2022 | NICHD Global Health Catalog

Office of the Director | Office of Global Health

Eunice Kennedy Shriver National Institute of Child Health and Human Development

2022 NICHD Global Health Activities Catalog

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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 that 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 new 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 intramural research (e.g., basic science) with international collaborators.

The NICHD Office of Global Health (OGH) resides within the Office of the Director 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, 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

COVID-19 Pandemic Research Response. Over this past year, the biomedical research community has aimed to transition from the predominant world-wide focus on the COVID-19 pandemic to other pressing health research areas. OGH represents NICHD in ongoing interagency discussions on the U.S. government's COVID-19 response organized by the HHS Office of Global Affairs (OGA), the Fogarty International Center (FIC) at NIH, and the United States Agency for International Development (USAID) Advancing Protection and Care for Children in Adversity (APCCA) Interagency Working Group. While discussions continue on best practices for addressing disrupted research and training activities in multiple countries, the Biden administration's renewed commitment to close collaborations between the United States and the World Health Organization (WHO) has helped facilitate this work. NICHD also provided input related to maternal and child health policy documents for the World Health Assembly held in May 2022.

NICHD Strategic Plan: The Wefting of Global Health. Although the implementation of the NICHD Strategic Plan was delayed by the COVID-19 pandemic, OGH has contributed in two capacities to the identification of research priorities in the plan: 1) as co-chair for Research Theme 4A focused on child health and development, and 2) as the lead for the "wefting" of global health research priorities throughout the different components of the plan. In the next phase of implementation, OGH intends to further improve real-time communications about global health priorities between the NICHD OD, including OGH, and other NICHD components, particularly on key global health research issues, science advances, and interagency activities.

NICHD virtual global health conference: Socio-ecological Factors and the Double Burden of Malnutrition Among Children and Adolescents in Low- and Middle-Income Countries (LMICs), October 19-20, 2022. Following discussions with senior NICHD leadership, it was determined that an important global health research priority area was better understanding the impact of malnutrition on child

growth and development in low-resource settings world-wide. In fact, to address global malnutrition as a high priority area, the Biden administration organized the *White House Conference on Hunger, Nutrition, and Health*, held September 28, 2022. Several themes from the White House conference complemented the NICHD conference. To conceptualize and identify priority research topics for the NICHD conference, OGH worked closely with NICHD staff from the Pediatric Growth and Nutrition Branch (PGNB), Population Dynamics Branch (PDB), Intellectual Development and Disabilities Branch (IDDB), and Maternal and Pediatric Infectious Disease Branch (MPIDB) and received input from FIC. The conference sought to better understand recent etiological and socio-ecological factors contributing to the increased prevalence of the double burden of malnutrition (i.e., the simultaneous manifestation of both undernutrition and overweight and obesity) and the implications for long-term health outcomes for children, age 3 to 18 years, in LMICs. Discussions included a holistic, multifaceted approach in line with the Socio-Ecological Model by examining behavioral changes for healthy eating and lifestyle practices, social determinants of health, implementation science, and double-duty approaches to interventions, programs, and policies. Proceedings from the meeting, including approaches to addressing identified research gaps by developing new research opportunities, trainings, and interagency partnerships will be published in a scientific journal. As a corollary to the conference, OGH also worked closely with FIC staff to develop the Global Food and Nutrition Insecurity webinar series.

NIH collaboration with the Bill and Melinda Gates Foundation (BMGF). In 2022, NIH continued to work closely with BMGF on accelerating progress related to the COVID-19 pandemic and the development of diagnostic tests, vaccines, therapeutics, among other resources. NICHD co-chairs the NIH Maternal, Neonatal, and Child Health (MNCH) and the Contraceptive Research Working Groups, which include representation from NICHD, BMGF, the National Institute of Mental Health (NIMH), the National Institute of Drug Abuse (NIDA), the National Institute of Neurological Disorders and Stroke (NINDS), National Heart, Lung, & Blood Institute (NHLBI), and the NIH Environmental Influences on Child Health Outcomes (ECHO) Program, among others. These working groups aim to identify new research collaborations in the areas of COVID-19, pregnancy outcomes, nutrition and growth, child neurodevelopment, neuroimaging, and contraception development, among other areas. This year's Annual NIH-BMGF Leadership Workshop held in December 2022 included over 200 representatives from the NIH and BMGF. The opening plenary sessions were co-chaired by Dr. Anthony Fauci (NIH) and Mr. Bill Gates (BMGF), with a focus on disruptive global health technologies targeting infectious diseases and

vaccine development. Subsequent sessions focused on the work of 14 working groups and covered an array of global health research topics. The NIH-BMGF MNCH Working Group highlighted the NICHD Global Network's Azithromycin-Prevention in Labor Use Study (A-PLUS) results, which found that azithromycin given to women in labor in LMIC settings was effective in reducing maternal death and sepsis.

U.S.-Africa Leaders' Summit, December 13-15, 2022, Washington, D.C. OGH assisted with preparations and reported on NICHD-funded research in Africa for the NIH and HHS events held as part of this Summit, organized by the Biden Administration. President Biden and Vice President Harris attended the opening plenary sessions of this Summit, which underscored the importance of U.S.-Africa relations and increased cooperation on shared global priorities. HHS Secretary Becerra held a health-focused auxiliary event, which included NIH, other HHS agencies, like the Centers for Disease Control and Prevention (CDC), to discuss innovation and research, regulatory harmonization, health workforce issues, and health systems strengthening. NIH also hosted a global health research meeting with several African Ministers of Health to discuss genomics, data science, and pandemic preparedness.

U.S.-Canada Health Dialog. Following an HHS-level U.S.-Canada Dialog on the COVID-19 pandemic and other health priorities in both countries in January 2022, NICHD leadership was approached by Canadian colleagues to explore joint research collaborations on the impact of the COVID-19 pandemic on children's health in both countries. OGH organized a joint meeting with the Scientific Director at the Institute of Human Development, Child and Youth Health (IHDCYH), part of the Canadian Institutes of Health Research (CIHR), the NICHD Director, and key scientific staff from both agencies in April 2022. Discussions during the meeting included a potential workshop to address mutual research priorities related to the impact of the COVID-19 pandemic on maternal and child health, health disparities/equity, and health priorities of minority populations in both countries.

NIH Global Health Reciprocal Innovation (GHRI) Workshop, October 24-26, 2022. OGH participated in an NIH-wide planning group led by the FIC to organize a workshop on reciprocal innovation in global health research. Reciprocal innovation is 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), to address a common health challenge and provide mutual benefit to both sides." During the workshop, OGH staff led a focus group discussion on GHRI frameworks, methods, and research. Next steps for the group include

writing articles on reciprocal innovation for a journal supplement and exploring future funding opportunities.

NIH Working Group: Promoting Equity in Global Health Research. FIC organized an NIH-wide working group, including OGH, to address ways to promote equity in global health research. OGH also represented NICHD as a co-author on an NIH Request for Information (RFI) on this topic that was published in May 2022. The working group is currently reviewing comments received from the global health community in response to the RFI to determine next steps.

NIH Global Health Program for Fellows and Scholars. Over the past three years, NICHD staff have participated in the peer review of research applications for the NIH Global Health Program for Fellows and Scholars. 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 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, 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 it started 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 whom come from 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 (ELSI) research. NICHD is currently funding DS-I Africa research grants on health research topics in line with the NICHD mission.

Global Alliance for Chronic Disease (GACD) Initiative. GACD brings together major international research funding agencies specifically to address the growing burden of noncommunicable diseases (NCDs) in LMICs and vulnerable populations

in HICs. OGH and PGNB staff represent NICHD on this initiative, which aims to reduce the burden of chronic non-communicable diseases in LMICs, and in populations facing conditions of vulnerability in high-income countries, by building evidence to inform national and international policies. NIH partners include NICHD, NHLBI, NIMH, NINDS, the National Cancer Institute (NCI), NIDA, the National Institute of Environmental Health Sciences (NIEHS), and the NIH Center for Scientific Review (CSR). OGH contributed NICHD-specific language to a funding opportunity for the Fogarty-led portion of this initiative, *Implementation Research to Reduce Noncommunicable Disease Burden in LMICs and Tribal Nations During Critical Life Stages and Key Transition Periods (R01 Clinical Trial Optional)*, published in March 2022. OGH staff also provided feedback to researchers interested in applying to this announcement.

NICHD Dissemination & Implementation Science (D&I) Workgroup. The purpose of the D&I Workgroup, led by OGH, is to plan and coordinate D&I activities across NICHD and NIH, and in collaboration with external agencies. The workgroup acts as a forum for internal information exchange and as a catalyst for developing D&I initiatives at NICHD. Staff members representing several NICHD branches/programs work with OGH to advance this important area of science. In 2022, group members prepared NICHD-specific language for a trans-NIH D&I research funding announcement and participated in the coding of related grants for capacity building and implementation science. The group is also planning a D&I scientific presentation and panels in the spring/summer 2023.

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

U.S. Government's Children in Adversity Initiative. This USAID-led, U.S. APCCA Interagency working group for the Children in Adversity Initiative has focused on

the impact of the COVID-19 outbreak on vulnerable children and families in LMICs over the past two years. Areas of interest have 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 has kept this working group apprised of NIH-wide research efforts on the COVID-19 outbreak most relevant for at-risk children and their families.

HHS Reproductive Access Working Group. In March 2022, OGH was invited to organize a group of NICHD staff specializing in reproductive health to participate in the HHS Reproductive Access Working Group led by Dr. Stephanie Psaki, Director for Global Health Response for the White House National Security Council. The purpose of this working group was to brainstorm potential activities and funding opportunities related to reproductive technology and family planning in global settings. NICHD staff from OGH, PDB, Fertility and Infertility Branch (FIB), and Contraceptive Research Branch (CRB) provided scientific input. This scientific exchange contributed to the development of an HHS policy document on global reproductive access.

Recent Achievements in Global Health

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

Given the ongoing COVID-19 outbreak, some global health activities, such as visits to the NIH campus by foreign delegations, high-level U.S. government staff visits to NIH international research sites, and international travel to scientific conferences continue to be sporadic or held virtually. Nonetheless, in collaboration with NICHD program staff, OGH has represented NICHD and prepared briefings for high-level global health leadership (e.g., HHS OGA, HHS Health Attachés in China & South Africa, Congressional Briefing for Senators Blunt, Coons, & Fitzpatrick on the Global Child Thrive Act), and provided input on relevant maternal and child health research for interagency documents (e.g., World Health Assembly, WHO Regional Meetings, Pan American Health Organization).

- **Visits by Foreign Delegations and Research Site visits by U.S. Government Delegations:** Participated in the coordination of meetings and preparation of briefing materials for visits or virtual meetings with foreign delegations including a visit to the NIH campus by Dr. Tshidi Moeti, WHO Regional Director for Africa, and her delegation. The purpose of the meeting

was to discuss WHO-Africa and NIH health and research priority areas, which included pandemic preparedness and responding to humanitarian emergencies, as well as finding ways to increase involvement with country-level WHO offices. OGH also worked with MPIDB staff to identify a potential research site in Thailand for a visit by the HHS Deputy Secretary Andrea Palm during her trip to Thailand and Laos.

- **Public Law 109-95 Congressional Report Data Call:** OGH has served as the NICHD lead for preparing the trans-NIH report on research projects studying the health and developmental outcomes of orphans and vulnerable children for this annual report to Congress.

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

- **Dissemination of Global Health Information Including Current NICHD Initiatives:** Regularly updated the OGH page on the NICHD Insider and prepared the annual NICHD Global Health Catalog to facilitate information exchanges related to global health.

- **Scientific Input for Interagency Global Health Documents:** Contributed to the writing of science and policy documents and requests for information from internal (e.g., NICHD, NIH, HHS) and external (e.g., USAID, WHO, United Nations Children's Fund [UNICEF]) sources that describe NICHD's mission and international activities.

Global Health Partnerships

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

Examples of Staff Membership on Global Health Committees/Working Groups

- NICHD Global Health Strategic Team: Drs. Vesna Kutlesic and Jenelle Walker
- NIH-BMGF MNCH Working Group: Drs. Vesna Kutlesic and Jenelle Walker
- WHO Nurturing Care Framework Advisory Group: Dr. Vesna Kutlesic
- USAID APCCA Strategy Working Group: Drs. Vesna Kutlesic and Jenelle Walker
- Trans-NIH Global Health Research Working Group: Dr. Vesna Kutlesic

- Trans-NIH Promoting Equity in Global Health Working Group: Dr. Vesna Kutlesic
- Trans-NIH International Clinical Research Subcommittee: Dr. Vesna Kutlesic
- FIC International Representatives Working Group: Drs. Vesna Kutlesic and Jenelle Walker
- Fogarty International Interest Group: Drs. Vesna Kutlesic and Jenelle Walker
- NICHD Reproductive Health Working Group: Drs. Jenelle Walker and Vesna Kutlesic
- NICHD Maternal Health Coordinating Committee: Drs. Jenelle Walker and Vesna Kutlesic
- White House Gender Policy Council, Science & Technology Interagency Working Group: Dr. Vesna Kutlesic
- White House Gender Policy Council, Women and Girl's Education, and Leadership Interagency Working Group: Dr. Jenelle Walker
- Global Nutrition Coordination Plan Technical Working Group: Dr. Jenelle Walker
- Trans-NIH D&I Working Group: Dr. Jenelle Walker
- NIH Global Health Interest Group: Dr. Jenelle Walker
- NICHD D&I Working Group: Drs. Jenelle Walker and Vesna Kutlesic
- STrategies to enRich Inclusion and achieVe Equity (STRIVE) Health Disparities Research Committee: Dr. Vesna Kutlesic
- STRIVE Scientific Workforce Committee: Dr. Jenelle Walker

Point-of-Contact

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Division of Extramural Research (DER)

DER develops, implements, and coordinates cross-cutting, multidisciplinary research activities within NICHD's mission. The research portfolio is quite broad, encompassing biological, behavioral, and clinical research related to conception and pregnancy, 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 in children and adolescents from diverse backgrounds (e.g., low socioeconomic status, racial/ethnic and language minorities) and subpopulations (e.g., individuals with Specific Learning Disorders) arise from or are differentially affected by genetic and environmental risk/protective factors. The branch uses these findings to inform translational prevention, intervention, and health promotion studies designed to enhance the lives of children and adolescents.

Major Global Health Initiatives over the Past Year

Parenting Across Cultures. CDBB is funding a longitudinal study in nine countries—China, Columbia, Jordan, Italy, Kenya, Philippines, Sweden, Thailand, and the United States—to examine parenting influences on youth behavior and development from childhood through early adulthood. The participants are currently in their early 20s, and the study is examining 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 in middle childhood, and whether improved parenting mediates child outcomes. The branch is also funding the design and testing of a parenting intervention to help fathers in Tanzania better engage with their children in ways that best promote early child development.

Violence Prevention. CDBB funds violence prevention work both domestically and internationally with a specific focus on prevention in youth. One such effort is a randomized clinical trial evaluating the effectiveness of a culturally tailored, community-based violence prevention program, delivered in elementary schools in Honduras. Another study conducted in Kenya is testing the dissemination of an app-based intervention, which attempts to prevent interpersonal violence for

women, increase safety, and improve health and resilience, through formal institutions and community-based networks.

Integrated Early Childhood Development (ECD) Interventions. Recent neurobiological and psychological research has established that vital progress occurs in language, cognitive, motor, and socio-emotional development during the first few years of life, and that early life outcomes are key determinants of adult outcomes, such as educational achievement, labor market outcomes, and health. Yet more than 200 million children younger than age 5 who live in LMICs will fail to reach their developmental potential as adults, predominantly due to poverty, poor health and nutrition, and inadequate cognitive and psychosocial stimulation. ECD interventions that integrate nutrition and child stimulation activities have been shown to effectively improve 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.

Pediatric Health Promotion Interventions. 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 outreach by community health workers 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 also collecting information on key elements of implementation that will help them quickly scale up the intervention if it is found to be effective. Study findings could also inform strategies to improve vaccination equity for children living in rural and underserved communities in the United States.

The branch also funds a longitudinal follow-up study of orphaned and separated children in five LMICs, Cambodia, Ethiopia, India, Kenya, and Tanzania, examining HIV risk and treatment because orphaned and separated children are at especially high risk of acquiring 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. Evaluating the differing acceptability of these interventions by site and participant gender is also a component of the study, and may be useful in future design and implementation of policies and interventions that focus on HIV risk and treatment engagement among this population.

In Ghana, the branch funds an investigation of a new model to examine risk and resilience in a prospective longitudinal cohort of children. This effort is a secondary analysis of data collected as part of the International Lipid-Based Nutrient Supplements Project in Ghana (2009-2012) and contains indicators of biological risks, psychosocial risks, and multilevel protective factors during pregnancy, at birth, in infancy, and at kindergarten age. The study intends to support children in fulfilling their developmental potential and to promote the development of human capital, broadly defined as the health, well-being, and productivity of populations.

These studies add to the evidence base that informs the design and implementation of interventions in LMICs on various aspects of pediatric health promotion.

Bilingualism and Cross-Linguistic Studies of Literacy and Language Development. The branch funds studies of infant perception, conceptual development, and early word learning in various languages. Some of these studies have demonstrated aspects of language development that are universal (the same for all languages), and that are language specific. Published studies have indicated a cognitive advantage in some aspects of executive function among bilingual children, which supports the value of encouraging the development of bilingualism and the maintenance of first language in English-learning children. In addition, the branch funds several monolingual studies of language development, reading, and reading disability, including their neurobiological and genetic bases, with integral foreign collaborators. This body of monolinguistic and cross-linguistic studies and those examining bilingual and second-language learning populations are helping to describe the timing and trajectory of early language development and of literacy learning. Locations for some of the data collection and/or subcomponents of this work include Canada, Germany, Israel, the Netherlands, Thailand, and the United Kingdom.

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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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

Contraceptive Method and HIV Risk. This research evaluated objective biological markers of HIV risk using a randomized contraceptive method within the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial to inform interpretation of the primary trial results. The ECHO trial, initiated in 2015, was the first to randomize women without HIV to depot medroxyprogesterone acetate (DMPA), the copper T intrauterine device (IUD), and a levonorgestrel (LNG) implant to compare HIV acquisition rates. The ECHO trial was conducted in Eswatini, Kenya, South Africa, and Zambia with the goal of providing high-quality evidence to inform women, service providers, and normative bodies (e.g., the WHO) on the comparative HIV risks associated with these three highly effective contraceptive methods. With support from ECHO trial leadership, this study tested stored genital specimens from a subset of ECHO trial participants, who provided consent for future research on prostate-specific antigen (PSA) and sexually transmitted infections (STIs). These data were combined with ECHO trial demographic, behavioral, laboratory, and clinical data to:

- Determine whether women randomized to DMPA have condomless vaginal sex more or less frequently than women randomized to the IUD or LNG implant during trial follow-up, by comparing vaginal PSA (a marker of recent semen exposure) among randomized contraceptive groups across multiple ECHO trial sites and then, secondarily, comparing the prevalence of non-viral STIs.

- Evaluate whether women randomized to DMPA are more or less likely to misreport condomless sex than women randomized to the IUD or LNG implant during trial follow-up, by evaluating the concordance of self-reported condom use or abstinence during trial follow-up with PSA detection for all groups, and by randomized contraceptive group, to inform use of self-reported data in planned trial causal modelling.

The research provided data, including objective markers of post-randomization sexual behavior change within the ECHO trial by randomized group, critical to the

accurate interpretation of ECHO trial results. Policymakers, providers, and contraceptive users can use these findings to minimize the risk of both unwanted reproductive outcomes and HIV acquisition among reproductive-age women worldwide.

A total of 558 randomized participants provided samples available for analysis at the three participating sites in South Africa and Kenya. Among those, 458 met the inclusion criteria. Analysis of baseline demographic, sexual behavior, and STI prevalence data found no statistically significant differences between this sub-sample of ECHO trial participants and the overall trial population. Other findings included significant differences in PSA detection between the DMPA-IM and LNG-implant groups and moderate discordance between self-reported sexual behavior and PSA results.

These data suggest that the frequency of condomless sex may have differed by randomized contraceptive method among ECHO trial participants at the three ECHO sites included in this sub-study.

Understanding the Impact of Lower Dose DMPA on Female Genital Tract Microbiome and Immunology. Depo-Provera, the most widely used injectable contraceptive worldwide, 150 mg delivered intramuscularly (150-IM) has been 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 LNG implant 150-IM, the copper IUD, Sayana® Press, 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.

Clinical Trial with the LNG Intrauterine System to Measure Changes in Hemoglobin and Serum Ferritin Among Anemic Women in Kenya. Anemia continues to disproportionately affect marginalized women in resource-poor countries. In Africa and Southeast Asia, over 270 million women of reproductive age are anemic, 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 is found to work as hypothesized, then the product can become another tool to alleviate anemia among reproductive-age women, resulting in healthier living and healthier beginnings to pregnancy, when desired.

Pharmacological Strategies to Use the LNG Implant in Women with HIV. Family planning options are essential for improving reproductive health, especially among women living with HIV. Prevention of unintended pregnancy decreases maternal and child mortality and reduces the risk of perinatal HIV transmission. 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, despite the lack of critically needed pharmacokinetic (PK) drug-interaction data to inform safe and effective concomitant use. Preliminary data demonstrated that combined use of efavirenz (EFV)-based ART, the only preferred first-line ART regimen in LMICs, with an LNG-releasing implant for one year reduced LNG plasma concentrations by approximately 50 percent compared to women not on ART. Importantly, 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 provide comprehensive, evidence-based guidance on the use of LNG implants with ART in women with HIV. The study will use samples obtained from woman in Uganda to:

1) identify strategies to overcome the drug-drug interaction between LNG and EFV-based ART; 2) advance contraceptive therapeutic options for women with HIV; and 3) advance the science of the drug-drug interaction field. By establishing an evidence-based approach to safely combine LNG implants with ART regimens spanning the continuum of HIV care, the 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. 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, the DMPA injectable is the most used contraceptive in the region, even though it requires repeat injections every 3 months, leading to a higher typical-use failure rate of 6 percent in the first year. Small studies suggest co-administration of the antiretroviral EFV may reduce the contraceptive efficacy of the LNG implant possibly due to PK interactions between the two drugs, causing some countries in sub-Saharan Africa to consider policy recommendations against use of implants for women on EFV. This study compares the typical-use pregnancy rates of the LNG implant versus the DMPA injectable in a prospective cohort of 1,420 women with HIV on EFV (710 initiating the LNG implant and 710 initiating DMPA). Researchers will follow study participants and collect data after 1 month and then every 3 months for at least 2 years and up to 4 years. In addition, a second effort with 240 women in a 2:1 nested case-control study of women from the cohort will determine if higher EFV concentrations are associated with LNG implant contraceptive failure. They will also evaluate the effect of switching ARTs on LNG, MPA and sex hormone-binding globulin concentrations and HIV viral load among a subset of 50 women and measure of viral suppression, adherence, and anti-retroviral 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. To address the high unmet need for PPFP options in Rwanda, this project will use an implementation science framework to test the hypothesis that the 'C4' intervention (involving Couples/clients, Clinic providers, Champions, and Community health workers) can be adapted to large-scale implementation and is cost-effective and sustainable. Working closely with the Rwandan Ministry of Health, a small-scale pilot study of long-acting reversible contraceptives (LARC) uptake saw significant increases among postpartum women

(2,687% for PP intrauterine device, 172% for PP implant). Among both 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, they are the only reversible methods that may be used safely. A critical goal of the program is to create a framework that is both adaptable and sustainable within Rwandan government facilities; therefore, the Ministry of Health and other local stakeholders have been engaged from the outset. During the project period, they 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.

Recent Achievements in Global Health

A PK and Pharmacogenetic Evaluation of Contraceptive Implants and ART among Women in Kenya and Uganda, 1995-2004. This study evaluated the PKs and pharmacogenetics of contraceptive implant progestin concentrations in women with HIV initiating EFV-containing or Nevirapine (NVP)-containing ART in Kenya and Uganda. Stored samples from women self-reporting implant use in the Partners Pre-Exposure Prophylaxis (PrEP) Study were analyzed. Concomitant use of EFV significantly reduced LNV or etonogestrel concentrations by 61 percent and 49 percent, respectively, compared with no ART use. In addition, allelic variants in hepatic enzymes influenced the extent of the observed drug interaction between progestins and EFV. (*AIDS,* 2019: PMID: 31306173)

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

Genital Inflammatory Status and the Innate Immune Response to Contraceptive Initiation. Data obtained previously on the effects of contraceptives on female genital tract immune mediators have been inconsistent, possibly because contraceptive initiation could influence immune mediator changes, especially in those with pre-existing conditions. In the ECHO trial, 161 South African women were randomized to injectable DMPA-IM, copper intrauterine 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 significantly increased 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)

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

In addition to an emphasis on structural birth defects and transdisciplinary research, 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 without a doubt foundational to our understanding of birth defects or "inborn errors of morphogenesis." Whether these perturbations are due to genetics, environmental insults, or a combination of both, understanding the underlying developmental mechanisms will only be achieved through multidisciplinary, collaborative efforts among developmental biologists, geneticists, genetic epidemiologists, obstetricians, neonatologists, and pediatricians. Consequently, the 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 birth defects research by providing leadership for the Gabriella Miller Kids First Pediatric Research Program.

Major Global Health Initiatives over the Past Year

International Activities Involving Human Subjects

China

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

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

Multinational Collaborations

To obtain enough subjects for studies that will result in statistically significant findings and to strengthen the power of their studies, members of our branch's

Structural Birth Defects Working Group collaborate with investigators in other countries.

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.

This project seeks to understand the mechanisms underlying XCI and how functional interactions between PRC2 and long noncoding RNA spread the silencing process through the X-chromosome in a locus-specific manner for proper developmental regulation.

- A collaboration with Canadian researchers will examine the structural aspects of the interaction between Polycomb proteins (PRC2, EZH2) and their interacting RNA partners to determine whether there are allosteric changes or physical changes (e.g., cleavage of transcript by the ribozyme function).
- In addition, a collaboration with China will examine the role of heterogeneous nuclear ribonucleoprotein K (HNRNPK) in the initiation and spreading of XCI and whether an associated phase transition, or a change from a liquid soluble to less soluble semi-liquid state, could explain how Xist and Polycomb proteins spread rapidly along the X chromosome.
- Finally, a collaboration with Spain will investigate the localization dynamics of PRC2 and how SirT7 mutations affect Xist and Polycomb spreading.

Single Country Collaborations

Canada

The wide use of animal models to elucidate the causes of human disease generates a great deal of genomic data. In recent years, it has become paramount to share these data among investigators doing basic research with different animal models, and physician-scientists doing clinical or translational research. One of the best ways to share data is through community databases, as exemplified by Xenbase. This *Xenopus* model organism database is not only one of the best available, but also 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 used to conduct basic biomedical studies that would be prohibitively difficult or expensive to conduct in humans. The database collects, annotates, and stores research data as well as provides access and tools for data analysis, providing a resource to the international research community, and ensuring that important data are available and easily accessible to guide further research projects without unnecessary duplication of effort. In serving this function, Xenbase provides an essential resource to the biomedical research community for understanding the molecular basis of development, health, and disease.

In the last year, a similar collaboration began with Echinoderm researchers in the United States and Canada to improve the existing Echinobase database using the software, hardware, and infrastructure of Xenbase. This effort will result in a highly reliable platform that delivers efficient and easy access to a broad range of data, including genomes, genome annotations, gene ontology, gene expression, gene regulatory networks, and relevant scientific literature, to researchers who are using Echinoderms as an experimental model organism.

Finally, short-stature syndromes are a family of structural birth defects important to the mission of NICHD. The short stature homeobox (*SHOX*) gene is associated with several short-stature syndromes, including Léri-Weill dyschondrosteosis and Langer syndrome, but little is known about the gene or the syndromes. The branch is funding a University of Calgary researcher, currently the only investigator in North America working on *SHOX* genes, to bring his unique expertise and experience regarding this gene to the United States and the overall field. Better understanding of the *SHOX* gene could significantly advance this area of birth defects research.

China

Some animals can regenerate their limbs after injury, but humans cannot. In this grant, the investigator proposed establishing an approach for stimulating digit regeneration in a mammalian system (the mouse), using a frog limb regeneration study conducted in China as a foundation. The investigators will engineer a transplantable, re-vascularizable, 3D fibrin scaffold containing a combination of multiple types of progenitor cells and growth factors. They will then test its ability to stimulate regeneration by transplanting to the mouse digit stump after middle-phalanx amputation. With no expenditure of NIH funds, the work on the non-mammalian frog model will inform/benefit the NIH study of limb/digit regeneration in mammals.

France

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 of this regulation 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 to regulate the trafficking and stability of human Robo receptors in vitro, and that loss of Ndfip1or Ndfip2 function in vivo in mice results in increased expression of Robo receptors and defects in axon guidance. In collaboration with investigators in France, NICHD-funded researchers are examining 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

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

Israel

The Principal Investigator (PI) of this study discovered a non-apoptotic developmental cell-death program that occurs in *Caenorhabditis elegans* linker cells, 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 grant will use cell lines from University of Haifa, Israel, to identify signaling pathways involved in LCD and determine relevance to mammals. No funds are going to the University of Haifa, and all the work will be performed within United States.

Italy

Congenital defects are a leading cause of morbidity worldwide, accounting for 330,000 newborn deaths every year. Brain malformations appear to be the most common congenital anomalies and are a major cause of death and lifelong disability. In the majority of cases the cause remains uncertain, due to the complexity and the multigenic origin of these anomalies. Genes encoding Transcription Factors (TFs) and epigenetic regulators have become relevant as candidate causes 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. 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. By functionally characterizing PRDM15 downstream effectors (e.g., NOTCH and WNT/PCP pathways), this effort found underappreciated genes mutated in patients with brain malformations (i.e., holoprosencephaly [HPE] and microcephaly). Because PRDM15 is, thus far, an uncharacterized critical regulator of embryonic development, knowledge of its downstream regulated pathways could have significant diagnostic and clinical implications for patients with holoprosencephaly and microcephaly, and may prove useful to the field of regenerative medicine. Targeted sequencing of PRDM15 and its key downstream targets can potentially be added to routine genetic testing in those at risk of carrying HPE-causing mutations (e.g., SHH, ZIC2, TGIF).

Switzerland

This project seeks to understand how DNA is organized, what mediates the organization, and how organization contributes to developmental gene expression by systematically teasing apart structural organization and units of gene regulation at a unified, developmentally important locus. This collaboration will test the contribution of three structural protein (CTCF) binding sites to a long-range enhancer-promoter interaction at the Sonic hedgehog locus in mouse embryonic brain tissue. The collaborators at the foreign site developed a technique to genetically engineer mouse embryonic stem cells (mESCs) cells with specific mutations of interest, and subsequently generate chimeric embryos with the aid of a surrogate mother. The foreign site will generate such chimeric embryos and implant them into a pseudo-pregnant adult female. At 12.5 days total gestation time (E12.5), the embryos will be harvested from the surrogate, fixed, and shipped to the University of Pennsylvania, where the current PI will then take care of the samples, including processing and downstream analyses.

United Kingdom

The goal of the project is to study mutant mouse embryos engineered to carry precise mutations in a special category of regulators, called epigenetic regulators, which are essential for mammalian development, and determine which components of this machinery are mutated in a variety of human diseases. This study aims to yield deep insights into the functions of epigenetic regulators in development and disease. The application was submitted in response to an NIH initiative requiring resulting data generated be deposited to the European Molecular Biology Laboratory (EMBL)/European Bioinformatics Institute (EBI-UK), which is supported by the NIH Knockout Mouse Phenotyping Program-2 (KOMP2). Depositing data into EBI does not involve any paid effort for any foreign collaborators. Although use of foreign resources is restricted to databases managed by EBI staff, the PI anticipates that this collaboration could lead to coauthored 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

Male Reproductive Tract and Male Fertility. Only fully mature, motile sperm can fertilize an egg without medical intervention, but male germ cells are still immature and unable to swim when they leave the testicles and transit through the male reproductive tract. The cells lining the interior of the epididymis play an important role in the timing of sperm maturation. FIB supports research in Canada to examine how a cell population (called the principal cells) of the epididymis help to keep sperm quiescent during maturation and storage, and then prime them for motility before ejaculation, by closely controlling local pH levels (PI: Dr. Breton).

Artificial Intelligence (AI) and Assisted Reproduction Technology (ART): 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 computation 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. Up to 15 percent of U.S. women have PCOS and experience infertility, obesity, and diabetes. Current diagnostic criteria fall into two major groups, which vary because they are based on the presence of particular symptoms, rather than on an understanding of the underlying disease mechanisms. Current hypotheses suggest that many genes contribute to PCOS, and that women with certain constellations of reproductive and metabolic phenotypes resulting from variations in PCOS-related genes have a PCOS sub-type. 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 sub-type of PCOS.

Global Health Collaborations in Fertility and Infertility Research. 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). 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 after treatment. GHDB currently supports several studies regarding risks and therapies for OF in sub-Saharan African communities.

- One study is addressing the critical gaps in knowledge on risk of adverse outcomes following fistula repair by conducting a longitudinal cohort study of 800 women who received fistula repair at one of nine Ugandan facilities. It seeks to identify predictors of post-repair fistula breakdown and recurrence, to identify predictors and characteristics of post-repair incontinence, and to engage key stakeholders in a theory-guided iterative process to develop a roadmap of intervention strategies likely to be feasible and acceptable within this setting.

- Another study aims to quantitatively estimate the incidence of adverse pregnancy outcomes following fistula repair. The project will also use in-depth interviews with key stakeholders (i.e., women, providers) to understand post-repair pregnancy decision-making and health care experiences of women who had genital fistula repair.

- A third study aims to assess the long-term mental health and physical sequelae of women who have had surgery for OF, and to determine predictors of reintegration success after surgical repair in a Ugandan population. This work will be followed by design of a post-surgical reintegration intervention for these women and their households, with

subsequent pilot testing for feasibility, acceptability, and impact on reintegration success.

- Lastly, another GHDB-funded study aims to quantify the effectiveness of a non-surgical insertable vaginal cup to manage fistula urinary incontinence, examine user and implementer acceptability, and quantify fistula management cost at two fistula care centers in Ghana. The researchers hope to provide 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). 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, is 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 girls and women in the United States 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.

GHDB funded a study to measure the health and psychological impacts of FGC among West African immigrant females now living in New York City, as well as the knowledge, attitudes, and practices regarding FGC among healthcare providers who care for these patients. The researchers seek to identify ways to improve interactions with the healthcare system, including the development of evidence-based approaches for providing culturally sensitive, effective interventions.

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

Vulvodynia. Although some therapies can help relieve symptoms of vulvodynia, chronic pain or discomfort of the vulva, the 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 age 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

Hotchkiss E, Nalubwama H, Miller S, Ryan N, Barageine J, Byamugisha J, El Ayadi AM. (2022). Social support among women with genital fistula in Uganda. *Cult Health Sex. Feb 24*:1-16. doi: 10.1080/13691058.2022.2041098. Epub ahead of print. PMID: 35200098.

Global Health Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

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Intellectual and Developmental Disabilities Branch (IDDB)

Scientific Scope

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

The mission of the 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. 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 convened 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 Institutes joined NICHD in funding these gene and variant curation expert panels (NCI, National Eye Institute [NEI], NIMH, and NINDS), and to date 15 awards have been made. In fiscal year 2022, NICHD-awarded expert panels included international experts spanning seven different countries to curate genes involved in syndromic disorders (PI: Dr. O'Donnell-Luria), and genes and variants involved in congenital heart disease (PIs: Drs. Roberts and Gelb). NICHD plans to reissue this funding opportunity in 2023.

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® website has attracted over 5,600 registrants in the United States and abroad and has supported recruitment for over 90 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 fully responsive to facilitate access on a wide variety of platforms. The DS-Connect® registry also includes a Medication Tracker, where participants enter information about medication and supplement use in people with DS to help inform research and future clinical drug trials. The DS-Connect® website incorporated functionality enabling users to more easily search https://clinicaltrials.gov/ for NIH-supported clinical trials and studies in DS that are active and recruiting. Currently, the registry is incorporating culturally appropriate

images and inclusive language to encourage participation from families of diverse backgrounds.

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 (additional details follow and are available in the Mobile Health section of this branch summary).

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 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 (IBIS) 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 (PI: Dr. Botteron).

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 utilizing 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 (EEG/REP and 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 (PI: Dr. Grigorenko) 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.

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 Down syndrome. This activity (PI: Dr. Handen), co-funded by NICHD, National Institute on Aging, and the INCLUDE Project, has numerous recruitment sites throughout the United States and in the United Kingdom. A related study (PI: Dr. Rafii) is investigating the adult DS population in France to create a trial-ready cohort for studying medications to prevent and/or treat Alzheimer's in this population.

A research collaboration between researchers in United States (PI: Dr. Arnold) and at the University of Oxford, in the United Kingdom, is examining how gonadal hormones and the X and Y chromosomes impact sex differences in homologous neural structures in mice and humans. Humans exhibit substantial variation in age-dependent sex differences across a variety of disorders and other domains (e.g., motor, language, and social skills). These findings can improve our understanding of the trajectory of sex differences within the context of age 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 studies in mice, at a level not possible in humans, aimed at understanding human sex differences in morphology and disease disparity. For instance:

- A novel sex chromosome trisomy mouse model is employed to examine the effects of gonadal status and sex chromosome complement on the emergence of sex differences.
- Single-cell RNAseq is used to determine sex differences in gene expression patterns and genetic pathways.
- High-throughput and bioinformatic approaches will allow for the analysis of an enormous amount of data.
- The generation of a 4-D map of brain development focused on sexually dimorphic brain regions and nuclei will be unique and will benefit all fields dependent upon accurate developmental maps of brain, not just those examining sex differences.

A research collaboration between United States (PI: Dr. Gibson) and Heidelberg University Children's Hospital, Germany, plans to establish the natural history of the succinic semialdehyde dehydrogenase deficiency (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, a blood spot GABA assay will be developed 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, leading to a validated GABA assay suitable for high-throughput newborn screening platforms, which could break the barrier to early detection and facilitate the establishment of disease prognosis and the assessment of the efficacy of novel therapeutics.

A research collaboration between the United States (PI: Dr. Zarbalis) and University College London, United Kingdom, to explore 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 expression of key folate enzymes and folate and vitamin B12 status indicators. There is growing evidence that excessive folic acid can produce negative outcomes with respect to fetal brain development and a possible association with ASDs; therefore, efforts to explore these connections 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 healthy conditions, making the study timely and important.

U.S. researchers (PI: Dr. Zhang) collaborating with investigators at the University of Eastern Finland are developing novel in vivo MRI methods to examine tissue microstructure and neuronal activity in the progression of hypoxic ischemic (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, but its protective mechanisms are not clearly understood. It has been assumed that hypothermia reduces cell swelling, inflammation, and vasogenic edema, and may delay the pseudo-normalization process. The team is examining the sensitivity of novel diffusion-MRI (dMRI) techniques to identifying 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 and are less susceptible to confounding pseudo-normalization of conventional dMRI

signals. The researchers plan to optimize the imaging protocols to detect key structural changes after neonatal HI insult.

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 (PI: Dr. Green) 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 (RMK)-genetic alterations on the human brain' and systems-level biology.

Understanding the Long-Term Outcomes of In Utero Zika Virus Exposure. 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 (PI: Dr. Bailey) 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. 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. Researchers are trying to determine the relationship between earliest spontaneous limb movements and developmental outcomes at 12 months of age in at-risk infants using measurements from wearable motion sensors. The researchers hope to determine whether wearable sensor assessment is more accurate than current clinical assessments in predicting developmental outcomes in at-risk infants. The study includes a cohort of children from birth to 6 months of age who will use wearable sensors. A related multidisciplinary project that involves pediatric medicine,

physical therapy, and biostatistics will help build research capacity through a partnership between the University of Southern California (PI: Dr. Smith) and the Maya Health Alliance in Guatemala.

- A research collaboration between investigators in the United States (PI: Dr. Idro) and Uganda 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 that found children in Uganda to be 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 (PI: Dr. Bielas) 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 for optimizing analysis and reanalysis of WES data to streamline 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 for making de-identified population-specific genetic data publicly available. This data resource could allow other LMICs globally to adopt the lessons learned by this team and could facilitate the integration of genetic counseling into clinical practice.

- Epilepsy is a significant health problem in Uganda, but its associated stigma and discrimination often lead to delays in accessing needed health care. A research collaboration between investigators in the United States (PI: Dr. Kakooza) and Uganda aims to reduce the public health burden and stigma around epilepsy among Ugandan adolescents. The project will use a multipronged approach, including deep clinical phenotyping to characterize disease severity and comorbidities and surveys to assess the magnitude and impact of stigma, with a long-term goal of improving affected individuals' psychosocial and functional outcomes.

- A collaboration between researchers at Harvard University (PI: Dr. Robinson), University of Oxford (United Kingdom), and the Kenya Medical Research Institute (Kenya) will undertake the phenotypic characterization and collection of biological samples from children, ages 2 to 17 years, and adults with NDDs residing in Kilifi and Mombasa counties in Kenya for genetic

studies. African individuals are severely underrepresented in genetic studies of NDDs, including IDDs, ASDs, and attention disorders. 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.

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

Mobile Health: Technology and Outcomes in LMICs (mHealth). IDDB participates in this FIC-led initiative to encourage exploratory/developmental research applications on the development, validation, feasibility, and effectiveness of innovative mHealth interventions or tools that 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 of mHealth intervention tools that use facial recognition software to screen for syndromic congenital anomalies, with a focus on DS, resulting in a health outcomes data registry in the Democratic Republic of the Congo (DRC). This partnership between Institut National de Recherche Biomédicale, a DRC national research institute, and Children's National Hospital (PI: Dr. Linguraru) in Washington, D.C., will create the infrastructure of a Birth Defects Registry, allowing for future surveillance and intervention programs in low-resource settings. These timely diagnoses will also enable screening for comorbidities, such as congenital heart defects and otitis media. Application of this research can improve the diagnostic rate of 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.

Rare Diseases Research. Many rare disorders manifest during childhood and can lead to lifelong disability and early death. IDDB participates in the Rare Diseases

Clinical Research Network (RDCRN), led by the Office of Rare Diseases Research within the National Center for Advancing Translational Sciences (NCATS). This network promotes clinical trial readiness by supporting natural history, biomarker development, and outcome measure studies, as well as pilot treatment studies, in partnership with researchers, clinical practitioners, patient groups, and industry. Many of the RDCRN consortia have international sites in Canada and/or Europe. 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 with early onset diabetes, optic nerve atrophy, and deafness in children, 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 women. As the HIV epidemic has evolved and other infectious diseases have emerged in the United States and globally, the branch has ensured that its funded research reflects these changes and addresses important research opportunities and gaps as they arise, including HIV-associated co-infections such as tuberculosis (TB), hepatitis, and malaria.

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

The branch supports research projects in 69 countries through grants, cooperative agreements, and contracts. For more information about the branch, please visit the MPIDB webpage and subscribe to our branch newsletter.

Major Global Health Initiatives over the Past Year

Study of Tecovirimat for Human Monkeypox Virus (STOMP). To address the 2022 monkeypox (mpox) outbreak, HHS and NIH initiated the STOMP study (ClinicalTrials.gov Identifier: NCT05534984), 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 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 will compare the clinical efficacy (time to clinical resolution of skin and visible mucosal lesions) between participants with mpox randomized to tecovirimat or placebo. 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). 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 in children across the world as a rare but serious condition weeks after they had or were exposed to COVID-19. The severity of MIS-C followed trends similar to those of 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 a spectrum of inflammatory processes, with features like those of toxic shock syndrome and Kawasaki disease, specific to children. Given the rise in child cases and deaths, MPIDB/NICHD leads 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 trans-NIH Rapid Acceleration of Diagnostics-Radical (RADx-rad) program to speed innovation in the development, commercialization, and implementation of technologies for COVID-19 testing and surveillance. NIH funded studies are enrolling children with diverse geographic, racial, and ethnic backgrounds across 30 U.S. states, Canada, the United Kingdom, and South America.

MPIDB/NICHD also participates in NIH collaborations that build upon and further utilize existing infrastructures and contributes to calls for research proposals and projects to understand the effects of the virus among 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 are working on HIV/AIDS research and on topics in line

with the NICHD mission. Additional program and award information is available on the FIC Global Health Program for Fellows and Scholars webpage.

NIH Common Fund: DS-I Africa. As also explained in the OGH section, NICHD participates in the DS-I Africa 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. NICHD organized a Maternal and Child Health Panel in October 2020 on Innovative Data Science Approaches to Improve Maternal and Child Health; a recording of the panel is available at https://youtu.be/HhbzKtQig0g. MPIDB also contributed to the funding of a DS-I Research Hub.

NICHD International and Domestic Pediatric and Maternal HIV Clinical Trials Network (NICHD Network). Since 1988, the NICHD Network has conducted clinical trials in infants, children, adolescents, and women, including pregnant women, with the goal of answering specific questions regarding the treatment, prevention, and persistence of HIV. Network research activities have expanded to include an additional focus on co-infections, especially TB. This Network was responsible for the first domestic trial in children with HIV (Intravenous immunoglobulin for prevention of bacterial infections). NICHD currently funds 16 domestic sites, including Puerto Rico, and 10 international sites in nine countries: Brazil, Botswana, India, Malawi, South Africa, Kenya, Tanzania, Thailand, and Uganda. Through collaborations with the National Institute of Allergy and Infectious Diseases (NIAID), NIMH, CDC, and other international partners, the NICHD Network has been able to conduct HIV-related trials including but not limited to the IMPAACT Network, ACTG, and the TB Trials Consortium.

Tuberculosis (TB). NICHD-supported sites in Tanzania, Uganda, and Thailand within the IMPAACT network participate in the ACTG PHOENIx study (A5300B/I2003B: Protecting Households On Exposure To Newly Diagnosed Index Multidrug-Resistant Tuberculosis Participants [ClinicalTrials.gov identifier: NCT03568383]), 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) of persons with multidrug resistant TB (MDR-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 (NIDDK), and NCI, supports regional data centers in Africa,

Asia, and North and South America to collect data on persons living with HIV who receive clinical care. NICHD plays a critical role in funding a maternal and pediatric component of IeDEA in four regions in Africa, as well as in the Asia-Pacific and South America/Caribbean regions. These projects have collected 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 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.

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

Active Global Health Initiatives

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

Emergency Awards: RADx-rad PreVAIL kIds (RFA-OD-20-023). Despite substantial numbers of children becoming infected with SARS-CoV-2 globally, 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, have increased attention to the varied pediatric manifestations of the infection and its post-infectious complications. To address these and other vital questions in this emerging and potentially devastating health threat among children, PreVAIL kIds was developed as an emergency phased-innovation funding opportunity announcement administered by NICHD in collaboration with other NIH institutes and offices (NIH OD, NHLBI, NIAID, 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 identify and characterize the spectrum of SARS-CoV-2 associated illness, including MIS-C and, through a prognostic algorithm, to predict the longitudinal risk of disease severity after a child is exposed to and may be infected with SARS-CoV-2 to properly tailor management and optimize health outcomes. For more information visit: NIH funds eight studies to uncover risk factors for COVID-19-related inflammatory syndrome in children.

Prevention and Treatment through a Comprehensive Care Continuum for HIV-affected Adolescents in Resource Constrained Settings (PATC^{3}H) (RFA-HD-18-032). MPIDB/NICHD issued this 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 PATC^{3}H 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 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.

As of 2022, NICHD in collaboration with NIDA, NIMHD, NIMH, OBSSR and FIC, has published two RFAs (RFA-HD-23-013 and RFA-HD-23-014) that will form the PATC^{3}H-Implementation Science Network (PATC^{3}H-IN) to expand and/or improve successes achieved by PATC^{3}H to new geographic areas, and/or in new populations affected by HIV.

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: 1) demonstrate the capacity to enroll infants, children, adolescents, and young adults who are HEU in clinical studies; and 2) utilize innovative epidemiological approaches to assess overall health in the established cohort. 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.

In 2022, NICHD, in collaboration with the International AIDS Society/Collaborative Initiative for Paediatric HIV Education and Research (CIPHER), WHO, Paediatric-Adolescent Treatment Africa (PATA), UNICEF, and others organized the 8th Workshop on Children and Adolescents with Perinatal HIV Exposure. The workshop presented up-to-date evidence on child neurodevelopmental outcomes following perinatal HIV exposure.

Utilizing Archived Data and Specimen Collections to Advance Maternal and Pediatric HIV/AIDS Research (RFA-HD-19-018, RFA-HD-20-020, and RFA-HD-21-030). This call for secondary analyses supported research and data translation and sharing using archived HIV/AIDS data and specimen collections to build upon original research. Awardees presented rigorous and new analysis methodologies to answer scientific questions about the epidemiology, pathogenesis, treatment, clinical manifestations, cure, and complications of HIV/AIDS in maternal, pediatric, and adolescent populations. Research topics include TB immune responses in women living with 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 institutes, including NICHD, encourages applications for research training programs to strengthen the scientific capacity of institutions in LMICs to conduct HIV research relevant to the evolving HIV epidemic in their country. NICHD-supported training programs include several focus areas, including 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, and RFA-AI-19-025). Since the inception of this program in 2013, this series of RFAs has solicited R01, R21, and U01 grants to establish and continue this binational program for collaborative research in the areas of HIV/AIDS, TB, and cancer with funding also provided by the South African Medical Research Council. The first round of awards included NICHD grants in maternal and pediatric HIV and in TB. Now in Phase 2, NICHD is one of five NIH institutes participating in this program to continue collaborations amongst investigators in the United States, South Africa, and other African countries. As a result of this collaboration, NICHD continues to pursue and support research 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 institutes, and the Office of the Global AIDS Coordinator released this RFA 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 serves as a 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 PATC^{3}H initiative, described earlier. PATC^{3}H benefits from leveraging expertise and collaborations from AHISA investigators and has implemented eight successful ongoing research programs across sub-Saharan Africa and Brazil.

Interaction of HIV and Neurodevelopment of Children in Resource-Limited Settings: Improving Assessment (RFA-HD-18-019, RFA-HD-18-020). MPIDB/NICHD issued this RFA in fiscal year 2018 and awarded three grants to investigate neurodevelopment assessment in South Africa, Tanzania, and Botswana. The widespread implementation of combination ART for HIV prevention and treatment has changed the presentation, manifestation, and course of development and impairment in children, globally, but especially in resource-limited settings most severely affected by HIV. Noninvasive assessment of child cognitive development using neuropsychological approaches is important for monitoring normally developing achievement, as well as emerging and continuing cognitive deficits related to HIV and its treatment.

HIV in Adolescents: Transitioning from Pediatric to the Adult Care Settings (RFA-HD-16-033). For individuals whose HIV is acquired or emerges during young adulthood, one of the most challenging obstacles to improving health outcomes is the transition from pediatric to adult HIV care programs. Issued by MPIDB/NICHD in fiscal year 2016, this RFA funds four grants in Kenya, Thailand, Malawi, and South Africa that offer a range of approaches for transitioning youth living with HIV to adult care with the goal of developing an evidence base to support guidelines applicable to low-, middle-, and high-income countries. The transition from pediatric to adult care is also a high-priority scientific research theme in the NICHD Strategic Plan.

Understanding and Addressing the Multilevel Influences on Uptake and Adherence to HIV Prevention Strategies among Adolescent Girls and Young Women (AGYW) in Sub-Saharan Africa (RFA-MH-17-550, RFA-MH-17-555, and RFA-MH-17-560). MPIDB/NICHD first issued this RFA in fiscal year 2017, in collaboration with NIMH, to: 1) enhance our understanding of the multilevel factors that influence HIV prevention strategy use; and 2) develop and test novel interventions to address these factors and enhance the uptake and adherence to HIV prevention strategies among AGYW in the region. In 2017, the NIH funded 11 grants in response to these companion RFAs, supporting research in Kenya, South Africa, Tanzania, Uganda, and Zimbabwe. The multidisciplinary investigative teams on the grants are addressing a wide range of issues affecting AGYW, including involvement in sex work, gender-based violence, and stigma by healthcare professionals. Different approaches are being evaluated to determine how to increase uptake and adherence to HIV prevention strategies, including testing of a risk screening tool, counseling using behavioral economic principles, determining PrEP knowledge, and engaging peer-networks. Investigators funded from this RFA have also participated in annual collaborative meetings with PATC^{3}H and AHISA.

International Health and Data and Biospecimen Sharing. The NICHD Data and Specimen Hub (DASH) offers de-identified data from NICHD-supported clinical research on a variety of topics. As a resource for collaboration and discovery, DASH includes 78 studies funded by MPIDB. Eight of those offer data from international sites; biospecimens are available from five, including the four NICHD International Site Development Initiative studies. Examples of branch-supported research networks and initiatives available in DASH include the following:

- Prospective Cohort Study of HIV and Zika in Infants and Pregnancy (HIV ZIP)
- A 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)
- Phase III Randomized Trial of the Safety and Efficacy of Three Neonatal Antiretroviral Regimens For Prevention Of Intrapartum HIV-1 Transmission (HPTN 040/P1043)
- A Prospective, Observational Study of HIV-Infected Pregnant Women and HIV-Exposed, Uninfected Children at Clinical Sites in Latin American Countries (NISDI LILAC)

- A Prospective, Observational Study of HIV-Exposed and HIV-Infected Children at Clinical Sites in Latin American and Caribbean Countries (NISDI Pediatric)
- A Prospective, Observational Study of HIV-Infected Pregnant Women and Their Infants at Clinical Sites in Latin American and Caribbean Countries (NISDI Perinatal)
- NISDI Pediatric Latin American Countries Epidemiological Study: A Prospective, Observational Study of HIV-infected Children at Clinical Sites in Latin American Countries (NISDI PLACES)
- Novel Strategies to Prevent Malaria and Improve Maternal-Child Health in Africa (PROMOTE II) - Prevention of Malaria in HIV-uninfected Pregnant Women and Infants - Birth Cohort 3 (PROMOTE BC3)

Selected Publications with Global Health Collaborators

- Tucker JD, Iwelunmor J, Abrams E, et al. Accelerating adolescent HIV research in low-income and middle-income countries: evidence from a research consortium. *AIDS*. 2021;35(15):2503-2511. PMID: 34870930.
- Mwangwa F, Charlebois ED, Ayieko J, et al. Two or more significant life-events in 6-months are associated with lower rates of HIV treatment and virologic suppression among youth with HIV in Uganda and Kenya [published online ahead of print, 2022 May 16]. *AIDS Care*. 2022;1-11. PMID: 35578398.
- Garofalo R, Adetunji A, Kuhns LM, et al. Evaluation of the iCARE Nigeria pilot intervention using social media and peer navigation to promote HIV testing and linkage to care among high-risk young men: A nonrandomized controlled trial. *JAMA Netw Open*. 2022;5(2):e220148. Published 2022 Feb 1. PMID: 35191969.
- Joseph Davey D, Hsiao NY, Spearman CW, et al. Low prevalence of hepatitis B virus infection in HIV-uninfected pregnant women in Cape Town, South Africa: Implications for oral pre-exposure prophylaxis roll out. *BMC Infect Dis*. 2022;22(1):719. Published 2022 Sep 1. PMID: 36050648.
- Brathwaite R, Ssewamala FM, Mutumba M, et al. The long-term (5-year) impact of a family economic empowerment intervention on adolescents living with hiv in uganda: Analysis of longitudinal data from a cluster randomized controlled trial from the Suubi+Adherence Study (2012-2018). *AIDS Behav*. 2022;26(10):3337-3344. PMID: 35429307.

- Deveaux L, Schieber E, Cottrell L, et al. Implementing a school-based HIV prevention program during public health emergencies: lessons learned in the Bahamas. *Implement Sci*. 2022;17(1):68. Published 2022 Oct 4. PMID: 36195879.

- Comfort AB, El Ayadi AM, Camlin CS, et al. The role of informational support from women's social networks on antenatal care initiation: qualitative evidence from pregnant women in Uganda. *BMC Pregnancy Childbirth*. 2022;22(1):708. Published 2022 Sep 16. PMID: 36114484.

- Kizito S, Namuwonge F, Brathwaite R, et al. Monitoring adherence to antiretroviral therapy among adolescents in Southern Uganda: Comparing Wisepill to Self-report in predicting viral suppression in a cluster-randomized trial. *J Int AIDS Soc*. 2022;25(9):e25990. PMID: 37074235.

Staff Membership on Global Health Committees/Working Groups

HIV Open Call on Informed Consent and Ethics in Research (VOICE) to develop a consensus statement on informed consent of adolescents and young adults (ages 10 through 24) in HIV research studies in LMICs. Member: Dr. Bill Kapogiannis

Point-of-Contact

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Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB)

Scientific Scope

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

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). The BPCA legislation promotes the prioritization of off-patent drugs and therapeutic areas that need further study in pediatrics and allows NICHD to sponsor clinical research of the prioritized therapeutics and disseminate results to improve drug labeling.

Major 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 has developed international collaborations with clinical sites in Canada, Israel, Singapore, Australia, Japan, and the United Kingdom to conduct clinical studies as part of the BPCA Clinical Program, and 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 development. 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. Diagnosing pediatric TB and evaluating its rapid response to pharmacotherapy is extremely challenging given the difficulties obtaining necessary samples, and the poor diagnostic value of the samples. Early detection is critical 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. The results from this project will be used to develop a novel tool for monitoring response to TB treatment and potentially guiding duration of treatment. The proposed research aims will be accomplished through international collaboration with well-known TB clinical investigators at the Stellenbosch University, Western Cape, South Africa.

Surveillance and Treatment tO Prevent Fetal Atrioventricular Block (AVB) Likely to Occur Quickly (STOP BLOQ). Complete (i.e., 3°) fetal anti-SSA/Ro-associated AVB identified in the 2nd trimester in an otherwise normally developing heart is fatal in one-fifth of cases, and those who survive require lifelong cardiac pacing. Reversal of an incomplete block is possible but challenging to identify with the 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 mothers can themselves identify reversible fetal cardiac injury by home monitoring, whether expeditious treatment of fetal incomplete AVB can restore normal rhythm, and if weekly echocardiographic testing is necessary to surveil for AVB. The STOP-BLOQ study is led by investigators at New York University and University of Colorado in collaboration with a consortium of centers across the United States along with the University of Alberta in Edmonton, Canada.

A Systems Pharmacology Approach to Predict the Effects of Pregnancy and Infectious Diseases on Transporter-mediated Drug Disposition. Both pregnancy and inflammation can alter drug PK processes, such as absorption, distribution, metabolism, and excretion. However, most published studies have focused on

cytochrome P450-mediated drug disposition, leaving a knowledge gap on transporter-mediated drug disposition in pregnant women. 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 regimens of drugs for pregnant women with HIV or other infectious diseases. This research is led by PIs at the University of Washington in collaboration with investigators at the University of Sao Paulo in Brazil and is co-funded by OPPTB and the NIH-São Paulo Research Foundation initiative (NOT-TW-16-001) via FIC.

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

A Novel Approach for Prevention of Bronchopulmonary Dysplasia (BPD) in At-Risk PreTerm Infants. BPD is a disease of preterm infants whose lungs are injured upon exposure to excess oxygen from ventilators, which impairs effective gas exchange. This project pursues the development of 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 lead compound in preclinical model mimicking the physiology of ventilated preterm human, as well as in vitro. Some of the analyses for the study are performed by laboratories located in Quebec, Canada. Results of this research could lead to much needed prophylactic treatment 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. Branch-funded researchers will conduct a clinical trial to address the significant gaps with respect to the limited understanding of best approaches of treating intestinal schistosomiasis in children ages 1 to 4 years. Over 200 million individuals worldwide are infected with one of three predominant species of schistosomes, and more than one-half of infections occur in children. Recent studies illustrate that many children experience first infections before the age 2, and that the prevalence of infection among children younger than 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 among adults and children older than age 4. The goals of this work are to conduct a randomized, controlled Phase II trial to be conducted 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, to address current gaps hindering treatment of young children.

Precision Alemtuzumab Therapy in Allogeneic Hematopoietic Cell Transplantation (HCT). Th is study will develop and evaluate a novel Precision Alemtuzumab 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 a webtool to perform modeling and simulations for clinicians. The study is led by PI Dr. Marsh at Cincinnati Children's Hospital Medical Center in collaboration with Medimatics of the Netherlands, which will build the pharmacokinetics dashboard.

Pulmonary Implications of Perinatal Acetaminophen Exposure. This work is evaluating the effects of acetaminophen exposure, while 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 of the United Kingdom.

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Characterize Drug-Drug Interactions (DDIs) in Infants. This work is using PBPK modeling and real-world data to accelerate the availability of age-appropriate drug dosing recommendations for infants, 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. In addition to the two prospective PK and safety studies it proposes, this work will also use a novel biomarker to examine underlying mechanisms of drug action for understanding the PK 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 specialized labs in South Africa to evaluate blood samples for specialized tests on participants' HIV strain.

T32 Cincinnati Pediatric Clinical Pharmacology Training Program. 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.

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 Innovative Research and Small Business Technology Transfer programs in branch-relevant areas. To carry out this mission, the branch engages with and supports investigators, helps identify gaps and opportunities for scientific advancement, and supports research to understand mechanisms of growth and development at the gene-molecular level and at higher levels of cell and organ function.

Areas of coverage include:

- Determining the role of nutrition throughout the life cycle—emphasizing the needs of reproductive-age women (including pregnant and lactating women), preterm and term infants, and children through adolescence—to promote health, optimal growth, and development and to prevent disease
- Exploring the role of nutrients within specific biological systems, such as reproduction, 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:

  - Factors affecting mammary gland development and function
  - Parental factors influencing human milk composition
  - Human milk composition including nutrients and bioactive substances within the human milk matrix
  - The role of the infant as not only a recipient of human milk but a factor influencing its composition and function.
  - Specific roles of nutrient and bioactive components of human milk in the health of term and pre-term 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 double burden 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 basis of linear growth and the onset of puberty, including studies of growth failure and precocious and delayed puberty
- Ascertaining the genetic, nutritional, and hormonal antecedents of bone health and the early origins of skeletal disorders with the aim of developing preventive strategies
- Determining and preventing the effects of hypo- and hyperglycemia on growth and development in children with diabetes
- Elucidating the molecular drivers of adverse intrauterine environments to prevent the development of obesity, insulin resistance, type 2 diabetes, and cardiovascular disease in individuals exposed to either overnutrition or undernutrition in utero

Current and Recent Initiatives

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 the implications of that complexity for assessment and interventions. PGNB staff also continue to serve as part of the WHO and global efforts to address anemia; these efforts 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.

Nutritional Assessments

Other specific activities led by PGNB to support the global nutrition and health agenda include the following:

- 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 research, clinicians, surveillance, program monitoring and assessment, and policy makers.

- In 2021, PGNB, in response to and collaboration with the U.S. Department of Agriculture (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: recognizing that the growing child is a complex biological system that interacts with its internal (biology, genetics, health) and external (social/behavioral, home, community, and physical) environments. BOND-KIDS will address 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

Nutrition and the "1000 Days" (Pregnancy through First 2 Years of Life)

- In 2012, the B-24 (Birth through 24 Months) effort was initiated 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 targeting the "1000 Days."
- In 2014, legislation codified the inclusion of pregnancy through the first 2 years of life into future iterations of the DGAs beginning in 2020.

- The subsequent results of the systematic reviews conducted 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 targeted funding opportunity to address evidence gaps.

Intersection of Climate, Food Systems, Health, and Nutrition

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

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

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

    - A 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 serves as co-chair with USDA/ARS of a new Research Interest Section within ASN focused on the intersection of climate, health, agriculture, and improving nutrition (CHAIN). This Section now has over 900 members representing the breadth of the domestic and international research community.

- In 2022, PGNB launched the Agriculture and Diet: Value Added for Nutrition, Translation and Adaptation in a Global Ecology (ADVANTAGE) Project, which is intended to better understand the intersections of agriculture, food systems, health, disease, and a changing environment across the lifespan by addressing 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?

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 a voluntary effort without specific funding to support its activities, it aims to enhance the impact of and synergies among the programs funded and implemented by the U.S. government 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 improving the prospects of future generations of children around the world, as well as 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 Changing Environment (CHANGE) technical subgroup, which is intended to integrate this important intersection into the efforts of the GNCP community to address malnutrition.

COVID-19

- PGNB initiated the COVID 19 Infant Feeding Research Interest Group (CIF-RIG) to address concerns and confusion resulting from the advent of the COVID-19 pandemic on safe and efficacious infant feeding practices.
- CIF-RIG leadership was asked to serve on the WHO COVID-19 Maternal, Newborn, Child, and Adolescent Research Network.
- An important outcome of these efforts was recognition of the need to develop a framework for resilient response to emerging infections and their potential impact on infant feeding practices. Addressing this need has become a focal point of the GNCP EPIC subgroup (described earlier).

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

International Partnerships

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

Staff Membership on Global Health Committees/Working Groups

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

Point-of-Contact

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Pediatric Trauma and Critical Illness Branch (PTCIB)

Scientific Scope

PTCIB was established during the institute's re-organization in 2012 to develop and support research and research training in pediatric trauma and critical illness. Priority areas of research include:

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

Major Global Health Initiatives over the Past Year

Novel Pediatric Sepsis Criteria and Clinical Decision Support Tools (5R01HD105939-02). 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 to diagnose pediatric sepsis are outdated, lack specificity, do not allow early detection and risk stratification in all settings, and are discordant with clinician-based diagnosis. The overall objective of this proposal is to derive and validate novel organ dysfunction-based pediatric sepsis 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.

Promoting Transportation Safety in Adolescence (5R01HD095248-05). The impact of teen and young adult motor vehicle crashes (MVCs) is substantial, with this age group constituting only 14 percent of the U.S. population but contributing to 30 percent of all fatal and nonfatal injuries due to MVCs, and 35 percent ($25 billion) of the medical and lost productivity costs. The long-term goal of this research is to identify effective programs that can reduce adolescents' risk for MVCs. The current best-practice policy approach to teen driver MVC prevention, state-level Graduated Driver Licensing (GDL) programs, have been effective largely by delaying licensure and restricting crash opportunity; they have not, however, directly led to increases in young drivers' skill, meaning success has come from a focus on restricting access to high-risk contexts instead of directly improving drivers' competence. There is a critical unmet need for efficacious interventions that address young drivers' inexperience directly to complement the structure put in place by GDL. This study is evaluating a comprehensive and integrated MVC prevention program that formally pairs on-road driver assessment (ODA) with brief face-to-face parenting sessions at two time points during the learner's permit period. This parent-teen intervention improves on the initial ODA and TeenDrivingPlan4 parent program evaluated in previous research by targeting both parents and teens with strengthened, expanded, and coordinated intervention content.

Mixed-Methods Evaluation of Mobile Health Adaptive Learning Training for Pediatric Healthcare Workers (HCWs) in Tanzania (1F32HD106683-01A1). Preventable illness in LMICs contributes to millions of pediatric deaths each year. Evidence-based guidelines (EBGs) created by the WHO are shown to improve outcomes for pediatric patients in LMICs and reduce this amenable burden of disease. Utilization of existing EBGs is highly variable among HCWs, however, and contributes to increased mortality. Mobile technology has transformed many aspects of public health, but is yet to be fully leveraged for HCW training. Adaptive learning, which uses electronic algorithms to deliver individualized content to learners, promotes increased learning efficiency in high-resource settings and could strengthen mobile training platforms in LMICs. To evaluate the efficacy of these tools in addressing the existing educational gap in LMICs, researchers designed an adaptive electronic learning curriculum based on existing EBGs for the management pediatric illness in LMICs. The researchers hypothesize that an adaptive electronic learning curriculum will increase HCW knowledge of EBGs for the care of serious illness in children, and that knowledge of learner perceptions will inform the creation and implementation of future electronic learning interventions. Using a mixed-methods study among a cohort of pediatric HCWs in

Mwanza, Tanzania, the project includes prospective randomized parallel-group double- blinded with an allocation ratio of 1:1. All participants will complete an electronic learning curriculum on priority content areas as defined by local stakeholders. Participants in the intervention arm will receive an adaptive electronic learning curriculum, and controls will receive a non-adaptive electronic learning curriculum. Knowledge acquisition will be measured using standard mean effect size comparing pre- and post-curriculum knowledge assessments. Semi-structured and group interviews with a random sample of quantitative participants will help determine HCW habits and perceptions relating to electronic learning interventions. Successful completion of the project will provide a foundation for the development of innovative solutions and low-cost implementation strategies to improve the care of seriously ill children worldwide.

Feasibility and Efficacy of Ambulance-Based mHealth for Pediatric Emergencies (FEAMER) Trial (1R21HD103049-01A1). Every hour, 300 children die globally as a result of acute or emergency conditions, and most of these deaths occur in LMICs. It is estimated that one-half of these lives could be saved through the appropriate and timely provision of acute/emergency care. Care during transport constitutes an essential component of the "chain of survival" of a modern emergency care system, extending from the scene of care to the appropriate health facility. For many emergency conditions, triage and care decisions during transportation play a critical role in the eventual outcome. Emergency Medical Systems with staff who are well-trained in pediatric acute/emergency care are scarce even in high income countries, and largely non-existent in LMICs. There is a critical need—globally, but particularly in LMICs—to address this expertise gap during the most critical time period while a child is transported to a fixed emergency care facility. 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 researchers are conducting a study of the feasibility of implementing an ambulance-based teleconsultation process (R21), and then executing a randomized controlled trial to confirm the efficacy of the approach on short-term clinical outcomes (R33) in Karachi, Pakistan.

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 to integrate and test three EBPs to prevent 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 with an outstanding track record of NIH-supported research and an extensive history of mentoring junior faculty, as well as from NGOs, all with extensive experience/commitment to preventing child maltreatment. The proposed 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.

Archiving and Harmonizing Data on Prevention and Treatment of Child Traumatic Stress (5R03HD105319-02). This project was developed in conjunction with the Global Collaboration on Traumatic Stress, a coalition of 10 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. By creating an ongoing research resource that promotes data sharing and facilitates novel integrative analyses that would not otherwise be possible, this work furthers the field's ability to understand how and for whom child trauma interventions work, allowing interventions to effectively address the impact of trauma on child health and well-being. This project also advances the NICHD goal of archiving and documenting existing datasets within the institute's scientific mission, enabling new analyses by the scientific community.

Infrastructure for Musculoskeletal Pediatric Acute Care Clinical Trials (IMPACCT) Consortium: Infrastructure for Musculoskeletal Pediatric Acute Care Clinical Trials (1U01AR079113-01). The management of two common upper extremity injuries, pediatric medial epicondyle fractures (MEF) and displaced distal radius fractures (DRF), is controversial with high practice variation. Within this context, children are either undergoing unnecessary procedures and anesthetic events when surgeons opt for reduction under anesthesia/ conscious sedation, or they are being undertreated by simple immobilization. Both scenarios are unacceptable in that children face either anesthetic risks and extra costs or poor alignment with potential long term functional disability to address such clinical

dilemmas. Using the IMPACCT consortium, which was organized to develop the infrastructure and experience necessary for multicenter randomized clinical trials, researchers will determine whether children treated with reduction under general anesthesia (MEF) or conscious sedation (DRF) have higher patient reported outcome scores, compared to those treated with simple immobilization alone. Trials on both types of fractures will be conducted simultaneously to take advantage of the economy of scale and ensure similar anatomic location, outcome measures, and intervention decisions. To date, 31 sites have agreed to recruit, randomize, and treat a total of 688 patients according to the pragmatic protocols. In addition, investigators have partnered with the Trial Innovation Network to increase the efficiency of trial development and execution. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) awarded this initiative an R34 Clinical Trials Planning Grant. The completion of these trials will provide a framework, infrastructure, and experience for future multicenter clinical trials in pediatric orthopedics as its results guide clinical decision-making.

Optimizing Prevention Approaches for Children Reintegrating from Orphanages in Azerbaijan (5R01HD099847-02). Due to the economic crisis following the collapse of the Soviet Union, Azerbaijan hosts a large population of "social orphans," children left by destitute parents in state-run institutions. Years of deprivation, separation from parents, and maltreatment in orphanages severely heighten the risk of mental health problems among institutionalized children. Current deinstitutionalization and family reunification initiatives provide basic case management services, but neither address the mental health problems of institutionalized children, nor attend to the poverty-related factors that led to institutionalization in the first place. To prevent mental health problems among children from orphanages reunited with their biological or extended families in Azerbaijan, 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.

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

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

Pediatric Severe Traumatic Brain Injury (sTBI) in Latin America: A Randomized Trial Comparing Two Management Protocols (5R01HD106273-02). Worldwide, TBI is the leading cause of death and disability among children and adolescents, and children who survive sTBI often live with profound impairments that alter their development and future possibilities. This scientific investigation will conduct a high-quality RCT to address a critical TBI management issue: whether a protocol with information from intracranial pressure monitoring to direct treatment of children with sTBI improves outcomes versus an aggressive management protocol based on imaging and clinical examination alone. Findings from the study, conducted in seven Latin American pediatric ICUs (PICUs), where infrastructures and practice patterns are optimal for strong internal validity and resources representative of trauma care in low-resource countries, will help guide U.S. and global clinical practices.

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 that aim 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 randomized across 250 villages of Leaders in Action, the Ministry's flagship GBV program, which trains local leaders on GBV and norms. The work experimentally assesses the impact of two main components: a household-based module, consisting of household visits by trained leaders; and a group-based module, with education sessions in small gender-segregated groups organized by trained facilitators. This study offers a unique opportunity to evaluate government programs to guide GBV programming, estimate cost effectiveness, and bring scientific evidence on GBV reduction and prevention to policy in Peru and worldwide.

Intergenerational Impact of Maternal Trauma History on Preschoolers' Behavioral Health Outcomes: Assessing Links with Caregiving Sensitivity and DNA Methylation (5R01HD102342-03). 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, intimate partner violence, and other traumas and related psychopathology. By enrolling a subset of mother-child dyads (n=1,700) over a 36-month recruitment period (~48 enrollees/month), this study collects follow-up data to examine the impact of maternal trauma on children's behavioral problems (internalizing and externalizing behaviors) across four time periods: 1) maternal experience of pre-pregnancy abuse in childhood (mothers < 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). By increasing knowledge regarding the intergenerational transmission of trauma using a life course theory approach and 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.

Post-Intensive Care Syndrome Pediatrics, Longitudinal Cohort Study (5R01HD098269-03). This prospective investigation examines child and family outcomes of pediatric patients who experienced 3 days of intensive care therapies at one of approximately 30 U.S. PICUs over 2 years post-PICU discharge. The study compares outcomes of these PICU patients with a control group of patients who received an overnight PICU stay (control), but who did not receive intensive care therapies, as well as with published quality of life data from the general and chronically ill pediatric populations. Children and their families are enrolled locally at each PICU, where baseline data are collected by local research staff, and post-discharge outcomes are followed centrally from the University of Pennsylvania and the Seattle Children's Research Institute in collaboration with co-investigators from the United Kingdom and Canada. The specific aims of this research are to: 1) determine the physical, cognitive, emotional, and social health outcomes and trajectory of recovery in a population of children post-critical illness; 2) determine the baseline health, presenting problem, and PICU factors associated with impaired physical, cognitive, emotional, and social outcomes among PICU survivors; and 3) determine the emotional and social health outcomes in parents and siblings of PICU survivors. The research hopes to explicate the impact of pediatric critical illness over a 2-year period to guide future intervention research that optimizes

child and family outcomes, while improving the health and well-being of PICU survivors and their families.

Stress Hydrocortisone in Pediatric Septic Shock (SHIPSS) Trial (5R01HD096901-03). The multicenter, international SHIPSS trial is examining adjunctive hydrocortisone treatment for children with refractory septic shock. The investigators hypothesize that hydrocortisone, compared to placebo, will decrease the proportion of subjects with poor outcomes, defined as death or severe, residual HRQL decrement, 28 days following study enrollment, without significant adverse events potentially attributable to hydrocortisone. The PIs continue to work with all committed U.S. sites that are not yet active to accomplish the remaining regulatory and training tasks so that screening and enrolling can begin as soon as possible. They will also continue to work with any newly identified interested sites. Their Canadian colleagues are in active discussions with interested PICUs in Brazil (the Latin American Sepsis Institute Network, consisting of 24 sites), Asia (the Pediatric Acute Critical Care Medicine Network, consisting of 12 sites) and Israel (2 sites). Enrolled subjects are randomized to hydrocortisone or placebo for up to 7 days, then assessed for the primary and additional endpoints at baseline, 28- and 90-days post enrollment.

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

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

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
- 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.

Global Health Data Archiving

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

- Integrated Public Use Microdata Series Demographic and Health Surveys (R01 HD069471). Boyle, Elizabeth H. (University of Minnesota): Africa South of the Sahara, Northern Africa, India.

- Integrated Global Health on Child Health and Development (R01 HD099182). Boyle, Elizabeth H. (University of Minnesota): More than 90 LMICs in the

Global South and Eastern Europe, including several countries in sub-Saharan Africa, Mozambique, Gambia, Ghana, Sudan, Cuba.

- Time Use Data for Health and Well Being (R01 HD053654). Sayer, Liana C. (University of Maryland, College Park): South Africa, United Kingdom, Mexico.

Archiving and Documenting Child Health and Human Development Datasets

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

- Public Use Datasets for Reproductive Health Research (R03 HD100680). Frost, Jennifer J. (Guttmacher Institute): Sub-Saharan Africa.

Global Health Population Dynamics Research

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

Developing and Disseminating Methodology to Improve Global Health Population Research

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

- Projecting the Future of Early Life Mortality in the Developing World (K01 HD 098313). Spears, Dean (University of Texas, Austin): India.

- Verbal Autopsy: Reimagining Data & Automated Cause Assignment (using Analysing Longitudinal Population-based HIV/AIDS data on Africa Network data) (R01 HD086227). Clark, Samuel J. (Ohio State University: South Africa, Zimbabwe, Kenya, Malawi, Tanzania, Uganda, India, Indonesia, United Kingdom.

- Global Age Patterns of Under-Five Mortality (R01 HD090082). Guillot, Michel (University of Pennsylvania): Sub-Saharan Africa, Bangladesh, France, United Kingdom.

- Improving the Measurement of Adolescent and Adult Mortality in Low-Income Countries (R01 HD088516). Helleringer, Stephane (New York University): Guinea-Bissau, Malawi, Uganda, Bangladesh, United Kingdom.

- Workshop on Migration Data and Analysis (R25 HD094676). Bloemraad, Irene (University of California Berkeley): Africa.

- Interdisciplinary Research Training Program for International Population Science (R25 HD101358). Axinn, William G. (University of Michigan, Ann Arbor): Nepal.

Supporting Offices of Research and Sponsored Programs

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

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

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

Reproductive Health

- A savings Intervention to Reduce Men's Engagement in HIV Risk Behaviors (R01 HD103563). Thirumurthy, Harsha (University of Pennsylvania): South Africa.

- Advancing Understanding and Measurement of Infertility, Related Fears and Stigma, and Associated Consequences in Low-Resource Countries (K01 HD107172). Bell, Suzanne O. (Johns Hopkins University): Uganda.

- An mHealth-Enabled Intervention to Prevent Partner Violence and Pregnancy among Adolescents and Young Women (R21 HD105202). Silverman, Jay G. (University of California, San Diego): Kenya.

- Biocultural Investigation of Maternal Adversity on Gene Expression and DNA Methylation in the Placenta (F30 HD097935). Hsiao, Chu (University of Florida): Democratic Republic of the Congo.

- Causal Pathways to Population Health Impact of HIV Antiretroviral Treatment (R01 HD084233). Tanser, Frank Courteney (Africa Health Research Institute): Burkina Faso.

- Determining Longitudinal Trends and Risk Factors for Adolescent Reproductive Health (R03 HD102740). Frank, Reanne (Ohio State University): Denmark, Germany.

- Development, Testing and Health Effects of a Multilevel Family Planning Intervention (R21 HD098523). Sileo, Katelyn Mary (University of Texas, San Antonio): Uganda.

- Effects of a Prosocial Intervention among Sellers of HIV and Reproductive Health Supplies on Young Women's Health (R03 HD109561). Liu, Jenny Xin (University of California, San Francisco): Tanzania.

- Enhancing Male Participation in Interventions to Prevent Unintended Pregnancy (R01 HD084453). Raj, Anita (University of California, San Diego): India.

- Ethics of HIV-Related Research Involving Underage Key Populations in Sub-Saharan Africa (R01 HD105684). Grosso, Ashley Lynn (Rutgers Biomedical and Health Sciences): Botswana.

- Female Sexual Orientation Genome-Wide Association Studies (R01 HD100180). Sanders, Alan R. (NorthShore University Health System): Australia, United Kingdom.

- HIV Risk and Access to Health Care Among Mobile Populations (R01 HD046886). Martinez Donate, Ana P. (Drexel University): Mexico

- Improving the Reproductive Health of Families (R01 HD094512). St Lawrence, Janet S. (Portland State University): Botswana.

- Increased Access to Highly Effective Contraception: An Opportunity Dividend? (R01 HD101480). Stevenson, Amanda Jean (University of Colorado): Sweden, United Kingdom.

- Mobile WACh Empower: Mobile Solutions to Empower Reproductive Life Planning for Women Living with HIV (R01 HD104551). Drake, Alison L. (University of Washington): Kenya.

- Pregnancy Context and Health Outcomes (R01 HD095181). Foster, Diana Greene (University of California, San Francisco): Nepal.

- Randomized Controlled Trial to Address Unintended Pregnancy Rates in Low-Resource Settings (R01 HD101453). Tumlinson, Katherine M. (University of North Carolina, Chapel Hill): Kenya.

- Reproductive Coercion and Related Risk Factors (F31 HD100019). Boyce, Sabrina Christine (University of California, Berkeley): Niger.

- Reproductive Responses to the Zika Virus Epidemic in Brazil (R01 HD091257). Marteleto, Leticia J. (University of Texas, Austin): Brazil.

- The Effect of Migration on Sexual Risk Behaviors and HIV Incidence among Non-Migrating Household Members: A Population-Based Study (F31 HD102287). Young, Ruth (Johns Hopkins University): Uganda.

Maternal Health and Child Health and Development

- A New Population-Scale Approach for the Study of Psychological Stress in the Transition to Adulthood (R21 HD104993). Axinn, William G. (University of Michigan, Ann Arbor): Nepal.

- Achieving Sustained Early Child Development Impacts at Scale: A Kenyan RCT (R01 HD107116). Lopez Garcia, Italo (University of Southern California): Kenya.

- Development-Induced Displacement and Women and Children's Well-Being (R21 HD107468). Randell, Heather (Pennsylvania State University): Brazil.

- Distilling the Relationship of Parental Psychiatric Illness to Offspring Productivity and Social Outcomes: Evidence Base for Preventive Strategies (R03 HD109468). Nordsletten, Ashley (University of Michigan, Ann Arbor): Sweden.

- Effects in Middle Childhood of Early Exposure to Water and Sanitation Interventions (R03 HD102468), Fernald, Lia C. (University of California, Berkeley): Bangladesh.

- Effects of Age at Marriage and Education on Health of Mothers and Children (R01 HD095189) Field, Erica M. (Duke University): Bangladesh, Italy.

- Experimental Evidence on Long-run and Intergenerational Impacts of Child Health Investments in the Kenya Life Panel Survey (KLPS) (R01 HD108281). Miguel, Edward Andrew (University of California, Berkeley): Kenya.

- Experimental Evidence on the Impact of Parental Income on Child Health and Well Being (R01 HD103699). Miller, Sarah (University of Michigan, Ann Arbor): Canada.

- Family Characteristics and Health: Select Populations (K01 HD099313). Weitzman, Abigail Mae (University of Texas at Austin): Costa Rica.

- Family Context, Socialization, and Children's Socio-Emotional Development (R01 HD101527). Eggum, Natalie Des (Arizona State University): Nepal.

- Improving Perinatal Outcomes Using Conditional and Targeted Transfers (R01 HD090231). Okeke, Edward N. (RAND Corporation): Nigeria.

- India Human Development Survey (R01 HD041455). Desai, Sonalde B. (University of Maryland, College Park): India.

- Initial Effects of Program Elimination on School Enrollment and Child Health Outcomes (R21 HD107407). Parker, Susan W. (University of Maryland, College Park): Mexico.

- Intergenerational Impacts of Health Investments (R01 HD090118). Miguel, Edward Andrew (University of California, Berkeley): Kenya.

- Intergenerational Influences on Marriage, Contraception and Childbearing (R01 HD099135). Axinn, William G. (University of Michigan, Ann Arbor): Belgium.

- Kin Network Experiences, Mortality Perceptions, and Health Behaviors in Malawi (R03 HD105834). Smith Greenaway, Emily (University of Southern California): Malawi.

- Kinship, Nuptiality and Child Health Outcomes in a Low-Income Urban Area (R01 HD101613). Madhavan, Sangeetha (University of Maryland, College Park): Kenya.

- Long Term Effects of an Intervention on Maternal Behavior, Child Health, and Community Influence (R01 HD102412). Okeke, Edward N. (RAND Corporation): Nigeria.

- Migration, Family Context, and Child Health (R03 HD098705). Treleaven, Emily (University of Michigan, Ann Arbor): Nepal.

- Paid Family Leave and Prevention of Respiratory Tract Infections in Young Infants (R03 HD108526). Ahrens, Katherine (University of Southern Maine): Canada.

- Pathways and Mediators of Change in Early Childhood Development (R21 HD099488). Lopez Garcia, Italo (RAND Corporation): Kenya

- Policy Change and Women's Health (R01 HD095951). Margerison, Claire E. (Michigan State University): United Kingdom.

- Projecting the Future of Early Life Mortality in the Developing World (K01 HD098313). Spears, Dean (University of Texas at Austin): India.

- Social Networks and Child Malnutrition in a Resource Limited Setting (R21 HD101268). Mohanan, Manoj (Duke University): India.

- Temporary Childbirth Migration: Understanding the Magnitude and Implications for Maternal and Infant Health (R01 HD107197). Diamond Smith, Nadia Griffi (University of California, San Francisco): India.

- The Impact of Group-Based Life Skills and Health Empowerment for Young, Married, Women to Avoid Unintended Pregnancies in India. (R01 HD108252). Diamond Smith, Nadia Griffi (University of California, San Francisco): India.

Population-Environment Interactions and Natural Disasters

- Environmental Change and Undernutrition among Women and Children (R03 HD101859). Gray, Clark (University of North Carolina Chapel Hill): 50 countries across Africa, Asia, and Latin America.

- Population Dynamics in Africa: Selected Outcomes and Causes (R03 HD098357). Gray, Clark (University of North Carolina Chapel Hill): Botswana, Burkina Faso, Kenya, Uganda.

- Longer Term Effects of a Natural Disaster on Health and Socio-Economic Status (R01 HD052762). Frankenberg, Elizabeth A. (University of North Carolina, Chapel Hill): Indonesia.

- Surviving an Epidemic: Families and Well-Being, Malawi 1998-2020 (R01 HD087391). Kohler, Hans Peter (University of Pennsylvania): Malawi.

- Structural and Social Transitions Among Adolescents in Rakai (SSTAR) (R01 HD091003). Santelli, John S. (Columbia University Medical Center): Uganda.

- Inequality and Health-Risk Behavior: Investigating Genome-Environment Interplay (K01 HD094999). Burt, Callie (Georgia State University): United Kingdom.

- Health Decision-Making in the Aftermath of Disaster (R01 HD102382). Yang, Dean (University of Michigan, Ann Arbor): Mozambique.

- The Impact of Natural Disasters on Child Health (R01 HD104835). Wagner, Zachary (RAND Corporation): Belgium.

- Training for Health Professionals (R01 HD092655). Rosser, B. R. Simon (University of Minnesota): Tanzania.

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, the branch supports research to understand fetal development and improve ways to diagnose, treat, and prevent diseases in pregnant women and newborns. As the focal point for NICHD extramural research and training in maternal-fetal medicine, neonatology, and related fields, branch staff also engage with and support investigators to identify knowledge gaps and opportunities for scientific advancement. 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) (RFA-HD-23-008 and RFA-HD-23-009). The Global Network 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 supports a Data Coordinating Center (DCC) and several multidisciplinary research units around the world, each comprising a partnership between a research institution in an LMIC and one in the United States. The goal is to evaluate low-cost, sustainable interventions to improve maternal and child health, and build local research capacity and infrastructure.

These collaborations have led to improvements in maternal and infant health outcomes of interest, a substantial expansion of the skills of local health workers and physicians, and improved use of EBPs. The Network has also afforded opportunities for local scientists to develop protocols, abstracts, manuscripts, and presentations and augmented local capabilities in information technology and data collection and management. These activities are designed to facilitate independent continuation of local research activities that will ultimately lead to improved heath, healthcare systems, and independent funding, while also providing opportunities for other NIH institutes and funders to collaborate with Network researchers. As of 2022, the NICHD has funded eight U.S. sites, each with an international partner institution, to conduct research on human subjects. RTI serves as the DCC to provide the scientific and operational resources to maximize the productivity and public health impact of the Global Network's research collaborations.

Active Global Network studies include the Maternal Newborn Health Registry and the Azithromycin-Prevention in Labor Use Study (A-PLUS). The Prevention of Iron Deficiency Anemia Post-delivery (PRIORITY Trial) is expected to start recruitment in 2023.

- **Maternal Newborn Health Registry.** The NICHD Global Network's Maternal Newborn Health Registry is a prospective, population-based study of pregnancies and outcomes at sites in LMICs, including the Democratic Republic of the Congo, Bangladesh, Guatemala, India (two sites), Kenya, Pakistan, and Zambia. With the addition of a new site in Bangladesh, it is anticipated that all pregnant women at participating sites are being registered and their outcomes tracked for 6 weeks post-delivery. The primary purpose of this observational study of approximately 60,000 women per year is to quantify and understand trends in pregnancy services and outcomes over time in defined, low-resource geographic clusters. The study goal is to provide population-based statistics on stillbirths and neonatal and maternal mortality 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. Data collection began in 2008 and is ongoing. To date, the registry has collected data from more than 1 million mother-baby dyads.

- **PReventIOn of IRon DefIciency Anemia PosT-deliverY (PRIORITY) Trial**. Planning activities for the NICHD PRIORITY Trial, a prospective, two-arm, randomized trial in LMICs, were completed in 2022, and participant recruitment (~600 participants at each of eight sites) will start in 2023. The trial aims to determine if a single-dose intravenous infusion of iron is more effective at increasing prevalence of non-anemia than the current WHO standard (oral iron taken twice daily for 6 weeks post-delivery) among postpartum women with moderate anemia. All women will receive folic acid postpartum per WHO guidelines. The planned study sites include Kinshasa (Democratic Republic of Congo), Eldoret (Kenya), Lusaka (Zambia), Guatemala City (Guatemala), Dhaka (Bangladesh), Belagavi (India), Nagpur (India), and Karachi (Pakistan).

- **Azithromycin-Prevention in Labor Use Study (A-PLUS): Prevention of maternal and neonatal death/infections with a single oral dose of azithromycin in women in labor.** The NICHD Global Network's A-PLUS trial, a randomized, placebo-controlled, parallel multicenter clinical trial at eight research sites in Latin America, South Asia, and sub-Saharan Africa, is

assessing whether a single, prophylactic intrapartum oral dose of 2 grams azithromycin given to women in labor will reduce maternal death or sepsis, and intrapartum/neonatal death or sepsis. Interim analyses—scheduled at ~70% enrollment for futility or efficacy—*showed that women in labor benefitted from the treatment*, *and that it reduced maternal death and sepsis.* The study was unable to ultimately detect a treatment effect of a single, prophylactic oral dose of 2 grams of azithromycin in reducing intrapartum/neonatal death or sepsis. However, there was an observed consistent direction and magnitude of treatment effect in the high-risk cohort for reducing maternal death or sepsis. There was low conditional power for making a definitive conclusion in the high-risk cohort regarding intrapartum/neonatal death or sepsis if the study were to complete enrollment in the all-comer population. Based on the interim analysis, NICHD accepted the DMC's recommendation to halt the study. All sites ended on August 15, 2022, and the final enrollment was 29,278 dyads. The primary manuscript was submitted to the *New England Journal of Medicine* in November 2022, and published in 2023 (PMID: 36757318).

Studies Utilizing Global Health Collaboration

Evaluating Maternal Depression among Adolescent and Adult Women in Kenya (F31HD101149-03). This F31 project aims to advance understanding of the manifestation and trajectory of maternal depression among adolescent Kenyan women (ages 15 to 19) compared to adults throughout pregnancy and postpartum, and to develop a risk score to identify pregnancies at high risk for adverse perinatal outcomes. In Year 3 of this award, the PI's findings were published (PMID: 35394987) identifying trajectories and cofactors of depression among women living with HIV during pregnancy and at multiple points postnatally through 24 months postpartum. The findings also identified predictors of persistent peripartum depression among these women.

Pre-Post Study of an Audit and Feedback Intervention to Reduce Intrapartum Stillbirth in Mombasa, Kenya (F31HD100070-03). The aims of this project are to: 1) identify factors associated with intrapartum stillbirth that could be addressed by modifying provider behavior; 2) conduct a pre-post study using interrupted time series analysis to determine if rates of stillbirth are reduced after implementation of an audit and feedback intervention; and 3) determine the incremental cost and budget impact of the audit and feedback intervention. The research will use quantitative and qualitative methods to assess change in both process indicators (e.g., time to cesarean section) and intrapartum stillbirth rates before and after the

(e.g., time to cesarean section) and intrapartum stillbirth rates before and after the audit and feedback intervention. Demonstrating effectiveness of an intervention at both changing targeted provider behavior and reducing stillbirth rates is critical to determining its public health impact. Audit and feedback provide a flexible approach that allows for context-specific factors to be considered and addressed. If found to be effective and low-cost, this approach could be expanded to other facilities in sub-Saharan Africa as a cost-effective means of lowering stillbirth rates.

An evaluation of how the COVID-19 pandemic impacted the outcomes of interest in this study, added within Aim 1 activities, is near completion. This analysis found that labor and delivery admissions dropped significantly during the pandemic, and data suggest increases in some adverse outcomes including stillbirth, though these findings did not reach statistical significance. Combined with results from staff interviews, the data suggest that while service delivery continued during the pandemic, labor and delivery care was accessed later and in lower numbers than before the pandemic, leading to a small increase in known adverse birth outcomes among those who were admitted to the hospital. The substantial drop in admissions likely reflects an increase in women who needed medical assistance but were unable to access care due to the pandemic.

Evaluating Perinatal Mood and Anxiety Disorder in Kenya: A Mixed Methods Approach (F32HD108857-01). This F32 research project leverages data from an ongoing cohort study (PrIMA-X, R01HD100201) of 1,300 Kenyan mother-infant pairs followed from pregnancy through 36-months postpartum with longitudinal assessment of maternal Perinatal Mood and Anxiety Disorder (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 (SED) 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 (K23HD100594-03). For neonatal deaths worldwide, nearly one-quarter 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 (HA-BSIs) 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, while infections from extended-spectrum β-lactamase-producing pathogens and carbapenem-resistant organisms (CROs), leading causes of infection in hospitalized neonates, are associated with mortality of 25 percent or greater. A comprehensive assessment of risk factors for HA-BSI must precede development of targeted infection prevention and control (IPC) strategies. This project aims to 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 CRO infections, to support NICU clinicians in selecting 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 factors engineering principles, the tool will enable healthcare facilities to optimize IPC strategies and reduce risk of hospital-acquired infections and associated mortality.

Operationalizing kangaroo Mother care among clinically unstable low birth Weight Neonates in Africa (OMWaNA) Study (K23HD092611-04). Of the 2.7 million neonatal deaths each year, the majority occur among unstable neonates within 48 hours of birth in low-resource settings. Kangaroo mother care (KMC) is associated with decreased mortality among stable neonates weighing ≤2000g. This study, in Uganda, will critically explore the use of KMC in unstable neonates weighing ≤2000g to determine whether, compared to incubators, KMC reduces mortality and leads to cost savings. Aims of the study include: exploring factors that affect KMC uptake and duration, and using findings to develop strategies to improve KMC practice in facilities; developing and implementing a model to compare the incremental cost and cost-effectiveness of KMC versus incubator care; and conducting a pilot trial to estimate the effect of KMC on mortality relative to incubator care, and to evaluate the feasibility of a full-scale RCT on KMC. Findings will inform the development of an RCT to determine the effect of KMC on mortality in unstable neonates within 7 days of birth compared to incubator care.

University of North Carolina (UNC) Global Women's Health Fellowship (T32HD075731-08). This collaborative program between UNC and its in-country partners in Malawi, South Africa, and Zambia emphasizes the training of obstetrician/gynecologists for careers in global women's health research to address the most relevant and pressing issues in the field through dedicated research time in international settings. Fellows participate in regular forums with peers, mentors, and resource faculty to review and critique work in progress, while also receiving guidance in submission of abstracts, publications, proposals for research funding, and career development. Fellows are selected based on their prior academic accomplishments, research activities, and the level of their research interests in global women's health, followed by personal interviews with the PD/PI and a faculty of experienced global health experts, both within and outside of the department. This careful selection process ensures an appropriate match between the career stage of the candidate and the program. The program's system of faculty mentoring is critical for supporting the fellows as they begin their independent research. Effective mentoring plays an important role not only for research supervision, but also to facilitate professional introductions, invitations to meetings, networking with colleagues in the field, and subsequent career placement. Collectively, the faculty has many years of experience teaching and mentoring students and trainees at a variety of levels.

Social and Gene Interactions to Understand the Risk of Gestational Diabetes Mellitus (GDM) (R21HD101778-02). The Tohoku Medical Megabank (TMM) Birth and Three-Generation (BirThree) Cohort Study combines population genomics and a prospective cohort study. The study, begun in 2013, enrolled pregnant women, their partners, their parents, and their offspring after birth—a total of 73,499 participants from 22,493 families. This large, three generational cohort dataset with rich individual-level data on lifestyle and social factors will allow researchers to devise personalized preventive GDM interventions to benefit mothers and their offspring, identify novel risk alleles for GDM, and demonstrate that some levels of physical activity and nutrition are especially effective for a subset (based on the genotypes of mothers and fetuses). By understanding which social and lifestyle determinants may most impact an individual given their genetic profile, the study can personalize approaches to GDM prevention. Given the complex interplay of multiple determinants, such an approach has great potential to lead to more effective prevention strategies.

Effect of Iodized Salt in Pregnancy and Lactation on Infant Neurodevelopment in Rural Ethiopia (R01HD107475-01). This study, a response to NOT-HD-19-028, 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 of mild-to-moderate iodine deficiency in rural Ethiopia. The overall goal is to examine the effects of iodine in pregnancy and lactation on infant brain function, as well as maternal and infant iodine status and thyroid function. The specific aims of this project are to: 1) determine the effects of an intensive salt intervention in pregnancy and lactation on infant visual-evoked potentials (primary outcome), as well as visual attention, motor function, and head circumference at 6 months of age; 2) determine the effect of the iodized salt intervention on maternal breastmilk iodine concentration, as well as infant iodine status and thyroid function; and 3) examine interactions between iron and iodine on thyroid function in pregnancy and lactation. This study will generate foundational knowledge about the role of iodine in the first 1000 days of life and inform the design and delivery of interventions to optimize the potential of children worldwide.

Novel Vacuum-Induced Postpartum Hemorrhage (PPH) Control: A Multicenter Randomized Trial (R01HD108210-01). A multidisciplinary team of investigators with expertise in obstetrics, global health, and clinical trials will enroll 424 women in two high volume obstetric units in Ghana, an LMIC with high PPH burden, to evaluate the effectiveness (Primary Aim), 2) safety (Secondary Aim 1), and 3) cost-effectiveness (Secondary Aim 2) of the Jada® System for treating PPH, compared to standard care. If proven effective, safe, and cost-effective, this simple and scalable device would have a profound impact on PPH-related maternal mortality and morbidity worldwide, especially in LMICs.

Effects of Household Concrete Floors on Child Health (R01HD108196-01). This study, in rural Bangladesh, will measure whether installing concrete floors in households with soil floors reduces child enteric infection. Researchers will randomize pregnant women in 800 eligible households and install concrete floors before the birth cohort is born. Follow-up measurements will occur when children are ages 6, 12, 18, and 24 months.

Effectiveness of an mHealth Interactive Education and Social Support Intervention for Improving Postnatal Health (R01HD108510-01). This study will test the effectiveness of the Maa Shishu Swasthya Sahayak Samooh (MeSSSSage) mobile platform intervention compared to standard care for improving maternal and neonatal health-related behaviors and health outcomes in am RCT among 2,100 perinatal Indian women. MeSSSSage provides group education and support, including referral, for postpartum and infant health. Primary outcomes, assessed at 6 months after birth, include exclusive breastfeeding, unmet need for postpartum

contraceptives, and postpartum depression. The specific aims are to: 1) estimate the effectiveness of MeSSSSage on postpartum behaviors for optimizing maternal and neonatal health in India; 2) characterize the mechanisms of impact of the MeSSSSage intervention on maternal and neonatal health in India; and 3) determine the cost-effectiveness of the MeSSSSage intervention in improving postpartum maternal and neonatal health as compared to the standard of care.

Placental miRNAs Paracrine and Endocrine Roles in Insulin Sensitivity in Pregnancy (R01HD109206-01). The overall goal of this study is to investigate mechanisms by which selected candidate placental miRNA participate in the interplay between placenta and glucose-insulin regulation during pregnancy. Evidence suggests that miRNA produced in the placenta, and regulated by maternal glycemia, act locally and peripherally to manipulate maternal insulin sensitivity during pregnancy. Investigators will leverage their existing perinatal cohorts, which include longitudinal prospectively collected plasma samples and insulin-sensitivity index data derived from oral glucose tolerance tests in the first, second, and third trimesters. 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.

Effect of Support for Low-Income Mothers of Preterm Infants on Parental Caregiving in the NICU (R01HD109293-01). This 1:1 RCT will rigorously test the impact of financial transfers versus standard of care (control) among 420 low-income mothers with infants between 25 and 33 weeks of gestation in 3 level 3 NICUs (1 urban, 1 urban/suburban and 1 suburban/rural). Mothers in the intervention arm will receive a transfer of $160 per hospital week, with a one-time "label" or scripted message that explains that the transfer is intended for them to visit and care for their hospitalized infant. The study posits that financial transfers can enable economically disadvantaged families to visit the NICU, reduce the negative psychological impacts of financial distress, increase maternal caregiving behaviors associated with positive preterm infant health and development, and potentially reduce health systems costs. The aims of this study are to: 1) examine the impact of financial transfers on primary NICU caregiving behaviors, breastmilk provision, skin-to-skin care, secondary 1–2-month post-discharge caregiving behaviors, and safe sleep practices; 2) consider mechanisms of action, including mediators such as NICU visitation, mental health, and cognitive function, of the relationship between financial transfers and caregiving behaviors of interest,

including qualitative exploration of maternal perspectives of financial transfers, mediators of its impact, and other barriers and facilitators to maternal caregiving; and 3) conduct exploratory analysis of cost drivers (length of stay, 30-day readmission and emergency department use). This simple and scalable intervention has tremendous potential to improve equity in health care access by enabling key populations to utilize existing clinical supports during the NICU hospitalization.

AI-Driven Low-Cost Ultrasound for Automated Quantification of Hypertension, Preeclampsia, and Intrauterine Growth Restriction (IUGR) (R01HD110480-01). In this NICHD-funded study, investigators collected point-of-care Doppler ultrasound recordings and developed a preliminary machine-learning approach for detecting IUGR and maternal hypertension to prospectively validate findings in two large, underserved pregnancy cohorts in rural Guatemala and urban Georgia. The investigators hypothesize that low-cost AI will perform as well in detecting maternal hypertension, preeclampsia, and IUGR as standard-of-care high-cost diagnostic approaches. Successful completion of this proposal could lead to a novel and cost-effective approach to screening for these conditions using point-of-care Doppler connected to a low-cost, AI-enabled edge-computing system.

Premature Infants Receiving Umbilical Cord Milking (UCM) or Delayed Cord Clamping (DCC) (R01HD088646-05). Preterm brain injury from intraventricular hemorrhage (IVH) is a pressing worldwide public health problem. The University of Alberta, Canada, University College Cork, Ireland, and University of Ulm, Germany, are participating in this study along with six U.S. sites. DCC, waiting to clamp the umbilical cord for 30 to 60 seconds after birth, provides the newborn with a significant autologous transfusion of blood from the placenta and is known to reduce IVH. DCC also reduces overall IVH (mainly lower grades 1 and 2) by 50 percent but does not reduce the incidence of severe IVH or death. This study will examine whether UCM is at least as good as or better than DCC in reducing bleeding in the brain or preventing death in preterm newborns. The investigators will study short- and long-term outcomes of infants delivered before 32 weeks of gestation who receive either UCM or DCC.

Umbilical Cord Milking in Non-Vigorous Infants: The MINVI Trial (R01HD096023-05). At birth, it is critical that an infant begins breathing quickly, switching from relying on the placenta for oxygen to using its lungs for the first time. Among infants who need resuscitation, the currently recommended practice is to immediately clamp the umbilical cord—UCM and DCC are not recommended in these cases because of a lack of evidence. However, animal studies show that

clamping the cord before the baby breathes can cause the heartbeat to slow and can decrease the amount of blood being pumped out of the heart each minute. In addition, several large studies from around the world found that infants needing resuscitation were more likely to develop conditions such as cerebral palsy, autism, and other developmental problems. MINVI will test whether infants in this situation benefit from UCM. The cord will be quickly milked four times before cutting, but this activity will not delay the resuscitation procedures. The trial is a cluster crossover design in which each hospital is randomly assigned, for a period of 12 months, to use either early cord clamping or UCM for any infant needing resuscitation. Then sites will change to the other method for an additional 12 months. In addition to eight U.S. sites, the study has sites in Alberta, Canada; Dallhousie University, New Brunswick, Canada; and University of Ulm, Germany.

Group Antenatal Care to Promote a Healthy Pregnancy and Optimize Maternal and Newborn Outcomes: A Cluster Randomized Controlled Trial in Ghana (R01HD096277-05). This project aims to improve health literacy and reduce preventable maternal and newborn morbidities and mortality in Ghana, with a focus on preparing for birth, identifying pregnancy complications, and understanding care-seeking patterns. The research team is testing the efficacy of providing antenatal care in groups of 8 to 12 women at similar points in gestation. Women will meet with the same group and the same provider over the course of their pregnancies for a 60-minute facilitated discussion in addition to their individual assessments. The team is recruiting 845 women older than 15 years of age, at less than 24 weeks of gestation, during their first antenatal care visit at health facilities in rural Ghana. Participants will be surveyed in person at the health facility or by cellphone at six time points: 1) initial enrollment, 2) third trimester (prior to delivery), 3) immediately postpartum, 4) 6-weeks postpartum, 5) 6-months postpartum, and 6) 1-year postpartum. Additional data will be collected from antenatal care and hospital medical records.

Addressing Provider Stress and Unconscious Bias to Improve Quality of Maternal Health Care (R00HD093798-05). Poor person-centered maternal health care (PCMHC) contributes to high maternal and neonatal mortality in sub-Saharan Africa, and disparities in PCMHC are driving disparities in use of maternal health services. In the K99 phase of this project, researchers conducted 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. They also conducted structured and in-depth interviews with 100 women and 20 to 40 providers, to examine the levels of provider stress and unconscious bias, and specific types of stressors and biases in Kenya. In the

current R00 phase, researchers will: 1) design an intervention that enables providers to identify and manage their stress and unconscious bias; 2) pilot the intervention to assess its feasibility and acceptability; and 3) assess preliminary effects of the intervention. The study will recruit 80 providers for the pilot and its evaluation. All study participants (i.e., healthcare providers) will be older than 18 years of age and recruited from health facilities in Migori County, Kenya. The results of the pilot will be refined to develop an R01 proposal for a multisite evaluation with a larger sample and longer follow-up to assess impact on PCMHC.

Two Year Outcomes After Dextrose Gel Prophylaxis for Neonatal Hypoglycemia (R01HD091075-05). Hypoglycemia, or low blood sugar, occurs very commonly in newborn infants and, if severe, can lead to significant brain injury. Yet there are many aspects of newborn hypoglycemia that remain unknown, including the definition of "normal" and "abnormal" blood sugar levels, and the severity level of hypoglycemia that causes brain injury. 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 if there are any benefits or adverse effects at two years' corrected age. Assessments will 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 that will be essential before introduction into clinical practice.

Global Health Partnerships

N/A

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 improving leadership and governance, service provision, financing, human resources, data collection, and research capacity for rehabilitation. NIH was a major contributor to this effort.

In 2022, NCMRR financially supported WHO Rehabilitation 2030 through a cooperative agreement mechanism managed by NIAID (U01AI139547-03) 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

N/A

Global Health Partnerships

Johns Hopkins University (JHU)-Hanoi University of Public Health Research Program on Health, Economic and Societal consequences of trauma and injuries in Vietnam (HEalS) (5D43TW012191-02). The overall goal of this program is to strengthen research capacity to generate data and interventions to address the post-injury and -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 Hanoi University of Public Health (HUPH), Vietnam. Each entity has a great commitment to understanding the public health impact of trauma and injuries, experience and expertise in researching trauma and injuries, and 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.

Designing Computer-Mediated Communication Supports to Improve Social Participation After TBI (R01HD071089-09). 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 platform is not accessible by individuals with cognitive disabilities. This project will develop software to aid individuals with TBI in using social media and computer-based communication. The investigators will test how individuals with TBI use and interact with the software, with the goal of improving use and communication among adults with TBI. A PI from McMaster University, Ontario, Canada, with expertise in communication after TBI and who developed clinical practice guidelines for the treatment of TBI, and her lab will assist with the evaluation of the software and future developments to implement the software more broadly. In 2021, early results from this research demonstrated that, while people with TBI maintain social media accounts, about one-quarter of study participants reported changes in their patterns of social media use caused by brain injury and listed concerns about accessibility, safety, and usability as major barriers.

A Client-Based Outcome System for Individuals with Lower Limb Amputation (R01 HD065340-10). Individuals with lower limb loss or structural difference can have a wide range of functional capabilities depending on the degree of loss or difference, the use of prosthetic limbs, and the type of prosthetic limbs used. There are many validated measures to assess functional abilities in individuals with limb loss, but they may be time consuming and 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 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. Collected data is being evaluated by researchers at the University of Washington to develop the new, computer-based, adaptive tool for assessing functional ability for individuals with lower limb loss or limb difference. In 2022, several manuscripts were published by the group, including the Japanese translation and linguistic validation of the tool.

A Longitudinal Population-Based Birth Cohort Study to Understand the Past, Present, and Future of Children and Youth with TBI (R03 HD104206-02). Some effects of pediatric TBI are evident immediately, but because pediatric TBI disrupts brain development, as well as brain health, many effects can take years to become

apparent. The CDC identifies pediatric TBI as an area with insufficient data repositories. The goal of this research project is to ascertain the short- and long-term effects of pediatric TBI by producing a dataset covering over 4 million live births in Ontario, Canada, between 1992 and 2020. It would be the first such dataset in the United States or Canada and could greatly inform clinical decision making in both countries. This grant, awarded to the University Health Network in Ontario, Canada, will take advantage of unique healthcare datasets that are collected as part of the Canadian healthcare system, allowing researchers to understand the incidence of pediatric TBI, the long-term impacts on neural development, and health care utilization of individuals with TBI.

Calibrating Transcutaneous Spinal Stimulation for Spasticity, Pain, and Motor Function in Spinal Cord Injury (SCI) (R01 HD101812-02). SCI 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, who is a leading international expert in transcutaneous spinal stimulation and who will assist with analysis and interpretation of results.

Multiscale Models of Proprioceptive Encoding to Reveal Mechanisms of Impaired Sensorimotor Control (R01 HD090642-07). Many neurological conditions, such as stroke, cerebral palsy, and Parkinson's disease, involve increased joint resistance to passive movements, including spasticity, rigidity, and dystonia. This project aims to understand how altered neural input to muscles drives hyper-resistance in joints for a variety of neurological conditions. 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. These data will inform clinical exams and allow better understanding of neurological deficits at the patient level and more personalized clinical care. The investigators are collaborating with an expert in computer modeling of humans with cerebral palsy, at Katholieke Universiteit Leuven in Belgium, who 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.

Quantifying the Energetic Cost of Support and Stabilization During Walking in Children with Cerebral Palsy (R21HD104112-01A1). Walking allows individuals to complete their daily activities and is a highly efficient metabolic activity. Individuals with cerebral palsy can require 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 walk, these interventions have not made meaningful improvements in the energy efficiency of walking. As a result, people with cerebral palsy may tire faster and walk less. The goal of this project is to measure the energy required for a person with cerebral palsy to support their body weight and maintain balance while walking. The research team is using a special treadmill that can provide weight support and balance support to the walker to measure how much energy is used during regular walking versus while the treadmill is providing these supports. An expert in experimental measurement and computation analysis of energy expenditure at Simon Fraser University in Canada will contribute to the design of experiments and the analysis of the results.

Lumbar Spine-Muscle Degeneration Inhibits Rehabilitation-Induced Muscle Recovery (5R01HD088437). Low back pain is a common and complex condition that will affect most Americans at some point in their lives. Symptoms can be persistent and recurrent, and treatments may be ineffective. Previous research showed that muscle in the lower back is weakened and altered in low back pain, making these muscles a key target for rehabilitation. This study will use MRI and gene expression profiles 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 will 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 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.

Perturbation Training for Enhancing Stability and Limb Support Control for Fall-Risk Reduction Among Stroke Survivors (5 R01 HD088543-05). Stroke survivors are at a greater risk of falls due to stroke-associated sensory and motor impairments, and these falls can lead to serious injuries, such as hip fracture, hospitalization, and death. Many stroke survivors also experience hemiparesis, in

which the one side is more impacted while the opposite side of the body maintains more robust motor capabilities. The goal of this project is to develop a training program to prevent falls in stroke survivors. In this study, researchers will train participants on using balance-recovery strategies to prevent falls. Participants will train on their non-paretic side first, and then get similar training on their paretic side to explore whether bilateral training improves outcomes overall, and to confirm that the training program is effective in stroke rehabilitation. A researcher at McGill University, Canada, with expertise in sensorimotor control of posture and gait in stroke rehabilitation, will serve as a consultant on this project, providing insight for data analysis and contributing to publication of the results.

Dynamic Stability in the Anterior Cruciate Ligament (ACL)-Injured Knee (5R37HD037985-19). This study, the continuation of a prospective international cohort study of patients after acute unilateral ACL injury, will help inform care by answering important clinical questions regarding the role and impact of dynamic knee stability on patient outcomes. The project builds on a 10-year collaboration between the University of Delaware and Oslo University Hospital, Norway, where the practice pattern requires a substantial period of rehabilitation prior to reconstructive surgery. The inclusion of an international sample from the 10-year study provides an opportunity to test the conventional wisdom that drives surgical decision-making in the treatment of ACL rupture in the United States. In addition, further elucidation of how those with different early compensation strategies for the injury are affected by neuromuscular training and reconstructive surgery will enable researchers to derive and test meaningful prediction rules for clinical management. In 2022, a comprehensive publication identified four distinct recovery trajectories of knee function and confirmed that 88 percent of the patients who followed the treatment algorithm experienced the moderate and high trajectories characterized by good improvement and high scores.

Neuroergonomic Assessment of Wheelchair Control in Real-World Environments with Both Healthy and Clinical Populations (1F30HD103527-03). 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).

Staff Membership on Global Health Committees/Working Groups

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

Point-of-Contact

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

The DIR research program utilizes a multidisciplinary environment to investigate the physics, chemistry, and biology of cells; the processes that govern and regulate cellular function; and the effects when these processes fail. The division includes 59 tenured and tenure-track investigators, organized into 12 affinity groups (AGs), and approximately 260 postbaccalaureate, clinical, and postdoctoral fellows and graduate students, in addition to the Division of Population Health Research.

Each of the 12 AGs is an intellectual hub for a group of investigators, creating a forum to share ideas and collaborate around common themes in support of the DIR mission. The AGs serve as catalysts for new initiatives. Each investigator has a primary affiliation with an AG most closely aligned with his or her scientific interests. Secondary affiliations allow for communication across specialties in support of translational research and new collaborations. Each AG has its own mission statement, shared research goals and objectives, and resources. Collectively, the AGs contribute to recruitment, mentoring, and the annual DIR scientific retreat. AGs are as follows:

- Aquatic Models of Human Development
- Bone and Matrix Biology in Development and Disease
- Cell and Structural Biology
- Cell Regulation and Development
- Developmental Endocrinology, Metabolism, Genetics, 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?

Division of Population Health Research (DiPHR)

Scientific Scope

With an ambitious, threefold mission, DiPHR, now within the NICHD DIR, aims to:

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

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

Global Health Partnerships

- NTDs: Biochemistry related to birth defects and GWAS with Trinity College in Dublin, Ireland. PI: Dr. J. Mills
- PrePARED (Preconception Period Analysis of Risks and Exposures influencing health and Development) Consortium. This international collaboration, with investigators across the United States, Canada, Australia, Denmark, China, and India, will first describe the data harmonization process between cohorts and then evaluate preconceptional exposures such as high blood pressure. Investigator: Dr. E. Yeung
- Pregnancy And Childhood Epigenetics (PACE) Consortium. In this international collaborative consortium, led by NIEHS, investigators use DNA methylation data to investigate the epigenetics of perinatal and pediatric exposures and outcomes. Studies are underway on evaluating the associations between multiple perinatal factors and newborn/childhood DNA methylation. Investigator: Dr E. Yeung

Epidemiology Branch Investigators Involved in Global Health Activities

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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

In an integrated program of laboratory and clinical investigation, the SHDBEM studies the molecular biology of the 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 (Names in Bold)

- **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

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

Point-of-Contact

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Section on Molecular Morphogenesis (SMM)

PI: Yun-Bo Shi, Ph.D.

AG: Cell Regulation and Development

Scientific Scope

SMM uses amphibian metamorphosis as its main model system to study the gene-regulatory mechanisms controlled by thyroid hormone (TH) receptor (TR), which establish the postembryonic developmental program in vertebrates. The laboratory recently showed that TR is both necessary and sufficient for *Xenopus* metamorphosis, by recruiting cofactors in a TH-dependent manner, and revealed the origin of TH-induced adult intestinal epithelial stem cells. The laboratory has also identified many TH target genes and has been 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 five years.

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

- Tail resorption during amphibian metamorphosis is perhaps the most dramatic developmental event controlled by TH. In collaboration with researchers at **Hiroshima University, Japan, and Chengdu Institute of Biology, China**, SMM recently discovered a unique role of TR β in regulating notochord resorption during Xenopus metamorphosis. The team has also analyzed the expression program underlying tail development during embryogenesis, as well as resorption during metamorphosis in the ornamented pygmy frog *Microhyla fissipes*, revealing conserved gene expression profiles between terrestrial and aquatic frog species.

- To investigate the function of endogenous genes during metamorphosis, SMM recently collaborated with scientists in **Xi'an Jiaotong University School of Medicine, 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 that was previously shown to be induced by TH during frog intestinal metamorphosis. Analysis of the mouse knockout line indicated that the transporter facilitates nutrient signaling in mouse skeletal muscle, and that a total knockout leads to embryonic lethality. Through a collaboration with researchers in **Kanazawa University Graduate School, Japan**, SMM then showed that the transporter also regulates osteoclastogenesis and bone homeostasis via the mTORC1 pathway.

- In collaboration with scientists at NCI/NIH and **South-Central University for Nationalities and Xi'an Jiaotong University School of Medicine, China**, SMM recently showed that a heterozygous dominant negative-TRα mutation leads to stem-cell defects in the adult intestine of a mouse model that mimics human patients with resistance to TH from TR α mutations. This finding is consistent with a previous SMM finding on the role of TH in adult intestinal stem cell development in Xenopus. Furthermore, the lab has shown that intestinal epithelial-specific knockout of protein arginine methyltransferase 1, a coactivator for TR, leads to, surprisingly, increased cell proliferation in adult mouse intestinal crypt. This finding suggests an important role for the protein other than as a TR coactivator for this methyltransferase in regulating adult intestinal stem cell function.

- In addition, collaborations with **Wuhan University and South-Central University for Nationalities in China** have 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.

- A new collaboration was recently initiated recently to study if and how epigenetic changes are involved in TH regulation of anuran development via a joint graduate student with **CNRS Muséum National d'Histoire Naturelle, France**.

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

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 to investigate the developmental impact of genes that modulate excitatory/inhibitory balance and neuronal network activity that affect behaviors and cognitive functions altered in psychiatric and neurodegenerative disorders.

Major International Research Initiatives

Through a collaborative agreement with Dr. Andreas Zimmer at the **University of Bonn in Germany**, Ms. Larissa Erben joined the SMN as a graduate student to work on her dissertation project, which focused on understanding the cellular expression patterns and functional roles of distinct ErbB4 splice variants in the brain. Specific ErbB4 splice variants (i.e., ErbB4 Cyt-1) are associated with maturation of the prefrontal cortex during juvenile development, and with cognitive deficits in persons diagnosed with schizophrenia. As part of her research, Ms. Erben helped establish a novel, highly sensitive, fluorescent in situ hybridization approach (i.e., Basescope) that allows detection and quantification of RNA splice variants at a single-cell level that can then be specified to a single short exon. Later, she went on to investigate how deletion of the ErbB4 Cyt-1 exon (26 base pairs), targeted by loxP/Cre recombination, affects development and behaviors of Cyt-1knockout mice. This work resulted in four publications (Refs. 1 and 2) and earned her a Ph.D. from the University of Bonn.

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 (Refs. 2 and 3). More recently, SMN used cutting-edge techniques, such as optogenetics, fiber photometry, and touchscreen-based behavioral paradigms, to investigate the roles of the NRG/ErbB4 and dopamine signaling pathways in regulating distinct cognitive domains.

The SMN 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 went on to show 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 (Ref. 4). 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

- Erben L., Welday J.P., Murphy R., and Buonanno A. (2022). Toxic and Phenotypic Effects of AAV_Cre Used to Transduce Mesencephalic Dopaminergic Neurons. *Int J Mol Sci 23(16):9462.* doi: 10.3390/ijms23169462. PMID: 36012727

- Erben L., Welday J.P., Cronin M.E., Murphy R., Skirzewski M., Vullhorst D., Carroll S.L., and Buonanno A. (2022). Developmental, neurochemical, and behavioral analyses of *ErbB4 Cyt-1* knockout mice. *J Neurochem 161(5):435-452.* doi: 10.1111/jnc.15612. PMID: 35523590

- 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

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

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

- Claudia Colina-Prisco, Ph.D.
  Postdoctoral Fellow
  NIAAA, NIH

- Larissa Erben, Ph.D.
  Postdoctoral Fellow

- Rolando Garcia, Ph.D.
  Senior Scientist
  Wellstat Therapeutics
  Gaithersburg, Maryland

- Carmen M. Gonzalez, Ph.D.
  Department of Pathology and Experimental Therapy
  University of Barcelona, Spain

- Ryoichi Kimura, Ph.D.
  Assistant Professor
  Department of Physiology, Hyogo College of Medicine
  Nishinomiya, Japan

- Oh-Bin Kwon, Ph.D.
  Assistant Professor
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  Department of Life Science, POSTECH
  South Korea

- Elias Leiva-Salcedo
  Assistant Professor
  Facultad de Química y Biología
  Universidad de Santiago, Chile

- Marines Longart, Ph.D.
  Principal Investigator
  Center for Biosciences, Institute for Advanced Studies
  Caracas, Venezuela

- Joerg Neddens, Ph.D.
  Senior Scientist
  Department of Histology
  JSW Life Sciences, Austria

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

- Zaheer Rana, Ph.D.
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International Partnerships

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

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

Staff Membership on International Committees/Working Groups

N/A

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