD organized a Maternal and Child Health Panel on Innovative Data Science Approaches to Improve Maternal and Child Health; a recording of the panel is available. MPIDB also contributed to the funding of a DS-I U54 research hub focused on the Role of Data Streams In Informing Infection Dynamics in Africa—INFORM Africa.

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) and was a major component of the AIDS Clinical Trials Group protocol 076 study (ZDV to prevent mother-to-child HIV transmission), the first demonstration that antiretroviral chemoprophylaxis can prevent HIV transmission, noted as "one of the seven great achievements in pediatric research in the past 40 years" (PMID: 27556199). 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 IMPAACT Network, ACTG, and the Tuberculosis Trials Consortium.

Tuberculosis (TB) (NCT03568383). Within the IMPAACT network, NICHD-supported sites in Tanzania, Uganda, and Thailand participate in the ACTG PHOENIx study (Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Participants), which includes multiple international locations. This study compares the safety and effectiveness of 26 weeks of delamanid, a newer medicine, versus 26 weeks of isoniazid, a standard medicine to treat or prevent TB, for preventing TB in high-risk household contacts, including children younger than under age 5 years, of persons with multidrug resistant TB.

International Epidemiologic Databases to Evaluate AIDS (IeDEA). IeDEA, co-funded by NIAID, NICHD, NIMH, NIDA, National Institute of Diabetes and Digestive and Kidney Diseases, 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. These projects collect data pertaining to over 180,000 children living with HIV and serve as an example for how such data can enable large multiregional studies to evaluate the effects of HIV and its treatment on children in resource-limited countries. Furthermore, these data continue to inform United Nations AIDS (UNAIDS) estimates of the global pediatric HIV epidemic. Data from IeDEA pediatric analyses are also critical to informing the WHO guidelines on pediatric treatment.

Zika in Pregnant Women, Infants, and Children. MPIDB/NICHD has coordinated and co-funded three epidemiologic cohort studies in Latin America and the Caribbean to investigate the risks and outcomes of Zika infection during pregnancy. Follow-up of study participants is now complete and data analysis is ongoing. Zika in Infants and Pregnancy (ZIP) is an international prospective observational cohort study that enrolled over 6,000 pregnant women and followed 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 with infant follow-up through baby's first year. Data for the HIV ZIP study are available in the NICHD Data and Specimen Hub (DASH).

Reducing Stigma to Improve HIV/AIDS Prevention, Treatment, and Care in LMICs. In collaboration with FIC, the 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.

Recent Achievements in Global Health

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, STIs, and TB in children, adolescents, and pregnant and non-pregnant people. These international studies are occurring in several countries, including but not limited to Brazil, Botswana, Kenya, Malawi, Mozambique, Nigeria, South Africa, Thailand, Uganda, Zambia, and Zimbabwe.

Emergency Awards: RADx-rad PreVAIL kIds ([RFA-OD-20-023](#)). Despite substantial numbers of children becoming infected with SARS-CoV-2 globally, early in the pandemic, the risk of severe disease or mortality was thought to be a concern exclusively for adults and the elderly. 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, increased attention to the varied pediatric manifestations of the infection and its post-infection complications. To address these and other vital questions, PreVAIL kIds was developed as an emergency phased-innovation funding opportunity announcement administered by NICHD in collaboration with other NIH ICOs (NIH OD, NHLBI, NIAID, NIAMS, NIDA, National Institute of Minority Health and Health Disparities [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 identifying and characterizing the spectrum of SARS-CoV-2 associated illness, including MIS-C. 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, is also part of this initiative to properly tailor management and optimize health outcomes. NIH funded eight studies to uncover risk factors for COVID-19-related inflammatory syndrome in children. Visit https://www.nichd.nih.gov/newsroom/news/122120-prevail-kids for details.

[Prevention and Treatment through a Comprehensive Care Continuum for HIV-affected Adolescents in Resource Constrained Settings (PATC³H)](#) ([RFA-HD-18-032](#)). MPIDB/NICHD issued this Request for Applications (RFA) in fiscal year 2018, in collaboration with NIMHD and the NIH Office of Behavioral and Social Sciences Research (OBSSR). These eight, large, cooperative agreements are supporting research projects in South Africa, Kenya, Nigeria, Uganda, Zambia, Mozambique, and Brazil, to prevent HIV acquisition among at-risk youth and maintain their status without HIV. Studies also are enrolling youth with HIV into treatment interventions to improve their health and prevent transmission to others. As a collective, the

projects in PATC³H seek 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. All eight grants have successfully met milestones and transitioned to large scale testing through randomized controlled trials (RCTs) and demonstration projects. Through the engagement and leveraging of multilateral relationships with local and national stakeholders, the foundations are in place for possible scale-up and sustainment of interventions in these regions should they be found effective. The results of a study looking at the demographic, biomedical, psychosocial, and behavioral characteristics of adolescents and young adults living with HIV in Nampula, Mozambique are available in the NICHD DASH: https://dash.nichd.nih.gov/study/416291.

In 2022, NICHD, in collaboration with NIDA, NIMHD, NIMH, OBSSR and FIC, published two RFAs (RFA-HD-23-013 and RFA-HD-23-014) intended to form the PATC³H-Implementation Science Network (PATC³H-IN) to expand and/or improve successes achieved by PATC³H to new geographic areas and new populations affected by HIV. NICHD issued a new RFA (RFA-HD-24-009) in 2023 for an Implementation Science Coordinating Center (ISCC) to establish infrastructure to support research education and capacity building across PATC³H-IN. The ISCC will complete the PATC³H-IN, which consists of interdependent functional components: 1) Clinical Research Centers, (2) a Coordination and Operations Center, (3) the ISCC, and (4) a Scientific Leadership Committee.

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 to demonstrate the capacity to enroll HEU infants, children, adolescents, and young adults in clinical studies; and utilize innovative epidemiological approaches to assess overall health in the established cohort. 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 utilizing robust platforms of linked maternal-child data, augmented by new recruitment, to answer life-course questions about HEU populations, and establishing and sustaining a life-long evaluation model of in utero and postnatal

HIV and ARV exposure. For more information on the five awarded projects check out the Science Highlights section of the MPIDB's [Research for Reducing Health Disparities](#) newsletter.

NICHD, in collaboration with the International AIDS Society/Collaborative Initiative for Paediatric HIV Education and Research, WHO, Paediatric-Adolescent Treatment Africa, the Pediatric HIV/AIDS Cohort Study, and others organized the [9th Workshop on Children and Adolescents with Perinatal HIV Exposure](#) in 2023. The workshop presented up-to-date evidence on child neurodevelopmental outcomes following perinatal HIV exposure, as well as a discussion on identifying and supporting families to thrive.

Utilizing Archived Data and Specimen Collections to Advance Maternal and Pediatric HIV/AIDS Research (**RFA-HD-19-018**, **RFA-HD-20-020**, **RFA-HD-21-030**). To build upon original research, these announcements supported secondary analyses of archived HIV/AIDS data and specimen collections. 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 included TB immune responses in women living with and without HIV, 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. The initiative was reissued in 2022 (**RFA-HD-24-006**) to sustain investments in the utilization of archived HIV data and biospecimen collections.

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 ICOs, including NICHD, encouraged applications for research training programs to strengthen the scientific capacity of institutions in LMICs for conducting HIV research relevant to the evolving HIV epidemic in their country. NICHD-supported training programs include several focus areas, such as implementation science, mental health, microbiology and immunology, bioinformatics, drug resistance and pathogenesis, comorbidities, and community-based research in women, children, and adolescents. This program supports research in the following LMICs: Malaysia, Kazakhstan, Eswatini, Mozambique, South Africa, Mali, Nigeria, Vietnam, 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; 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 additional funding 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 NIH ICOs 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 on 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 ICs, and the Office of the Global AIDS Coordinator released the RFA for this initiative in fiscal year 2016, providing supplementary funding for 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. Researchers in Kenya, Ghana, Nigeria, Malawi, Tanzania, Uganda, Zambia, Rwanda, Zimbabwe, South Africa, and Botswana received grants. This ongoing collaboration continues to inform factors driving uptake and adherence to HIV prevention and treatment strategies for adolescents and advance policy through evidence and data. An AHISA-convened forum provides the platform for further 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 PATC³H initiative, described earlier. PATC³H and PATC³H-IN benefit from leveraging expertise and collaborations from AHISA investigators and have implemented 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 and RFA-HD-18-020). After issuing this RFA in fiscal year 2018, MPIDB/NICHD awarded three grants to investigate neurodevelopment assessment among children in South Africa, Tanzania, and Botswana. The widespread implementation of combination ART for HIV prevention and treatment over the last decade changed the presentation, manifestation, and course of development and impairment in children, globally, but especially in resource-limited settings most severely affected by HIV. Noninvasive assessment of child cognitive development using neuropsychological approaches is

important for monitoring typically developing achievement, as well as emerging and continuing cognitive deficits related to HIV and its treatment.

International Health and Data and Biospecimen Sharing. NICHD's DASH offers de-identified data from NICHD-supported clinical research on a variety of topics, including 81 studies funded by MPIDB. Nine of the studies in DASH include data from international sites, while biospecimens are available from five, including the four [NICHD International Site Development Initiative (NISDI)](#) studies. As of 2023, DASH fulfilled 61 data and 13 biospecimen requests from MPIDB-supported studies.

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

- CombinADO, a Combination Intervention Strategy to Improve Health Outcomes for Adolescents Living with HIV, Protocol #2: Understanding the Characteristics and Experiences of Adolescents Living with HIV in Nampula, Mozambique, a Mixed-methods Study: https://dash.nichd.nih.gov/study/416291

- Prospective Cohort Study of HIV and Zika in Infants and Pregnancy (HIV ZIP): https://dash.nichd.nih.gov/study/424250

- Phase IV Randomized Trial to Evaluate the Virologic Response and Pharmacokinetics of Two Different Triple Antiretroviral Regimens in HIV Infected Women Initiated Between 28 and 36 Weeks of Pregnancy for the Prevention of Mother-to-Child Transmission (P1081): https://dash.nichd.nih.gov/study/416372

- Phase III Randomized Trial of the Safety and Efficacy of Three Neonatal Antiretroviral Regimens for Prevention of Intrapartum HIV-1 Transmission (HPTN 040/P1043): https://dash.nichd.nih.gov/study/13019

- Prospective, Observational Study of HIV-Infected Pregnant Women and HEU Children at Clinical Sites in Latin American Countries (NISDI LILAC): https://dash.nichd.nih.gov/study/6

- Prospective, Observational Study of HIV-Exposed and HIV-Infected Children at Clinical Sites in Latin American and Caribbean Countries (NISDI Pediatric): https://dash.nichd.nih.gov/study/2

- Prospective, Observational Study of HIV-Infected Pregnant Women and Their Infants at Clinical Sites in Latin American and Caribbean Countries (NISDI Perinatal): https://dash.nichd.nih.gov/study/5

- NISDI Pediatric Latin American Countries Epidemiological Study: A Prospective, Observational Study of HIV-infected Children at Clinical Sites in Latin American Countries (NISDI PLACES): https://dash.nichd.nih.gov/study/3

- 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): https://dash.nichd.nih.gov/study/20027

Selected Publications with Global Health Collaborators

- Obungoloch J, Muhumuza I, Teeuwisse W, et al. On-site construction of a point-of-care low-field MRI system in Africa. *NMR Biomed. 2023;36*(7):e4917. doi:10.1002/nbm.4917. PMID: 36914258.

- Mulkey SB, Peyton C, Ansusinha E, et al. Preschool neurodevelopment in Zika virus-exposed children without congenital Zika syndrome. *Pediatr Res. 2023;94*(1):178-184. doi:10.1038/s41390-022-02373-5. PMID: 36446920.

- Marwa MM, Kinuthia J, Larsen A, et al. COVID-19 vaccine hesitancy among pregnant and postpartum Kenyan women. *Int J Gynaecol Obstet. 2023;162*(1):147-153. doi:10.1002/ijgo.14773. PMID: 37036449.

- Sabo MC, Lokken EM, Srinivasan S, et al. Changes in vaginal bacteria and inflammatory mediators from periconception through the early postpartum period in a cohort of Kenyan women without HIV. *J Infect Dis. 2023;228*(4):487-499. doi:10.1093/infdis/jiad168. PMID: 37207618.

- Byansi W, Nabunya P, Muwanga J, et al. The relationship between life satisfaction, personal health, quality of life, and medication adherence among adolescents living with HIV in southwestern Uganda. *Z Gesundh Wiss. 2023;31*(7):1177-1184. doi:10.1007/s10389-021-01632-9. PMID: 37576468.

- Linnemayr S, Huang HC, Wagner Z, Onkundi FK, Mukasa B, Odiit M. Goals for Adherence with Low-cost Incentives (GOALS): a protocol for a randomized controlled trial evaluating the impact of small airtime incentives on ART adherence among young people living with HIV in Kampala, Uganda. *Trials.*

2023;24(1):511. Published 2023 Aug 9. doi:10.1186/s13063-023-07449-z. PMID: 37559069.

- Shivakoti R, Laughton B, Shafiq M, et al. Feasibility Study of a Powder-Based Supplement Intervention for a future Synbiotic Trial in Breastfed Children from South Africa. Preprint. *Res Sq. 2023*;rs.3.rs-2842773. Published 2023 May 15. doi:10.21203/rs.3.rs-2842773/v1. PMID: 37559069.

- Wara NJ, Mvududu R, Marwa MM, et al. Preferences and acceptability for long-acting PrEP agents among pregnant and postpartum women with experience using daily oral PrEP in South Africa and Kenya. *J Int AIDS Soc. 2023;26*(5):e26088. doi:10.1002/jia2.26088. PMID 37221983.

Staff Membership on Global Health Committees/Working Groups

Planning Group for the October 2022 NICHD Global Health Conference: *Socio-Ecological Factors and the Double Burden of Malnutrition Among Children and Adolescents in Low- and Middle-Income Countries*. Member: J. Moye

Point-of-Contact

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Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB)

Scientific Scope

OPPTB aims to assure that there are safe and effective therapeutics for children and for 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, in these groups. It is responsible for developing and supporting a comprehensive national effort to increase the knowledge base on how to appropriately treat disease during pregnancy, lactation, infancy, childhood, and adolescence using evidence-based therapeutic approaches, including expansion of 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 intended populations.

Because of multiple gaps in knowledge regarding the use of therapeutics in children and pregnant and lactating women, labeling of prescription drugs is inadequate and off-label use is frequent. One of the branch's major activities is implementation of the [Best Pharmaceuticals for Children Act (BPCA)](). 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 Global Health Initiatives over the Past Year

[Pediatric Trials Network (PTN)](). As part of its BPCA initiative activities, OPPTB sponsors clinical trials of drugs and other therapeutic approaches (including devices) in children and adolescents primarily through the PTN. The network maintains 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, these international sites participate primarily in clinical studies that evaluate 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 of neonatal drug development in several specific areas are underway, and plans for

harmonization activities are in progress. Many nations are represented in this effort, including Canada, England, Japan, and France, among others.

Direct Quantitation of the Circulating *Mycobacterium Tuberculosis* Peptides for Improved Pediatric TB Diagnosis and Management ([HD090927-06](#)). Diagnosing pediatric TB and evaluating its rapid response to pharmacotherapy is extremely challenging given the difficulties obtaining necessary samples and the often-poor diagnostic value of the samples. Early detection is critical to 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. OPPTB funded a project to develop a rapid blood assay for both diagnosis and treatment monitoring of active TB in children. Researchers will apply the results from this project to develop a novel tool that monitors response to TB treatment and potentially guides treatment duration. The 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 (AVB) Likely to Occur Quickly (STOP BLOQ) ([HD100929-04](#)). Complete (i.e., 3°) fetal AVB, associated with anti-SSA/Ro autoantibodies and identified in the 2nd trimester in an otherwise normally developing heart, is fatal in one-fifth of cases; those who survive require lifelong cardiac pacing. Reversal of an incomplete block is possible, but challenging to identify using standard 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 arranging immediate feedback on perceived abnormalities; and 3) treating fetuses with maternal-detected abnormal monitoring later 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 home monitoring can identify reversible fetal cardiac injury, whether expeditious treatment of incomplete fetal 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 and 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 ([HD102786-02](#)). Both pregnancy and inflammation can alter drug PK processes, such as absorption,

distribution, metabolism, and excretion. Most published studies have focused on cytochrome P450-mediated drug disposition, leaving a knowledge gap on transporter-mediated drug disposition in pregnant women. This 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 drug regimens 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; it is co-funded by OPPTB and the NIH-São Paulo Research Foundation initiative (NOT-TW-16-001) via FIC.

Bumped-Kinase Inhibitor Drug Development for Toxoplasmosis (HD102487-03). *Toxoplasma gondii* infection is devastating during pregnancy and in immunocompromised individuals, but is not addressed well by available therapeutics. This project pursues development of a new therapeutic, a bumped-kinase inhibitor, to optimize safety and efficacy of use in pregnancy and in immunocompromised individuals. This research is led by a PI at the University of Washington in collaboration with investigators at the University of Bern, Switzerland, and the University Completense Madrid, Spain.

A Novel Approach for Prevention of Bronchopulmonary Dysplasia (BPD) in At-Risk Preterm Infants (HD107857-01A). BPD is a disease of preterm infants whose lungs are injured upon exposure to excess oxygen from ventilators, impairing effective gas exchange. This project pursues a novel class of immunomodulating compounds derived from chitin that decrease inflammation and pulmonary hypertension and improve lung vascularization. The investigators from a small business in Fort Worth, Texas, seek to validate and test efficacy of a compound in preclinical model that mimics the physiology of ventilated preterm human, as well as in vitro. Some analyses for the study are performed by laboratories in Quebec, Canada. Results of this research could contribute to much-needed prophylactic treatments for BPD and treatment for other life-threatening lung conditions.

Phase II PK/PD Driven Dose Finding Trial of Praziquantel (PZO) in Children Younger than Age 4 Years (HD095562-05). More than 200 million individuals worldwide are estimated to be infected with one of three predominant species of schistosomes annually, and more than one-half of infections occur in children. Recent studies illustrate that many children experience first infections before age 2, and that the prevalence of infection among children younger than age 4 mirrors the prevalence of older children from the same community. Importantly, PZQ, the drug used worldwide for the treatment of schistosomiasis, is only FDA approved for

adults and children older than age 4. The goals of this research are to conduct a randomized, controlled Phase II trial, in an *S. mansoni*-endemic region of Uganda and an S. japonicum endemic region of the Philippines, with N=600 children ages 1 through 4 years, to address current gaps hindering treatment of young children.

Precision Alemtuzumab Therapy in Allogeneic Hematopoietic Cell Transplantation ([HD107690-02](#)). This study is developing and evaluating a novel precision dosing strategy that enables optimal alemtuzumab therapeutic ranges following allogenic bone marrow transplants to decrease graft failure and graft-versus-host disease. To facilitate the dosing strategy, the investigators plan to develop a physician-driven electronic health record dashboard and webtool that enables clinicians to perform modeling and simulations. The study is led by PI Dr. Mehta, at Cincinnati Children's Hospital Medical Center, in collaboration with Medimatics, in the Netherlands, which will build the pharmacokinetics dashboard.

Pulmonary Implications of Perinatal Acetaminophen Exposure ([HD107700-02](#)). This work is evaluating the effects of acetaminophen exposure, in utero or in early life, on lung development. The preclinical study hypothesizes that saccular/early alveolar stage lungs are uniquely susceptible to acetaminophen-induced injury due to developmentally regulated pulmonary CYP2E1. The study is led by PI Dr. Wright at the University of Colorado-Denver, with mouse models provided by the MRC Harwell Institute, in the United Kingdom.

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Characterize Drug-Drug Interactions (DDIs) in Infants ([HD102949-02](#)). This work is using PBPK modeling and real-world data to accelerate the availability of age-appropriate drug-dosing recommendations for infants, while considering the DDI potential. The study is a collaboration between PI Dr. Gonzalez, at the University of North Carolina, Chapel Hill, and the University of Waterloo's Dr. Edginton, who will provide technical and PK modeling advice.

Mind the Gaps: PK Research to Advance Pediatric HIV/TB Cotreatment and TB Prevention ([HD107726-01](#)). This work not only proposes two prospective PK and safety studies, but it will also use a novel biomarker to examine the underlying mechanisms of drug action to improve the PK understanding of newer HIV/TB cotreatment and TB prevention strategies for use in children. Led by PI Dr. Rawizza at Brigham and Women's Hospital, in collaboration with the AIDS Prevention Initiative in Nigeria, and University of Cape Town, the effort will use specially equipped labs in South Africa to evaluate blood samples and conduct specialized tests on participants' HIV strains.

T32 Cincinnati Pediatric Clinical Pharmacology Training Program ([HD069054-12](#)). The objectives of the Alternative Dosing and Prevention of Transfusions (ADAPT) study, conducted in Uganda, are to quantify the reduction in blood transfusion needs for hydroxyurea-treated children with sickle cell anemia, and to assess the feasibility of locally determined PK-guided dosing of hydroxyurea in these children. Drs. Vinks and Power-Hays at Cincinnati Children's Hospital Medical Center are responsible for calculating PK-guided starting doses and evaluating clinical outcomes, in collaboration with researchers at Jinga Regional Referral Hospital, which collected original patient data and enrolled the patients.

Neurodevelopmental Effect of Acetaminophen Exposures ([HD109213-01A1](#)). This collaborative study will evaluate the potential effects of acetaminophen exposure on fetal development using data from the Danish National Birth Cohort and Danish medical registries. Dr. Liew at Yale University and his Danish collaborators will investigate the impact of fetal exposure to acetaminophen on six outcome domains, including milestones in infancy, craniofacial markers, neurobehavioral disorders, motor function, school performance, and mental health.

Recent Achievements in Global Health

N/A

Global Health Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

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

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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 the role of nutrition in 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 pursuing research in branch-relevant areas, as well as supporting small business programs in branch-relevant areas. To carry out this mission, the branch engages with and supports investigators, helps identify gaps in 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 people), 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, body composition/linear growth, 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

- Understanding human milk production and delivery using an ecological approach that examines human milk as a complex biological system that interacts with both an internal ecology (genetics, health, nutrition) and external (social-behavioral, cultural, physical, environment) ecology and is actualized via interactions amongst the breastfeeding "triad" of the parent,

human milk matrix, and the breastfeeding infant; areas of emphasis include but are not limited to:

- o Factors affecting mammary gland development and function

- o Parental factors influencing human milk composition

- o Human milk composition, including nutrients and bioactive substances within the human milk matrix

- o The role of the infant as not only a recipient of human milk, but also as a factor influencing its composition and function.

- o Specific roles of nutrient and bioactive components of human milk in the health of term and preterm infants, 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, the multiple burdens of malnutrition, 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 regulation 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

- Elucidating the molecular drivers of adverse intrauterine environments to prevent the development of obesity, insulin resistance, and cardiometabolic disorders

Moreover, the branch focuses on the application of an ecological approach to improve the precision of nutritional assessment for determining the presence, etiology, and functional consequences of nutritional status across multiple developmental stages, health, and environmental contexts.

Major Global Health Initiatives over the Past Year

Anemia, Iron, and Micronutrient Assessment. 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 adjunct projects that continue today. Among the most prominent of these related projects is the [Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) Project](#), which has provided guidance to USAID, WHO, and the global community about factors that influence the impact of inflammation on the assessment of anemia, nutritional iron, and micronutrient deficiencies.

In 2020, PGNB program staff were invited by USAID to chair its [Advancing Nutrition Anemia Task Force](#), which is developing resources to further understand the multidimensional nature of anemia, and studying implications of that complexity for assessment and interventions. Those efforts are [summarized in a series of reports](#) (*J. Nutr.*, 2023) describing the "anemia ecology": the biology and etiology, application of an ecological approach to assessment of anemia, and factors to consider in the development of context-specific equitable approaches to interventions. PGNB staff also continue to serve as part of the WHO and global efforts to address anemia.

Other anemia-related activities include a collaboration between NICHD and BMGF to explore the safety and efficacy of intravenous iron to treat anemia during pregnancy in low-resource settings via the [NICHD Global Network for Women and Children's Health Research](#).

Nutrition and the "first 1000 Days" (Pregnancy through Age 2 Years). In 2012, the B-24 (Birth through 24 Months) effort was initiated by PGNB to support the Dietary Guidelines for Americans (DGAs), 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 supporting the "1000 Days."

In 2014, legislation codified the inclusion of pregnancy through the first 2 years of life (P/B-24) into future iterations of the DGAs beginning in 2020. The subsequent results of the systematic reviews, conducted by the Food and Nutrition Service (FNS) within the U.S. Department of Agriculture (USDA) as part of the generation of the 2020 DGAs, revealed a priority-need related to the lack of understanding of factors affecting human milk composition.

In 2021, PGNB initiated the [Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN) Project](#) to address that priority need. Outputs from BEGIN include a 6-part supplement in the *American Journal of Clinical Nutrition* published in 2023 and a focused funding opportunity to address evidence gaps (*[American Journal of Clinical Nutrition,](#)* [2023: Volume 117, Supplement 1](#)).

Nutrition and the "Next 7,000 Days" (ages 2 to 21) and Assessment of Nutritional Status. The Biomarkers of Nutrition for Development (BOND) project, launched in 2010, was initially 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 researcher, clinicians, surveillance staff, program monitoring and assessment experts, and policy makers.

In 2021, PGNB, in response to and collaboration with the USDA, Foreign Agriculture Service, the World Food Program, the Global School Meals Coalition and the London School of Hygiene and Tropical Medicine's Global Children's Nutrition Research Consortium, initiated the [BOND-Knowledge Indicating Dietary Sufficiency (BOND-KIDS) Project](#) to examine the nutritional needs and assessment issues for school-age children (5 through 19 years). Using the existing BOND platform and process, four thematic working groups were established to apply an ecological approach; BOND-KIDS recognized the growing child as a complex biological system that interacts with its internal (biology, genetics, health) and external (social/behavioral, home, community, and physical) environments.

BOND-KIDS addresses the following:

- Impact of biology/nutritional needs on key biological systems such as linear growth/body composition, neurodevelopment, immune-competence/inflammation, and reproductive health

- Impact of external environmental factors including psychosocial and related environments in the home, school, and community as well as the physical environment including climate change on the functional outcomes of interest

- Assessment of factors for consideration in efforts to evaluate the impact of programs and interventions that provide nutritional support to school-age children

- Development of a framework for translating and implementing current and emerging evidence to inform program, policy, and standards of care,

ensuring both the safety and efficacy of programs that address nutritional needs of school-age children domestically and globally, and identifying how best to inform efforts to measure these impacts

Intersection of Climate, Food Systems, Health, and Nutrition. PGNB program staff initiated a series of symposia in partnership with the USDA Agricultural Research Service (ARS) to focus on various aspects of the intersection of climate/environmental change (CEC), food systems, health, and nutrition. This work includes a:

- Collaboration with the American Society for Nutrition (ASN) and the Keystone Policy Center on Protein in a Changing Environment

- Symposium at the annual ASN meeting to address the intersection of CEC, food systems, nutrition, and health using the current guidance on increasing fruits and vegetable consumption to address diabetes

- Symposium at the 2019 ASN annual meeting to address the role of animal source foods to meet micronutrient nutrition in a changing environment

Program staff also initiated and serve as co-chair with ARS/ARS of a new Research Interest Section within ASN focused on the intersection of Climate, Health, Agriculture, and Improving Nutrition. This Section now has over 1,000 members representing the breadth of the domestic and international research communities.

In 2022, PGNB launched the [Agriculture and Diet: Value Added for Nutrition, Translation, and Adaptation in a Global Ecology (ADVANTAGE) Project](#) to better understand the intersections of agriculture, food systems, nutrition, and health in a changing environment across the lifespan. The ADVANTAGE Project addresses the following core questions:

- How are the current realities of CEC affecting dietary choices/patterns and relevant aspects of the food system, and what are the implications for specific public health outcomes of interest?

- How can we apply an ecological approach to assessing the nature and impact of these relationships?

- How can we best translate the evidence generated to support dietary guidance to promote health and prevent disease?

The ADVANTAGE Project working groups focused on the following five topics:

- Implications of CEC on priority health outcomes

- Impact of CEC on dietary patterns, attitudes, beliefs, and choices

- Impact of CEC on food systems

- Measures and metrics: an integrated approach to understand the intersection of CEC, food systems, nutrition, and health

- Translation and implementation: data needs and approaches to the translation of emerging evidence to support context-specific, equitable, safe and efficacious interventions, dietary guidance and standards of care in a changing environment

Global Nutrition Coordination Plan (GNCP). PGNB program staff contributed to the development of GNCP 1.0 (2016 to 2021) and [GNCP 2.0 (2021 to 2026)](). Although the GNCP is voluntary, without specific funding to support its activities, the effort aims to enhance the impacts of and synergies among programs funded and implemented by the U.S. government to address malnutrition in all its forms. The inception of GNCP 1.0 reflected recognition of the central importance of nutrition to saving lives and to improving the prospects of future generations 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 development, implementation, and evaluation.

The GNCP is organized around several technical subgroups. PGNB has played a central role in the creation and leadership of:

- Ecology of Parental, Infant, and Child (EPIC) Nutrition technical subgroup: originally called the "First 1000 Days" group in GNCP 1.0, EPIC was formed in 2022 to meet the more inclusive priorities of GNCP 2.0 to include not only the 1000 days but also the nutritional needs of children and adolescents.

- PGNB initiated and co-leads the newly created Climate, Health, Agriculture and Nutrition in a Global Ecology (CHANGE) technical subgroup, which is intended to integrate this important intersection into the efforts of the GNCP community to address malnutrition.

Recent Achievements in Global Health

- BOND-KIDS Project: Exploring the Nutritional Ecology of School-Aged Children: [Webinar Recording](#)

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- Raiten DJ, Steiber AL, Papoutsakis C, Rozga M, Handu D, Proaño GV, Moloney L, Bremer AA. The BEGIN Project: executive summary. *Am J Clin Nutr. 2023 Apr*;117 Suppl 1:S1-S10. doi: 10.1016/j.ajcnut.2022.12.020. PMID: [37173057](#).

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Perrine CG. Improving Nutrition in the First 1000 Days in the United States: A Federal Perspective. *Am J Public Health. 2022 Oct*;112(S8):S817-S825. doi: 10.2105/AJPH.2022.307028. Epub 2022 Sep 19. PMID: [36122314](#).

- Ahuja JKC, Casavale KO, Li Y, Hopperton KE, Chakrabarti S, Hines EP, Brooks SPJ, Bondy GS, MacFarlane AJ, Weiler HA, Wu X, Borghese MM, Ahluwalia N, Cheung W, Vargas AJ, Arteaga S, Lombo T, Fisher MM, Hayward D, Pehrsson PR. Perspective: Human Milk Composition and Related Data for National Health and Nutrition Monitoring and Related Research. *Adv Nutr. 2022 Dec 22;13*(6):2098-2114. doi: 10.1093/advances/nmac099. PMID: [36084013](#).

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Global Health Partnerships

PGNB maintains close working relationships 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, the United Nations (UN) International Children's Emergency Fund (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 Global Health Initiatives over the Past Year

Feasibility and Efficacy of Ambulance-Based mHealth for Pediatric Emergencies (FEAMER) Trial (1R21HD103049-01A1): Pakistan. Of the 16,000 children who die every day worldwide, 7,000 die because of five acute illnesses—pneumonia, diarrhea, injuries, meningitis, and malaria—largely in LMICs. Appropriate and timely acute and emergency care of these children can reduce such deaths by about one-half. This study is evaluating whether, in a low-resource setting, linking ambulances that transport acutely ill children to a pediatric emergency physician using a simple audio-video device is feasible, acceptable, and improves the quality of medical decisions and the health outcomes of these children. The purpose of the study is first to assess the feasibility of implementing an ambulance-based teleconsultation (ABT) process (R21) and, if feasible, carry out a clinical trial to confirm the efficacy of the approach on the short-term clinical outcomes (R33) in Karachi, Pakistan.

Novel Pediatric Sepsis Criteria and Clinical Decision Support Tools (5R01HD105939-03). Pediatric sepsis is a major global public health problem. In 2017, an estimated 25 million cases of pediatric sepsis worldwide were associated with 3.3 million deaths. Early diagnosis, accurate risk stratification, and treatment are needed to reduce mortality. However, the current criteria for diagnosing pediatric sepsis are outdated, lack specificity, do not allow early detection and risk

stratification in all settings, and are discordant with clinician-based diagnosis. This project aims to derive and validate novel organ dysfunction-based, pediatric sepsis diagnostic criteria that generalize beyond the intensive care unit (ICU) and to differently resourced settings. Using clinical data from six U.S. children's hospitals and four international sites in Bangladesh, China, Colombia, and Kenya, researchers aim to accomplish the following: 1) determine the optimal clinical criteria for each pediatric organ dysfunction in differently resourced settings and care environments; 2) develop and validate novel pediatric sepsis criteria; and 3) design, build, and evaluate prototype clinical-decision support tools to facilitate use of the new pediatric sepsis criteria. The results of this activity could have a powerful and sustained impact on the science of pediatric sepsis and organ dysfunction, to ultimately improve sepsis recognition, accelerate appropriate effective treatment, decrease unnecessary treatment, and improve the outcomes of children with sepsis around the world.

Integrating Evidence-Based Program (EBP) Approaches to Prevent Child Maltreatment in Kyrgyzstan (1K01HD106070-01A1). The centerpiece of this project is use of a community-engaged approach that integrates and tests three EBPs for preventing child maltreatment, domestic violence, and other Adverse Childhood Experiences (ACEs) in Kyrgyzstan. The project features innovative training for the PI on integration and adaptation of EBPs to child/family outcomes, longitudinal intervention, research, and quantitative measurement/analysis. It also features strong mentoring from group of senior mentors, who have an outstanding track record of NIH-supported research and an extensive history of mentoring junior faculty, and others from NGOs, all with extensive experience/commitment to preventing child maltreatment. The program will adapt and pilot a family-focused (multiple family groups), school-based (school children and their families) economic empowerment program to promote positive health and socioeconomic outcomes for children.

Training Leaders to Prevent and Reduce Domestic Violence in Their Communities: Experimental Evidence from Peru (1R01HD101581-02). Gender-Based Violence (GBV), which affects one in three women in the world, has long-term welfare consequences for survivors and families and incurs indirect costs to the health sector, the legal system, and the economy. Yet there has been little rigorous research on the efficacy of interventions to reduce or prevent GBV. This project takes advantage of a long-standing partnership with the Peruvian Ministry of Women to conduct an experimental evaluation of Leaders in Action, the Ministry's flagship GBV program, which trains local leaders on GBV and norms, randomized across 250 villages. 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 for guiding GBV programming, estimating cost effectiveness, and bringing scientific evidence on GBV reduction and prevention to policy in Peru and worldwide.

Dissemination, Implementation, and Effectiveness of an Intervention to Prevent Intimate Partner Violence (IPV) ([5R01HD099144-04](#)). IPV is a widespread and serious public health problem. Glaring gaps exist in meeting the health and safety needs of survivors through the formal and informal support systems in low-resource settings. In high-resource settings, an interactive, personalized safety decision application ("App"), called myPlan, was shown to be effective in increasing use of helpful safety strategies, perceived support, and safety. The objective of this 5-year study is to: 1) disseminate the myPlanKenya app through formal systems (i.e., health, education, justice) and informal, community-based networks in Nairobi, Kenya, and document and compare reach and adoption; 2) compare the nature and intensity of myPlanKenya implementation at 6-month follow-up and maintenance at 12-month follow-up by organizational characteristics; and 3) evaluate the effectiveness of myPlanKenya referral on resilience, health, and safety among a cohort of women referred to the myPlanKenya app based on disclosure of IPV or assessed to have IPV related risks.

Miles de Manos ("Thousands of Hands"): Testing the Efficacy of a School-Based Youth Violence Preventive Intervention in a High-Risk International Context ([5R01HD102984-04](#)). Violence against and by youth in Central America disrupts communities and is one cause of migration north and into the United States. Disrupting youth violence connected to international contexts requires an approach that includes prevention efforts both in the United States and in other countries linked to youth violence and youth and adult gang activity. The proposed study seeks to examine the impact of Miles de Manos (MdM), a universal, multimodal, evidence-informed, and community-based youth violence prevention intervention, on youth violence in Honduras. Unlike most violence prevention programs delivered in Honduras and other countries in the region, MdM was developed by and for Central Americans; a U.S.-based research team was involved in the development of three relevant evidence-based interventions and is available for ongoing consultation as the project continues.

Archiving and Harmonizing Data on Prevention and Treatment of Child Traumatic Stress (5R03HD105319-02), Performance Sites: United States, Australia, Netherlands, Norway, South Africa, Switzerland, United Kingdom. This project was developed in conjunction with the Global Collaboration on Traumatic Stress, a coalition of 10 world-wide scientific societies, and is inspired by the growing movement to make scientific research data more Findable, Accessible, Interoperable, and Re-usable (FAIR). The project's overarching objective is to build an expandable research resource for the child trauma field that will enhance the utility and value of child trauma studies by applying FAIR tenets and facilitating integrative cross-study analyses to advance child trauma intervention science. This effort includes building a parallel archive of intervention studies, the Child Trauma Prevention and Treatment Studies Data Archive, by gathering data on studies that evaluated interventions with children who experienced trauma such as injury, violence, medical trauma, and maltreatment. This ongoing research resource promotes data sharing and facilitates novel integrative analyses that would not be possible otherwise, thereby furthering the field's ability to understand how and for whom child trauma interventions work and effectively address the impact of trauma on child health and well-being. This project also advances the NICHD Strategic Plan goal of archiving and documenting existing datasets within the institute's scientific mission, enabling new analyses by the scientific community.

Global Perspectives on Gender Inequality, Parental Violence, and Child Development (1R15HD110944-01). Worldwide, parental physical abuse is a common form of family violence to which children are exposed at alarming rates. Parental physical abuse is linked to negative child outcomes including depression, anxiety, and aggression that may persist into adulthood. Despite the substantial scholarship on parent- and family-level predictors of parent-to-child physical violence, important questions remain about societal-level predictors of parental physical abuse and its associations with young children's development in developing and transitional countries. The lack of studies examining the role of individual child gender in the associations between gender inequality and parental violence against children is also a key gap, especially considering that girls are likely more vulnerable to gender inequality than boys. Using data from over 520,000 families in 57 LMICs, this project seeks to address these research gaps by examining the associations of country-level gender inequality and violent social contexts with caregivers' use of physically abusive behavior and child social-emotional development. Investigators employ multilevel models using data on parental physical violence against children, family socio-economic characteristics, and children's social-emotional development from the UNICEF Multiple Indicator

Cluster Survey, as well as data on country-level gender inequality and violent social contexts from the UN Development Programme on Human Development and the WHO Global Health Observatory.

Optimizing Prevention Approaches for Children Reintegrating from Orphanages in Azerbaijan ([5R01HD099847-05](5R01HD099847-05)). The UN estimates that, globally, between 2 to 8 million children live in orphanages, and countries of the former Soviet Union and Eastern Europe have the highest number of children—up to 1.3 million—in institutional care worldwide. 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. Although current deinstitutionalization and family reunification initiatives provide basic case management services, 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, this activity 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. Researchers will test the adapted interventions with 400 child-caregiver dyads in a trial using the Multiphase Optimization Strategy (MOST) to compare different intervention components and identify the most optimal combination. The study will evaluate the effects of each intervention component on children's mental health outcomes, including symptoms of depression and anxiety, disruptive behaviors, post-traumatic symptoms; and disturbances of attachment. If efficacious, the study results study could transform large-scale deinstitutionalization initiatives implemented by UNICEF or other organizations in Azerbaijan and in the former Soviet Union region.

Intergenerational Impact of Maternal Trauma History on Preschoolers' Behavioral Health Outcomes: Assessing Links with Caregiving Sensitivity and DNA Methylation ([5R01HD102342-04](5R01HD102342-04)): Peru. This study seeks to better understand maternal trauma history as a driver of behavior health problems in 4-year-old children. The work will examine the impact of maternal trauma across four time periods: 1) maternal experience of pre-pregnancy abuse in childhood (when mothers were younger than 18 years); 2) maternal experience of pre-pregnancy of abuse in adulthood; 3) maternal experience of abuse during pregnancy; and 4) maternal report of postnatal abuse (after childbirth to time of

assessment) on their children's behavioral problems (internalizing and externalizing behaviors). This effort builds on an existing prospective longitudinal cohort of Peruvian women, recruited in the first trimester of pregnancy, that was established as part of a prior NICHD-funded grant (n=4,472 live births). The cohort had a high prevalence of childhood maltreatment, IPV, and other traumas and related psychopathology. The study will collect data on a subset of mother-child dyads (n=1,700) over a 36-month recruitment period (about 48 enrollees/month). By increasing knowledge regarding the intergenerational transmission of trauma using a life-course theory approach, and by incorporating epigenetic markers that provide a mechanistic pathway for this relationship, this innovative study marks the first genome-wide study of maternal trauma and child DNA methylation.

Recent Achievements in Global Health

N/A

Global Health 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; Member: Zsuzsanna Kocsis

- Intra-NIH Disaster Interest Group. Co-Chair: Dr. Cinnamon Dixon; Member: Zsuzsanna Kocsis

- 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. Member: Dr. Cinnamon Dixon

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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.

Major Global Health Initiatives over the Past Year

The United Republic of Tanzania: Reproductive Health, including the Reproductive Health of Individuals with Disabilities ([HD092655](#) and [HD108351](#)). Tanzania has among the most significant sexual and reproductive health challenges of any country in the world. Rates of HIV, STIs, teen unplanned pregnancy, and sexual violence are among the highest in sub-Saharan Africa and contribute to substantial morbidity and mortality. To address these public health problems, this grant examines the effects of a comprehensive reproductive and sexual health training for health care students—midwives, nurses, and doctors—in Tanzania. An associated program seeks to specifically train health workers in dealing with the reproductive and sexual health needs of individuals with disabilities.

India: Postpartum Contraception ([HD108351](#)). By reducing the prevalence of unintended pregnancy and short inter-pregnancy intervals, expanding access to family planning among postpartum people can reduce maternal and infant morbidity and mortality. This project focuses on India, the country with the highest number of women with unmet needs for contraception. The study will pilot test a

program offering family planning counseling and, if desired, contraceptives to postpartum rural women when they bring their infants in for vaccine appointments.

Eswatini: Contraception and HIV ([HD108636](#)). In sub-Saharan Africa, 24 percent of pregnancies are among adolescent girls and young women (ages 15 to 24 years); this group also accounts for 75 percent of new HIV infections. This project is developing methods to collect high-frequency, population-representative longitudinal data on contraceptive dynamics and on perceptions of HIV risk from adolescent girls and young women in in Eswatini (formerly Swaziland), a high HIV prevalence setting. The goal is to identify key time points for sexual and reproductive health interventions.

Uganda: Pregnancy Preferences ([R21HD110900](#)). The goal of this project is to improve measurement of women's and men's prospective pregnancy preferences in Uganda. The researchers are adapting and evaluating an existing measure—the Desire to Avoid Pregnancy Scale—that was developed using U.S. populations, so that it can be used in settings outside the United States. In this case, the changes will make it more appropriate for low-resource, high-fertility settings in sub-Saharan Africa.

Mali: Violence and Maternal Health Outcomes ([R03HD113833](#)). Violence is known to disrupt provision of health services and individuals' ability to utilize certain health services, including antenatal care and facility delivery. These disruptions likely contribute to poor maternal health outcomes, as well as to disparities in maternal and newborn mortality and morbidity. The project uses three linked datasets from rural Mali to estimate how the precise location, timing, and intensity of community-based violence affect maternal health outcomes. Data include—four waves of a household panel survey, health facility records, and conflict event data collected before and after the onset of high-intensity community-based violence. The project also plans to document whether and how exposure to violence contributes to disparities in maternal health via the timing and quality of antenatal care, and whether women deliver at a health facility.

Mexico and the United States: Migration, Children of Immigrants ([R03HD107298](#)). More than 500,000 U.S.-born children currently live in Mexico, but research has largely overlooked this important population of U.S. citizen children, particularly in comparison with children of immigrants who remain in the United States. This study will provide a detailed socio-demographic portrait of the large binational population of Mexican American children of immigrants who live in the United States and in Mexico.

Mexico, El Salvador, Guatemala, Honduras, and the United States: Migration (R01HD112384). During the first two decades of the 21st century, unauthorized migration from Mexico has declined, while unauthorized migration from El Salvador, Guatemala, and Honduras has steadily increased. This project is working to fill a void in the available data for studying these new migration flows. Innovative features of this work include methodological improvements in sampling, questionnaire content, and use of social media data. Questions will address family migration, the migration of children, multiple border crossings, transit through Mexico, and experiences of abuse during migration, violence and gang intimidation, crop and livestock loss, and food insecurity. A compilation of weather, climate, and homicide data from the municipal level is also planned.

Bangladesh and Mozambique: Mortality in Early Childhood (HD107015). Globally, in 2020, approximately 5.0 million children died before age 5 years. To develop, evaluate, and implement life-saving childhood interventions, accurate data on children's mortality is necessary. These data are often not available in low-resource settings, especially those with limited civil registration systems. This project will develop data collection strategies and state-of-the-art statistical methods to improve age- and cause-specific mortality rates for children younger than age 5 years in two countries, Bangladesh and Mozambique.

China, Germany, and the United States: Early Childhood Traits and Preferences, and Health and Productivity in Later Life (HD107079). This international multidisciplinary project examines how personality traits, executive function skills, and economic preferences that start in childhood evolve and how they are associated physical and mental health, well-being, educational outcomes, and productivity in later life. The project focuses on the United States, China, and Germany and draws on research perspectives psychology, child development, and behavioral economics.

Mexico: Preprimary Education and Child Outcomes (HD112800). Research in high-income countries suggests that preprimary education improves children's educational and life outcomes. Between 2006 and 2013, Mexico implemented a policy requiring three years of preprimary education. This policy provides a unique natural opportunity to study the nationwide effects of preprimary education in an LMIC context. This study uses nation-wide longitudinal data from after the preprimary reform on children until they are approximately 5 years of age. The study examines how effects of the policy vary by gender, indigeneity, and disability and socio-economic status. Outcomes include ages of primary school entry, grade

retention, and primary school achievement; the role of preprimary education quality on outcomes; and parental investments in children.

Uganda: HIV Orphans ([HD112241](#)). Loss of one or both parents can have devastating consequences for children, adolescents, extended families, communities, and nations. Although recent improvements in HIV treatment and prevention have led to dramatic declines in orphanhood, substantial challenges continue to exist for those already orphaned. The Rakai Orphans in Communities Study in Uganda is exploring the impact, measurement, and policy issues at the intersection of orphanhood, HIV risk among adolescents and young adults, adolescent social transitions, and family and social contexts. Impacts of interest include HIV risk and social and economic consequences, as well as the understudied issue of how the economic benefits of combination HIV prevention are weighed against the costs.

Colombia: Women's, Children's, and Adolescents' Health and Energy Insecurity ([HD104872](#)). Household access to adequate, affordable, reliable, acceptable, and clean sources of energy seems to play a key role in improving health outcomes among women, infants, and children. In fact, this effect is distinct from the effects of food and water insecurity. Despite its potential importance, no validated scale for measuring household energy security currently exists; furthermore, research has not examined the effects of energy security on health outcomes systematically, especially in Latin America and the Caribbean. This study is developing and validating an adaptable scale for measuring household energy insecurity using quantitative and qualitative data to be collected in Colombia. Once validated, researchers will use this scale to examine the effects of energy security on disease and nutritional outcomes for women and young children (ages birth to 4 years) and older children and adolescents (ages 5 to 15 years) in the same locations.

Malawi: Nuptiality and Health ([HD111618](#)). Extensive research in Europe and North America has demonstrated a strong relationship between marriage and health. However, research on this topic in sub-Saharan Africa is limited, and studies done outside of Africa generally do not consider the implications of key features of the African context, such as different marriage patterns and customs (e.g., early marriage, polygyny), persistence of traditional gender norms, and the HIV/AIDS epidemic. This project applies statistical approaches to longitudinal data from Malawi to reduce common biases in examinations of the connection between marriage and mental and physical health. Such biases may include unobserved characteristics associated with both marriage and heath, and the selection of

individuals with different health status into marital change (mainly remarriage and dissolution).

Global Health 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, PPB 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 engage with and support investigators to identify knowledge gaps and opportunities for scientific advancement. For more information about the branch, please visit the [PPB webpage](#).

Major Global Health Initiatives over the Past Year

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

The Global Network, which began in 2001, is a partnership dedicated to improving maternal and child health outcomes and building health research capacity in resource-poor settings by testing cost-effective, sustainable interventions that provide guidance for the practice of evidence-based medicine.

The Global Network, which is re-competed every seven years, currently supports a [Data Coordinating Center (DCC) and seven U.S.-based research centers and their counterparts](#) in low- and lower middle income countries, each comprising a partnership. RTI serves as the DCC, providing scientific and operational resources to maximize the productivity and public health impact of the Global Network's research collaborations.

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 worldwide. The Global Network also affords opportunities for local scientists to develop protocols, abstracts, manuscripts, and presentations and augment local capabilities in information technology and data collection and management. This work facilitates independent continuation of local research activities that ultimately lead to improved heath, healthcare systems, and independent funding, while also providing opportunities for other NIH ICOs and funders to collaborate with Network researchers.

- **Maternal Newborn Health Registry (MNHR).** The Global Network's MNHR, established in 2008, is a prospective, population-based study of pregnancies and outcomes at sites in LMICs. The registry continues to be the only database of pregnancy and pregnancy-related outcomes of its magnitude focused on low-resource settings. All Global Network sites enroll pregnant women in the MNHR, employing trained registry administrators to collect and enter the data. Birth attendants are trained to collect data and are educated about how to differentiate types of birth outcomes and fatalities for accurate record keeping. The primary purpose of this observational study, which includes 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 to help inform healthcare practices and policies. [Data from the registry](#) also provide the mortality and morbidity outcomes for other Global Network trials and help investigators plan future Network studies. To date, the registry has collected data from more than 1 million mother-baby dyads.

- **[Prevention of Iron Deficiency Anemia Post-Delivery (PRIORITY) Trial](#).** The Global Network's PRIORITY Trial is a prospective, two-arm, randomized trial in LMICs. The study will enroll women with moderate anemia based on samples taken immediately (6 to 48 hrs) post-delivery, who deliver at study hospitals or birthing facilities in Global Network sites. The trial is assessing whether there is a difference in achievement of non-anemic state between women receiving intravenous iron compared to women receiving standard care with oral iron 6 weeks post-delivery.

- **[Azithromycin-Prevention in Labor Use Study (A-PLUS)](#).** The Global Network's A-PLUS trial, co-funded by the BMGF through a grant to the Foundation for NIH, found that a single, oral 2-gram dose of the antibiotic azithromycin given to women in labor reduces by one-third the risk of postpartum sepsis and death among women who deliver vaginally. Findings from the A-PLUS trial have the potential to change clinical practice by providing a safe, effective, and low-cost approach to reducing the global burden of maternal sepsis and death. Results from the trial were published in the *New England Journal of Medicine* (PMID: [37467509](#)) and presented at the Society for Maternal-Fetal Medicine's 43rd Annual Pregnancy Meeting.

- **[Azithromycin: Brain Neuroprotection for Children (ABC) Study](#).** The Global Network's ABC study is a prospective, masked, matched study

evaluating the neurodevelopmental outcomes of children whose mothers were in the A-PLUS trial, and who survived birth asphyxia. The ABC Study will enroll 420 birth asphyxiated infants (≥ 34 weeks of gestation) with no, mild, moderate, or severe hypoxic-ischemic encephalopathy born to mothers enrolled in the A-PLUS trial, meaning they received either a single, oral 2-gram dose of azithromycin or placebo during labor. If intrapartum azithromycin is found to be neuroprotective in children who survived birth asphyxia, it could become the intrapartum antibiotic of choice in selected deliveries in LMICs.

Other Branch Projects

Evaluating Perinatal Mood and Anxiety Disorder (PMAD) in Kenya: A Mixed Methods Approach (HD108857-02). This F32 research project leverages data from an ongoing cohort study (R01 HD100201) of 1,300 Kenyan mother-infant pairs, followed from pregnancy through 36-months postpartum with longitudinal assessment of maternal PMAD, mother-infant engagement, and infant-child social-emotional development. Aim 1 relies on dyadic data collected monthly, during pregnancy and from 6 months through 36 months postpartum, to prospectively assess impact and timing of PMAD on social-emotional developmental delays among Kenyan mother-infant pairs. Aim 2 is examining the relationship between mother-infant engagement and PMAD remission timing, longitudinally through 36 months postpartum, to potentially highlight an effective avenue for intervention. Aim 3 evaluates acceptability and preferences for PMAD management approaches among perinatal Kenyan women. Researchers will then use these data and qualitative methods (guided by the Theoretical Framework of Acceptability) to inform patient-driven intervention design. This large-scale mixed method study will contribute novel data toward informing a future PMAD intervention.

Preventing Antimicrobial Resistance and Infections in Hospitalized Neonates in Low-Resource Settings (HD100594-04). Worldwide, nearly one-quarter of all neonatal deaths occur in India alone, and over 30 percent of these deaths are due to infectious causes. Facility-based births are increasing, and the number of Neonatal ICUs (NICUs) is growing exponentially. However, healthcare-associated bloodstream infections are common, and infections due to antimicrobial resistant (AMR) pathogens are on the rise in neonates. As a middle-income country, India's capacity for neonatal care has risen dramatically over the last several decades, but the quality of care, especially in terms of infection prevention, has not kept pace with technological advancements. India has some of the highest AMR rates worldwide, and infections from extended-spectrum β-lactamase-producing

pathogens and carbapenem-resistant organisms, leading causes of infection in hospitalized neonates, are associated with mortality of 25 percent or greater. A comprehensive assessment of risk factors for these infections must precede development of targeted infection prevention and control strategies. This project will design an assessment tool specifically for healthcare facilities in LMICs. Using a decision-tree algorithm, the prediction model will help identify babies at highest risk of carbapenem-resistant organism infections, to help NICU clinicians select the right antibiotics when infection is suspected, reduce time to appropriate therapy, and decrease unnecessary use of last-resort antibiotics, such as colistin. By incorporating human-factor engineering principles, the tool will enable healthcare facilities to optimize infection prevention and control strategies and reduce risk of hospital-acquired infections and associated mortality.

Operationalizing Kangaroo Mother Care (KMC) among Clinically Unstable Low Birth Weight Neonates in Africa Study (HD092611-05). The overarching hypothesis of this study is that, compared to incubators, KMC for unstable neonates will reduce mortality and lead to cost savings. Aims of the study include: exploring social, cultural, and economic factors that affect KMC uptake and duration in Uganda, and using findings to develop strategies that improve KMC practice in facilities; building and implementing a model to estimate the incremental cost and cost-effectiveness of KMC relative to standard care (incubator or radiant warmer); and evaluating the validity of data on KMC duration (defined as skin-to-skin contact in the KMC position) from caregiver report and healthcare workers' report, compared to a gold standard of direct observation. The proposed research, which will take place in a regional referral hospital in Uganda, will add innovative evidence on the use of KMC in this vulnerable population and may be generalizable to many low-resource settings.

Wireless Physiologic Monitoring of Postpartum Women in Rural Uganda (HD097300-05). Women in sub-Saharan Africa continue to face unacceptable levels of death and disability related to pregnancy and childbirth, even when delivering at a health facility. Close monitoring during childbirth is a critical component of preventing death and disability. This project is using a simple, wireless monitor to improve detection of complications immediately after childbirth, so that clinicians can provide disability-averting and lifesaving interventions when needed.

Maternal Stress and Undernutrition: Interactive Effects on Newborn and Child Outcomes in Ethiopia (HD110651-01). This K99/R00 study involves a clinical nutrition intervention trial in rural Ethiopia. The trial will determine interactive effects of maternal prenatal stress and nutrition intervention on newborn weight-

for-age and stress-sensitive child outcomes related to visual attention, memory, stress reactivity, and socio-emotional functioning at 36 months postpartum. The study will also examine whether maternal and newborn telomere length serves as a biomarker of the biologic mechanism underling hypothesized associations. Insight from this project will cast light on the importance of antenatal intervention to reduce commonly co-occurring maternal prenatal stress and undernutrition among millions of women residing in low-resource settings.

mHealth-Community Health Worker (CHW) Tool for Comprehensive Post-Cesarean Follow-Up in Rural Rwanda (HD103052-02). This study will develop a comprehensive, mobile health app to support CHWs in monitoring maternal health, beginning shortly after a cesarean section delivery, in rural Rwanda. The presence of CHWs significantly decreases physician travel burden, and the app can support the need to identify complications and refer for follow-ups. This research will inform and quantify CHWs' ability to provide safe, accessible, and affordable in-home cesarean section follow-up care to women in rural Africa, which could decrease the physical and financial burden of facility-based follow-up for new mothers.

Methods for Understanding the Cesarean Birth Surgical Disparity in Rural Ethiopia and Considering a Mobile Cesarean Birth Center as a Solution (HD102720-02). This R21 seeks to address the problem of maternal and neonatal mortality in rural Ethiopia with an intervention that provides mobile, emergency Cesarean section delivery units in areas where pregnant women experience delays in seeking and receiving emergency obstetric care. The study will explore barriers to Cesarean delivery with a focus on a clinical solution (i.e., mobile community-based Cesarean section delivery) guided by the Exploration-Preparation-Implementation-Sustainment Framework.

Mobile, Virtual Simulation Training in Essential Newborn Care for Healthcare Workers in LMICs (HD107984-02). This R21 is developing and testing virtual simulations on essential newborn care procedures to improve the training of healthcare workers. Such simulations have the potential to increase the skills and knowledge of healthcare workers, in this case in Nigeria, and to reduce neonatal mortality, both pressing needs in LMICs, where the decline in neonatal mortality has slowed compared to post-neonatal or child mortality in recent years. The virtual simulations also address the need for remote training and continuing education for healthcare workers during periods of restriction on assemblies due to epidemics (e.g., COVID-19), disasters, and other situations.

The Role of Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation in Preterm Birth (HD102822-02). This study is the first to investigate the possible association between time-integrated measures of cortisol secretion (measured via scalp hair cortisol concentrations) and preterm birth in a large cohort of pregnant women. This study leverages [one of the few existing cohorts](#) with prospectively collected hair samples among low-income Hispanic women in Lima, Peru, a population highly exposed to trauma and mental health disorders. If results from this study indicate a role for HPA axis dysregulation, researchers can apply the findings to designing mechanistic and intervention studies aimed at reducing the impact of early life adversities and other risk factors of adverse perinatal outcomes in vulnerable populations. Study findings will also illuminate the role of HPA axis dysregulation in pregnancy, which may explain the etiopathogenesis of pregnancy complications such as preterm birth.

mHealth and Mobile Ultrasound for Mothers in Myanmar (HD103053-03). Currently, less than 10 percent of births in Western Myanmar take place in a healthcare facility because most women must travel two or more days, on foot through mountainous regions, to reach one. This study combines mobile health (mHealth) population surveillance with portable ultrasound to improve rates of attended births and successful transfers of high-risk pregnancies to hospitals in Western Myanmar. The long-term goal is to improve maternal health outcomes and use mHealth to support population surveillance in Myanmar.

An Integrated mHealth Strategy to Improve Newborn Resuscitation in Low and Lower-Middle Income Countries (HD103058-03). This study, conducted in the DRC, hopes to reduce newborn mortality by improving the use of bag mask ventilation (BMV) by midwives. When BMV is delayed or interrupted, newborns may fail to breathe, which contributes to newborn mortality. The researchers propose to improve BMV by developing and testing LIVEBORN, a mHealth application, and then conducting a trial to evaluate its effectiveness.

Addressing Provider Stress and Unconscious Bias to Improve Quality of Maternal Health Care (HD093798-05). When optimal, person-centered maternal health care (PCMHC) contributes to improved maternal and neonatal outcomes. However, if PCMHC is poor, as in sub-Saharan Africa, maternal and neonatal mortality is high, and disparities in PCMHC drive disparities in use of maternal health services. In this project, researchers will conduct secondary data analysis on existing data from approximately 1,000 women, 50 providers, and 50 facility-levels to examine factors associated with PCMHC, with a particular focus on the role of provider stress in outcomes.

Effect of Iodized Salt in Pregnancy and Lactation on Infant Neurodevelopment in Rural Ethiopia (HD107475-02). This study presents a unique opportunity to build upon an ongoing RCT to address the consequences of iodine deficiency on fetal and infant neurodevelopment in a population with mild-to-moderate iodine deficiency in rural Ethiopia. The overall goal is to examine the effects of iodine during pregnancy and lactation on infant brain function, as well as on maternal and infant iodine status and thyroid function. This study will generate foundational knowledge about the role of iodine in the first 1,000 days of life and will inform design and delivery of interventions to help children reach their optimal potential.

Novel Vacuum-Induced Postpartum Hemorrhage (PPH) Control: A Multicenter Randomized Trial (HD108210-02). PPH is the leading cause of maternal mortality worldwide, responsible for 25 percent of maternal deaths from obstetric causes, with 99 percent occurring in LMICs. This study will provide high quality evidence on the effectiveness of the Jada® System in managing PPH. If proven effective, safe, and cost-effective, this simple and scalable device would have a profound impact on PPH-related maternal mortality and morbidity in LMICs, as well as worldwide.

Effects of Household Concrete Floors on Child Health (HD108196-02). This randomized trial will rigorously measure whether replacing soil household floors with concrete floors reduces household fecal contamination, child soil-transmitted helminth infection, and child diarrhea in a low- resource, rural setting in Bangladesh. Quality evidence from the trial will help inform policies on whether concrete flooring installation may serve as a public health intervention to improve child health.

Effectiveness of an mHealth Interactive Education and Social Support Intervention for Improving Postnatal Health (HD108510-02). The major goals of this study are to provide tailored interactive education and support to women in India during their postnatal period using a mobile social network that improves knowledge of health-promoting behaviors, parental self-efficacy, and empowerment. By appropriately identifying infant and maternal health danger signs, encouraging timely care-seeking for routine and emergency visits, and changing perspectives on best maternal and infant care practices, the investigators seek to impact behaviors and outcomes that can reduce both infant and maternal morbidity. Furthermore, mHealth group support could help encourage and sustain exclusive breastfeeding and improve uptake of postnatal family planning and childhood vaccination, which positively affect both short- and long-term maternal and child health.

Placental miRNAs Paracrine and Endocrine Roles in Insulin Sensitivity in Pregnancy (HD109206-02). Evidence suggests that micro RNA (miRNA) produced in the placenta and regulated by maternal glycemia, act locally and peripherally to manipulate maternal insulin sensitivity during pregnancy. This study is investigating mechanisms by which previously identified placental miRNA candidates may participate in this interplay between placenta and glucose-insulin regulation during pregnancy. Investigators are leveraging existing perinatal cohorts and data, including longitudinal prospectively collected plasma samples and insulin-sensitivity index data derived from oral glucose tolerance tests in the first, second, and third trimesters. Use of in vitro human primary cellular models will allow researchers to directly test the function of placenta-derived miRNA locally (paracrine actions in placenta), and in insulin-sensitive peripheral tissues (endocrine actions). A detailed understanding of the function and regulation of these placental miRNA may provide novel targets for treatment of pathophysiological decreases in insulin sensitivity.

AI-Driven Low-Cost Ultrasound for Automated Quantification of Hypertension, Preeclampsia, and Intrauterine Growth Restriction (IUGR) (HD110480-01). Challenges in accessing affordable technologies to screen and monitor high-risk maternal-fetal conditions, such as IUGR and preeclampsia, contribute to high rates of perinatal mortality in low-resource settings in part to. To address these challenges, this work will apply a novel AI approach to diagnosing of IUGR, maternal hypertension, and preeclampsia using a low-cost, easily available, and easy to operate (1-D doppler ultrasound) solution for unique populations in rural Guatemala and urban Georgia.

Premature Infants Receiving Umbilical Cord Milking or Delayed Cord Clamping (HD088646-05). Preterm brain injury from intraventricular hemorrhage is a pressing worldwide public health problem. Delayed cord clamping reduces overall bleeding in the brain of preterm infants, but is not effective for the most severe types. "Milking" the umbilical cord, a method used to transfer blood from the placenta into the baby before the umbilical cord is clamped, may provide additional blood volume to the brain and other vital organs, thereby reducing bleeding in the brain and improving long-term outcomes in these babies. This study will determine whether umbilical cord milking reduces bleeding in the brain or death in preterm newborns delivered by Cesarean section compared to delayed clamping of the umbilical cord. Sites in Canada, Ireland, and Germany are participating in this study along with six U.S. sites.

Spreading the Integrated District Evidence-to-Action (IDEAs) Program for Neonatal Mortality Reduction in Mozambique (HD092449-05). Researchers based in the United States and Mozambique are investigating the implementation and dissemination of the evidence-based clinical intervention called IDEAs, an audit and feedback implementation intervention, to improve the coverage and quality of evidenced-based clinical interventions for neonates in Mozambique. If proven successful, this approach has the capacity to reduce the burden of neonatal mortality in low-income countries.

Development and Validation of MRI methods for In Vivo Assessment of Placental Perfusion and Oxygen Transport (HD108833-01A1). This study is implementing and validating a multimodal MRI approach to comprehensively study maternal and fetal-side placental perfusion characteristics in a translational animal model. U.S. investigators are collaborating with researchers at King's College and University College, both in London. By combining the expertise of their research teams, researchers will leverage the nonhuman primate model to conduct studies that cannot be achieved in humans. The experimental design will test the diagnostic sensitivity of the methodology to identify placental insufficiency, with an overall goal of translating these methods for future clinical diagnostic use.

Umbilical Cord Milking in Non-Vigorous Infants: The MINVI Trial (HD096023-05). This trial is the first to compare outcomes for non-vigorous term and near-term infants after cord milking or immediate cord clamping. The trial will provide important new physiological insights into the effects of immediate cord clamping and umbilical cord milking on term non-vigorous infant. Sites in Canada are participating in this study along with eight U.S. sites.

Mobile WACh NEO: Mobile Solutions for Neonatal Health and Maternal Support (HD098105-06). This RCT aims to determine the effect and mechanisms of a two-way mobile health (mHealth) SMS intervention, called Mobile WACh NEO, in Kenya. Key goals of this work are to reduce neonatal mortality and improve essential newborn practices, care-seeking, and maternal mental health outcomes during the first 6 weeks postpartum.

University of North Carolina (UNC) Global Women's Health Fellowship (HD075731-09). The UNC Global Women's Health Fellowship, currently in its second 5-year cycle, is a collaborative program between UNC and its in-country partners in Malawi, South Africa, and Zambia that emphasizes training of obstetrician/gynecologists for careers in global women's health research. These fellows help address the most relevant and pressing issues in the field through

dedicated research time in international settings. They participate in regular forums with peers, mentors, and resource faculty to review and critique work in progress, while also receiving guidance on submission of abstracts, publications, proposals for research funding, and career development.

Group Antenatal Care to Promote a Healthy Pregnancy and Optimize Maternal and Newborn Outcomes: A Cluster RCT in Ghana (HD096277-05). To address the significant gaps in health literacy and the resulting poor outcomes among pregnant women in Ghana, this study proposes a bold, new approach to antenatal care. This work takes antenatal care out of exam rooms and brings it to small groups of women in similar stages of pregnancy, at primary care community health centers. Group antenatal care has the potential to shift the current clinical practice paradigm of antenatal care for highly vulnerable women to improve maternal and newborn outcomes both globally and domestically.

Two-Year Outcomes After Dextrose Gel Prophylaxis for Neonatal Hypoglycemia (HD091075-05). Researchers from Liggin's Institute and the 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. This follow-up study aims to determine benefits or adverse effects at two years' corrected age. Assessments include standardized measures of neurological status, developmental status, executive function, vision and visual processing, physical size, general health, and family environment. Approximately 30 percent of babies are born at risk of hypoglycemia and, hence, may be eligible for dextrose gel prophylaxis if it proves effective. This follow-up study will provide crucial evidence of longer term efficacy and safety for the gel that is essential before widespread introduction into clinical practice.

Maternal Antecedents and Electronic Fetal Monitoring in Term Asphyxia (MAESTRA) (HD099216-01A1). There is an urgent need to increase the sensitivity and specificity of electronic fetal monitoring (EFM) to discriminate fetuses at high risk for hypoxic-ischemic encephalopathy (HIE), and to do so with sufficient lead time to implement effective preventative interventions. Past EFM research was limited by an inability to access and manually analyze datasets large enough to study HIE. The researchers, in collaboration with McGill University in Canada, will use automated methods to analyze digital EFM signals, measure standard fetal heart rate patterns, and discover new aspects of the EFM tracing that may not be readily detectable by a clinician at the bedside. Massive improvements in machine-

learning techniques and the ability to aggregate large amounts of digital data provide an unprecedented opportunity to apply these powerful techniques to this important clinical problem.

Global Health Partnerships

PPB collaborates with the BMGF and the Foundation for NIH to support the Global Network.

Staff Membership on Global Health Committees/Working Groups

N/A

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National Center for Medical Rehabilitation Research (NCMRR)

Scientific Scope

NCMRR fosters the development of scientific knowledge needed to enhance the health, productivity, independence, and quality of life of persons with disabilities, by supporting research to enhance the functioning of people with disabilities in daily life, and to develop and evaluate 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 Global Health 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 recommends coordinated and collaborative global action on several fronts, including improvements to leadership and governance, service provision, financing, human resources, data collection, and research capacity for rehabilitation. NIH was a major contributor to this effort.

In 2022-2023, NCMRR financially supported WHO Rehabilitation 2030 through a cooperative agreement mechanism managed by NIAID to:

- Increase the global capacity for biomedical and health systems research in rehabilitation

- Develop an open-source web-based tool to increase access and uptake of the WHO package of evidence-based rehabilitation interventions

- Develop a clinical management resource to facilitate the integration of the WHO package of evidence-based rehabilitation interventions into primary health care

- Develop a global rehabilitation "tracer" indicator that will enable the collection of reliable information about effective coverage of rehabilitation through population-based surveys

- Develop a guide and exercise book to support implementation of the [District Health Information Systems 2 (DHIS2) Rehabilitation module](#)

Recent Achievements in Global Health

At the World Health Assembly in May 2023, [participants unanimously passed a resolution on strengthening rehabilitation in health systems](#). The resolution calls for expanding and integrating rehabilitation in health systems as part of Universal Health Coverage, emphasizing the importance of rehabilitation in both primary care and as part of emergency preparedness and response.

In July 2023, NIH participated in the [3rd Global Rehabilitation 2030 meeting and launch of the World Rehabilitation Alliance](#), to launch new tools developed by WHO to facilitate implementation of the World Health Assembly resolution.

Global Health Partnerships

Johns Hopkins University (JHU)-Hanoi University of Public Health (HUPH) Research Program on Health, Economic and Societal Consequences of Trauma and Injuries in Vietnam ([5D43TW012191-03](#)). The overall goal of this program is to strengthen research capacity for generating data and interventions that address the post-injury and post-trauma rehabilitation needs of individuals in Vietnam, as well as to understand the long-term health, economic, and societal consequences of trauma and injuries. The approach involves close collaboration between two institutions: JHU Bloomberg School of Public Health, USA, and HUPH, Vietnam. Each entity is strongly committed to understanding the public health impact of trauma and injuries, building experience and expertise in researching trauma and injuries, and contributing to a history of collaborative work. The program will use

collaborative resources and expertise to strengthen HUPH; promote a sustainable research enterprise focused on injuries, trauma, and their consequences; and use research evidence to inform national health policy in Vietnam. In the first two years of the project, the team has made progress on developing research capacity, hosting educational workshops, and establishing competency frameworks in Hanoi.

Designing Computer-Mediated Communication Supports to Improve Social Participation After TBI (HD071089-09). Adults with TBI experience less social participation and more social isolation than 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 platforms are 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 are testing how individuals with TBI use and interact with the software, with the goal of improving use and communication among adults with TBI. The PI from McMaster University, Ontario, Canada, has expertise in communication after TBI, and helped develop clinical practice guidelines for the treatment of TBI; her lab will assist with evaluation of the software and future developments to implement the software more broadly. In 2023, the PIs published findings in the journal *Brain Injury* (PMID: 37902249), namely that people with TBI had poorer accuracy for labeling social emotions depicted by emojis compared to basic emotions depicted by emojis. This outcome may be reflective of impaired understanding of functional communication and may contribute to reduced social participation after brain injury.

A Client-Based Outcome System for Individuals with Lower Limb Amputation (HD065340-10). Individuals with loss or structural difference of the lower limb 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. Many validated measures allow assessment of functional abilities in individuals with limb loss, but those measures may be time-consuming and 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 began by compiling a pool of 100 candidate questions or tasks that could be included in the final instrument. The project team then recruited 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.

Researchers at the University of Washington are evaluating the collected data to develop the new, computer-based, adaptive tool for assessing functional ability in these individuals. In 2022, the group published [several manuscripts](#), including a Japanese translation and linguistic validation of the tool. In 2023, the PIs published data on the Prosthetic Limb Users Survey of Mobility (PLUS-M) tool, including the 7- and 12-item short forms. The evaluation showed that the tools measured with precision across a wide range of respondents, exhibited little-to-no ceiling or floor effects, correlated expectedly with scores from existing patient reported outcome measures, and differentiated between groups of respondents expected to have different levels of mobility.

A Longitudinal Population-Based Birth Cohort Study to Understand the Past, Present, and Future of Children and Youth with TBI ([HD104206-02](#)). Some effects of pediatric TBI are evident immediately. Because pediatric TBI disrupts brain development, as well as brain health, many effects can take years to become apparent. This research project will ascertain the short- and long-term effects of pediatric TBI, an outcome and audience that the CDC notes has insufficient data repositories, by producing a dataset covering over 4 million live births in Ontario, Canada, between 1992 and 2020. It will 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, takes advantage of unique healthcare datasets 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 levels of health care utilization for individuals with TBI.

Calibrating Transcutaneous Spinal Stimulation for Spasticity, Pain, and Motor Function in Spinal Cord Injury (SCI) ([HD101812-03](#)). SCI typically results in the loss of sensation and control of muscles below the level of the injury. Individuals with SCI can also experience uncontrolled muscle contractions, called spasticity, and severe pain that can greatly disrupt their ability to participate in activities of daily living and maintain employment. This study uses transcutaneous spinal stimulation to relieve spasticity and pain in individuals with SCI, while also restoring some motor function. Transcutaneous spinal stimulation involves placing an electrical device over the lower spine to stimulate nerves where they exit the spinal cord. The effort includes a PI at the Medical University of Vienna, Center for Medical Physics and Biomedical Engineering, in Austria; as a leading international expert in

transcutaneous spinal stimulation, the investigator will assist with analysis and interpretation of results.

Multiscale Models of Proprioceptive Encoding to Reveal Mechanisms of Impaired Sensorimotor Control (HD090642-08). 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 is exploring how altered neural input to muscles drives hyper-resistance in joints for a variety of neurological conditions. Utilizing computer models and animal experiments, investigators will study changes in different types of neural input, and how those changes may lead to hyper-resistance in joints. Researchers will then use these data to inform clinical exams and better understand neurological deficits at the patient level for more personalized clinical care. The investigators are also collaborating with a computer-modeling expert, who specializes in modeling humans with cerebral palsy, at Katholieke Universiteit Leuven in Belgium; the collaborator will provide vital input allowing comparison of models and data from this study to the human condition. Applying this expertise will help increase the impact of the work and provide an avenue for clinical translation in the future. In 2023, the PIs published several papers including a review in the *Journal of Biomechanics* (PMID: 37285780) summarizing the efforts to develop muscle and musculoskeletal models for biomechanics in the last 50 years.

Quantifying the Energetic Cost of Support and Stabilization During Walking in Children with Cerebral Palsy (HD104112-02). Walking not only allows individuals to complete their daily activities, but it is also a highly efficient metabolic activity. Individuals with cerebral palsy can require twice the energy to walk the same distance as someone without cerebral palsy. Although assistive technology, rehabilitation, and surgery can help individuals with cerebral palsy to walk, these interventions have not made meaningful improvements in the energy efficiency of walking for these groups. 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. Using a special treadmill that can provide weight and balance support to the walker, researchers can measure how much energy is used during regular walking versus walking with the treadmill providing these supports. An expert in experimental measurement and computation analysis of energy expenditure, at Simon Fraser University in Canada, is contributing to design of experiments and analysis of the results. In 2023, the PIs published in *PloS One* (PMID: 37224117) a study of over 2,000 children with cerebral palsy showing that gait patterns deviations had the greatest effect on metabolic power, suggesting that children

with cerebral palsy may benefit more from treatments that improve their gait pattern and motor control, than from treatments that improve spasticity or strength.

Lumbar Spine-Muscle Degeneration Inhibits Rehabilitation-Induced Muscle Recovery (HD088437). 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. Using MRI and gene expression profiles, the study seeks to characterize the structural, physiological, and adaptive potential of back muscles in response to exercise among patients with disc injury. A collaborator at Balgrist University in Switzerland is conducting a similar, but independent study, and agreed to share data with the PI of this project to draw broader conclusions and potentially increase the impact of the work. In 2022, this collaboration resulted in a publication that revealed fibrogenic and adipogenic/metabolic genes were related to pre-operative muscle quality, and that myogenic genes were related to pre-operative muscle size (PMID: 35739523). These findings provide insight into molecular pathways associated with muscle health in the presence of lumbar spine pathology, establishing a foundation for future research that addresses how these changes impact outcomes in this patient population. Although this grant has ended, the PIs continue to publish outcomes, including differences in gene expression based on underlying lumbar pathologies.

Neuroergonomic Assessment of Wheelchair Control in Real-World Environments with Both Healthy and Clinical Populations (HD103527-03). Neuroergonomics is an emerging field that investigates the neural brain mechanisms underlying human perceptual, cognitive, and motor functioning in relation to behavioral performance in natural environments and everyday settings to expand understanding of this scientific area, with a focus on real-world contexts. This study uses neuroergonomics 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 and provide a new framework for understanding human-machine interactions. In 2022, the international group published a study in *Scientific Reports* demonstrating that developmental coordination disorder is a motor-cognitive disability; functional near infrared spectroscopy during gross motor/complex tasks revealed neuro-hemodynamic deficits and dysfunction within the right middle and superior frontal gyri of the

prefrontal cortex (PMID: [35715433](#)). Even though this fellowship has ended, the group continues to publish, including a paper in *Clinical Biomechanics* (PMID: [36764101](#)), which noted that rhythmic cueing showed strong promise for enhancing motor learning in children with probable developmental coordination disorder.

A Neuromusculoskeletal Interface for Bionic Arms: A Randomized Crossover Study ([NS127063-01A1](#)). In this collaboration between Northwestern University, the Shirley Ryan Ability Lab, the University of Chicago, and Chalmers Tekiniska Hogskola in Sweden, the PIs are extending osseointegration technology, pioneered in Sweden, with implanted electromyography electrodes to control a prosthesis and provide sensory feedback to the patient. The study is collecting preliminary safety data and will validate the efficacy of this implant system for individuals with upper limb transhumeral amputation at home.

Full Participation of People with Physical Disabilities in Active eSports ([HD111712-01](#)). Active eSports—virtual activities that use the player's body as the "controller"—are the world's fastest growing sport, especially with increasing recognition by bodies such as the International Olympic Committee. Additional research on the barriers to and benefits of participation is needed for people with disabilities to fully participate in these activities. This project, led by an early-stage investigator from Canada who is now at Cedars-Sinai Medical Center in Los Angeles, hopes to capitalize on two international groups—the Canadian Disability Participation Project and Invictus Games Foundation—to understand the experiences and perceptions of people with disabilities who participate in active eSports. This project seeks to create a knowledge base that can inform future research to promote full participation in the active eSport community.

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

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Division of Intramural Research (DIR)

DIR plans and conducts the institute's laboratory, clinical, and epidemiological research programs to:

- Seek fundamental knowledge about the nature and behavior of living systems through basic, clinical, and population-based research

- Determine how to apply such knowledge to illuminate developmental origins of health and disease, in pursuit of the NICHD mission

DIR 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 59 tenured and tenure-track investigators, organized into 12 affinity groups (AGs), and approximately 260 postbaccalaureate, clinical, and postdoctoral fellows and graduate students.

DIR also includes the Division of Population Health Research (DiPHR), which designs and conducts research that addresses critical data gaps to advance understanding of factors that impact human health. DiPHR research is particularly relevant to the health and well-being of the public and special populations, and utilizes novel methodologies and statistical tools, including those developed by DiPHR investigators. The work also identifies critical data gaps and designs research to answer etiologic questions and evaluate interventions aimed at modifying behavior. DiPHR does not have any global health research activities to report at this time.

The 12 AGs are intellectual hubs for groups of investigators, offering 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, and 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

AG 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 Pediatric and Adolescent Gynecology (PAG)

PI: Veronica Gomez-Lobo, M.D.

AG: Reproductive Endocrinology & Infertility and Pediatric & Adolescent Gynecology

Scientific Scope

PAG's major scientific focus is on research regarding fertility preservation.

Major International Research Initiatives/Collaborators

Dr. Gomez-Lobo is mentoring and collaborating with Dr. Anthony Kayiira, an FIC Global Fellowship recipient from Uganda, in studying fertility preservation issues in low-resource settings. They have collaborated on three publications. Dr. Kayira is enrolled in the leadership group of the Oncofertility Consortium's Pediatric Initiative Network and presented a webinar on their work. Dr. Gomez-Lobo is mentoring Dr. Kayira as he applies for future funding to study dry ovarian tissue preservation.

PAG also collaborates on a large study to develop clinician-led digital tools for improved diagnosis and treatment of pediatric adolescent and young adult oncofertility patients. The study is funded through the funded through the Australian government and focuses on patients involved in the Australian and New Zealand College of Anesthesiologists (ANZCA) Clinical Trials Network.

The section also works with Dr. Yasmin Jayasinghe, a pediatric gynecologist and Director of Oncofertility at The Royal Children's Hospital, Australia, to create a digital ovarian histology image bank. This effort is also using AI to predict ovarian function after cancer therapy.

Publications with International Collaborators

- Kayiira A, Xiong S, Zaake D, Balagadde JK, Gomez-Lobo V, Wabinga H, Ghebre R. Shared decision-making about future fertility in childhood cancer survivorship: Perspectives of parents in Uganda. *J Adolesc Young Adult Oncol.* 2023 Feb 14. doi: 10.1089/jayao.2022.0127. Epub ahead of print. PMID: 36787466.

- Kayiira A, Neda John J, Zaake D, Xiong S, Kambugu Balagadde J, Gomez-Lobo V, Wabinga H, Ghebre R. Understanding fertility attitudes and outcomes among survivors of adolescent and young adult cancers in a low-resource setting: A registry-based computer-assisted telephone interview survey. *J*

Adolesc Young Adult Oncol. 2022 Dec 28. doi: 10.1089/jayao.2022.0114. Epub ahead of print. PMID: [36579945](#).

Recent Achievements in International Research

N/A

International Research Trainees

N/A

International Partnerships

N/A

Staff Membership on International Committees/Working Groups

N/A

Point-of-Contact

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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, including pheochromocytoma and paraganglioma.

Major International Research Initiatives/Collaborators

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 Research

N/A

International Research Trainees

N/A

International Partnerships

N/A

Staff Membership on International 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

The SHDBEM uses an integrated program of laboratory and clinical investigation to study the molecular biology of heritable connective tissue disorders collectively known as osteogenesis imperfecta (OI). The lab's objective is to elucidate the mechanisms by which the primary gene defect in OI causes skeletal fragility and other connective-tissue symptoms, and to apply this knowledge to patient treatment.

Major International Research Initiatives/Collaborators

- Prof. Antonella Forlino, University of Pavia, Italy

- Prof. Nadja Fratzl-Zelman, Osteology Institute of Vienna, Austria

Publications with International Collaborators

- Fratzl-Zelman, N., Rochger, P., Kang, H, Jha, S., Roschger, A., Blouin, S., Deng, Z., Cabral, W.A., Ivovic, A., Katz, J., Siegel, R.M., Klaushofer, K., Fratzl, P., Bhattacharyya, T., Marini, J.C. (2019). Melorheostotic bone lesions caused by somatic mutations in MAP2K1 have deteriorated microarchitecture and periosteal reaction. *J Bone Miner Res.* 34:833-895. PMID: 30667555

- Kang, H., Jha, S., Ivovic, A., Fratzl-Zelman, N., Deng, Z., Mitra, A., Cabral, W.A., Hanson, E.P., Lange, E., Cowen, E.W., Katz, J., Roschger, P., Klaushofer, K., Dale, R.K., Siegel, R.M., Bhattacharyya, T., and Marini, J.C. (2020). SMAD3 somatic activating mutations cause melorheostosis with an endosteal radiographic pattern by upregulating the TGFb/SMAD pathway. *J Exp Med May 4; 217*(5) e:20191499. PMID: 32232430

- 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 osteogenesis imperfecta bone dysplasia. *Matrix Biology Aug;* 90:20-39. PMID: 32112888

- Hedjazi, G., Gutterman-Ram, G., Blouiin, S., Schemenz, V., Wagermaier, W., Fratzl, P.,Hartmann, M.A. Zwerina, J., Fratzl-Zelman, N., Marini, J.C., (2022). Alterations of bone material properties in growing Ifitm5 p.S42L knock-in mice, a new model for atypical type VI osteogenesis imperfecta. *Bone*, 162: 116451. PMID: [35654352](#)

- Besio, R., Chow, C-W, Tonelli, F., Marini, J.C., Forlino, A. (2019). Bone biology: Insights from osteogenesis imperfecta and related rare fragility syndromes (Invited Review). *FEBS J. 2019 Aug;286*(15):3033-3056. doi: 10.1111/febs.14963. PMID: [31220415](#)

- Garibaldi, N., Contento, B.M., Babini, G., Morini, J., Siciliani, S., Biggiogera, M., Raspanti, M., Marini, J.C., Rossi, A., Forlino, A., Besio, R. (2021). Targeting cellular stress improves osteoblast homeostasis and matrix in murine models of osteogenesis imperfecta. *Matrix Biology. Apr*;98:1-20. doi: 10.1016/j.matbio.2021.03.001. Epub 2021 Mar 31. PMID: [33798677](#)

- Garibaldi, N., Besio, R., Dalgleish, R., Villani, S., Barnes, A.M., Marini, J.C., Forlino, A. (2022). Dissecting the phenotypic variability of Osteogenesis Imperfecta. *Disease Models and Mechanisms. May 1:15*(5): dmm049398; doi: 10.1242/dmm049398. PMID: [35575034](#)

- Besio, R., Contento, B.M., Garibaldi, N., Filibian, M., Sontagg, S., Shmerling, D, Biggiogera, M., Brini, M., Jovanovic, M., Marini, J.C., Forlino, A. (2023). CaMKII inhibition due to TRIC-B loss-of-function dysregulates SMAD signaling in osteogenesis imperfecta. *Matrix Biology*, 120:43-59. PMID: [37178987](#).

- Jovanovic, M., Mitra, A., Besio, R., Contento, B.M., Wong, K.W., Derkyi, A., To, M., Forlino, A., Dale, R.K., and Marini, J.C. (2023). Absence of TRIC-B from Type XIV OI osteoblastos alters cell adhesion and mitochondrial function: A multi-omics study. *Matrix Biology*, Jun 20:S0945-053X(23)00075-6. doi: 10.1016/j.matbio.2023.06.004. Online ahead of print. PMID: [37348683](#).

Recent Achievements in International Research

N/A

International Research Trainees

N/A

International Partnerships

N/A

Staff Membership on International 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 and Translational Imaging

Scientific Scope

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

Major International Research Initiatives/Collaborators

- Morphological analysis of extracellular vesicles generated by cytomegalovirus-infected cells and their role in HIV infection: A collaborative project. PI: Dr. Eva Povedra, Virology and Pathogenesis Department, Galicia Sur Health Research Institute, Spain

- Educational project. PI: Dr. D. Mikeladze, Ilia University, Tbilisi, Republic of Georgia

Publications with International Collaborators

N/A

Recent Achievements in International Research

N/A

International Research Trainees

N/A

International Partnerships

N/A

Staff Membership on International Committees/Working Groups

N/A

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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 and is investigating the regulation and function of selected TH target genes during TH-dependent organ remodeling in Xenopus and/or mouse.

Major International Research Initiatives/Collaborators

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

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 in regulating notochord resorption during Xenopus metamorphosis. The team also analyzed the expression program that underlies 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, China. 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 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 at Gifu Pharmaceutical University, Japan, SMM then showed that the transporter also plays a role in mouse hypothalamic neurons, to maintain energy and bone homeostasis.

In collaboration with scientists at South-Central University for Nationalities and Xi'an Jiaotong University School of Medicine, China, SMM showed that intestinal epithelial-specific knockout of the protein arginine methyltransferase 1, a coactivator for TR, leads to, surprisingly, increased cell proliferation in adult mouse intestinal crypt. This finding suggests an important role for the protein, beyond being 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, both in China, revealed that hepatitis B virus affects viral replication and hepatocellular migration and invasion by using miRNAs, and that that placenta-specific protein 9 inhibits proliferation and stimulates motility of human bronchial epithelial cells.

Another collaboration, recently initiated via joint graduate student with CNRS Muséum National d'Histoire Naturelle, France, will study if and how epigenetic changes are involved in TH regulation of anuran development.

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

Publications with International Collaborators

- Wang, S., Liu, L., Shi, Y.-B., Jiang, J. (2021). Transcriptome profiling reveals gene regulation programs underlying tail development in the Ornamented Pygmy frog *Microhyla fissipes*. *Frontiers In Bioscience-Landmark. 26*(11):1001-1012, DOI:10.52586/5004. PMID: 34856748.

- 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. PMID: 31794731.

- 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. PMID: [33076783](#).

- 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 regulates amino acid transporter Slc7a5 and so constrains the integrated stress response in mouse embryos. *EMBO Reports.* 21: e48469, 1-20. PMID: [31789450](#).

- 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. doi: 10.1186/s13578-021-00627-z. PMID: [34158114](#).

- Bao, L., Shi, B., and Shi, Y.-B. (2020). Viewpoint: Intestinal homeostasis: A communication between life and death. *Cell & Bioscience. 10*:66, 1-3. PMID: [32477489](#)

- 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. PMID: [34123785](#).

- Liu, Y., Wang, J., Chen, J., Wu, S., Zeng, X., Xiong, Q., Guo, Y., Sun, J., Song, F., Xu, J., Yuan, S., Li, C., He, Y., Wang, M., Chen, L., Shi, Y.-B., M. Guo, Guo, D., and Sun, G. (2022). Upregulation of miR-520c-3p via hepatitis B virus drives hepatocellular migration and invasion by the PTEN/AKT/NF-κB axis. *Mol Ther Nucleic Acids. 29*:47-63. https://doi.org/10.1016/j.omtn.2022.05.031. PMID: [35795482](#).

- Paul, B., Sterner, Z.R., Buchholz, D.R., Shi, Y.-B., and Sachs, L.M. (2022) Thyroid and corticosteroid signaling in amphibian metamorphosis. *Cells 11*:1595, 1-23. https://doi.org/ 10.3390/cells11101595 PMID: [35626631](#).

- Park, G., Fukasawa, K., Horie, T., Masuo, T., Inaba, T., Tatsuno, T., Yamada, T., Tokumura, K., Iwahashi, S., Iezaki, T., Kaneda, K., Kato, Y., Ishigaki, Y., Mieda, M., Tanaka, T., Ogawa, K., Ochi, H., Sato, S., Shi, Y.-B., Inoue, H., Lee, H., Hinoi, E. (2023) l-type amino acid transporter 1 in hypothalamic neurons in mice

maintains energy and bone homeostasis. *JCI Insight. 8*(7):e154925, 1-19. https://doi.org/10.1172/jci.insight.154925 PMID: 36862514.

Recent Achievements in International Research

N/A

International Research Trainees

- Shouhong Wang, Graduate Student, Chengdu Institute of Biology, China

- Lingyu Bao, Graduate Student, Xi'an Jiaotong University School of Medicine, China

- Zhaoyi Peng, Graduate Student, Xi'an Jiaotong University School of Medicine, China

- Emeric Louis, Graduate Student, UMR 7221 CNRS Muséum National d'Histoire Naturelle, FRANCE

International Partnerships

N/A

Staff Membership on International 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

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. This multidisciplinary work aims to generate holistic models for investigating 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 Research Initiatives

SMN collaborated with Dr. Miguel Skirzewski, who began his scientific career at the University of the Andes in Venezuela and presently works at the University of Western Ontario in Canada, to understand how modulation of ErbB4 receptor activity regulates numerous behaviors with relevance to schizophrenia in rodents. Work with Dr. Skirzewski originally used neurochemical techniques to measure changes in dopamine levels in NRG2 and ErbB4 knockout mice. More recently, SMN is applying 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 also collaborated with Dr. Tanveer Ahmad, presently at the Department of Biochemistry, University Grants Commission in New Delhi, to investigate how initially unprocessed proNRG3 is proteolytically cleaved by BACE-1 in the Golgi apparatus and, subsequently, packaged and transported to axons by transcytosis. This collaboration found that, by a mechanism denoted as "trans-synaptic retention," the biologically active NRG3 peptic accumulates selectively at presynaptic axonal terminals by virtue of its stable interactions with ErbB4 receptors, Neuregulin receptors that are specifically expressed on postsynaptic GABAergic interneurons. The team proposed that trans-synaptic retention may

account for polarized expression of other neuronal transmembrane ligands and receptors. 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

- 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. PMID: 32354758

- Ahmad T., Vullhorst D., Chaudhuri R., Guardia C.M., Chaudhary N., Karavanova I., Bonifacino J.S., and Buonanno A. (2022). Transcytosis and trans-synaptic retention by postsynaptic ErbB4 underlie axonal accumulation of NRG3. J Cell Biol 221(7):e202110167. doi: 10.1083/jcb.202110167. PMID: 35579602

Recent Achievements in International Research

N/A

International Research 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, USA

- Swagata Roychowdhury-Basu, Ph.D.
  Technical Writer for Neuroscience Advances
  Inscopix, Inc.
  Mountain View, California, USA

- Soledad Calvo, M.D., Ph.D.
  Assistant Professor
  Facultad de Medicina at Alicante University
  Spain

- Claudia Colina-Prisco, Ph.D.
  Postdoctoral Fellow
  National Institute on Alcohol Abuse and Alcoholism, NIH
  Universidad Central de Venezuela

- Larissa Erben, Ph.D.
  Postdoctoral Fellow
  NICHD
  University of Bonn, Germany

- Rolando Garcia,Ph.D.
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  Gaithersburg, Maryland, USA

- Carmen M. Gonzalez, Ph.D.
  Department of Pathology and Experimental Therapy
  University of Barcelona
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- Ryoichi Kimura, Ph.D.
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  Department of Physiology, Hyogo College of Medicine
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  Facultad de Química y Biología Universidad de Santiago
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- Joerg Neddens, Ph.D.
  Senior Scientist Department of Histology
  JSW Life Sciences
  Austria

- Daniel Paredes, Ph.D.
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  Lieber Institute for Brain Development
  Baltimore, Maryland, USA

- 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.
  Research Associate
  University of Western Ontario
  Canada

- Raluca Yonescu, Ph.D.
  Senior Research Specialist
  Johns Hopkins Cytogenetics
  Maryland, USA

International Partnerships

- Universidad de los Andes, Merida, Venezuela. Memorandum of Understanding (MOU) and joint graduate student stipend for Dr. Miguel Skirzewski

- University of Bonn, Bonn, Germany. MOU for graduate student stipend for Dr. Larissa Erben

Staff Membership on International Committees/Working Groups

N/A

Point-of-Contact

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