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<tr>
<th>Acronym</th>
<th>Full Term</th>
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<tbody>
<tr>
<td>ABI</td>
<td>Acquired Brain Injury</td>
</tr>
<tr>
<td>ACL</td>
<td>Anterior Cruciate Ligament</td>
</tr>
<tr>
<td>ACS</td>
<td>Antenatal Corticosteroids</td>
</tr>
<tr>
<td>ACT</td>
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<tr>
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<td>Attention Deficit/Hyperactivity Disorder</td>
</tr>
<tr>
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<td>Affinity Group</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>AP</td>
<td>Abruptio Placenta</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>ASA</td>
<td>Acetylsalicylic Acid</td>
</tr>
<tr>
<td>ASPIRIN</td>
<td>Aspirin Supplementation for Pregnancy Indicated Risk Reduction in Nulliparas</td>
</tr>
<tr>
<td>BPCA</td>
<td>Best Pharmaceuticals for Children Act</td>
</tr>
<tr>
<td>BMGF</td>
<td>Bill and Melinda Gates Foundation</td>
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<tr>
<td>BPD</td>
<td>Bronchopulmonary Dysplasia</td>
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<tr>
<td>BRAD</td>
<td>Biomedical/Behavioral Research Administrators Development Award</td>
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<tr>
<td>CATCH</td>
<td>Counseling and Testing for Children at Home</td>
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<td>CCRT</td>
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<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CHAP</td>
<td>Community Health Advocacy Program</td>
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<tr>
<td>CIPHER</td>
<td>Collaborative Initiative on Pediatric HIV Research</td>
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<td>Collaborative for Enhancing Emergency Care Research in Low- and Middle-Income Countries</td>
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<td>CNRS</td>
<td>French National Center for Scientific Research</td>
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<tr>
<td>CNS</td>
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<td>CP</td>
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<td>CPAP</td>
<td>Continuous Positive Airway Pressure</td>
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<td>CRISPR</td>
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<td>Gestational Diabetes Mellitus</td>
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<td>Full Term</td>
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<td>Global Network</td>
<td>Global Network for Women's and Children's Health Research</td>
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<td>GU</td>
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<td>Genome-Wide Association Studies</td>
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<td>Hyperglycemia and Adverse Pregnancy Outcome Study</td>
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<td><em>Haemophilus influenzae</em> type B</td>
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<td>HIV Testing and Enhanced Counseling</td>
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<td>ICs</td>
<td>NIH Institutes and Centers</td>
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<tr>
<td>IeDEA</td>
<td>Pediatric International Epidemiologic Databases to Evaluate AIDS</td>
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<td>IMPAACT</td>
<td>International Maternal Pediatric Adolescent AIDS Trials Network</td>
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<tr>
<td>INRIA</td>
<td>French Institute for Research in Computer Science and Automation</td>
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<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
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<tr>
<td>IRDiRC</td>
<td>International Rare Diseases Research Consortium</td>
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<tr>
<td>IUD</td>
<td>Intrauterine Device</td>
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<tr>
<td>IUGR</td>
<td>Intrauterine Growth Retardation</td>
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<tr>
<td>LBW</td>
<td>Low Birth Weight</td>
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<td>LDA</td>
<td>Low-Dose Aspirin</td>
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<td>LMICs</td>
<td>Low- and Middle-Income Countries</td>
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<td>MODS</td>
<td>Multiple Organ Dysfunction Syndrome</td>
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<td>MINERVa</td>
<td>Multigenerational Familial and Environmental Risk for Autism Network</td>
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<tr>
<td>MOU</td>
<td>Memorandum of Understanding</td>
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<tr>
<td>mTBI</td>
<td>Mild Traumatic Brain Injury</td>
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<td>NCI</td>
<td>National Cancer Institute</td>
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<td>National Center for Medical Rehabilitation Research</td>
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<td>NeOProM</td>
<td>Neonatal Oxygenation Prospective Meta-analysis Collaboration</td>
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<td>National Institute on Alcohol Abuse and Alcoholism</td>
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<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
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<tr>
<td>NICHD</td>
<td><em>Eunice Kennedy Shriver</em> National Institute of Child Health and Human Development</td>
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<td>NIDA</td>
<td>National Institute on Drug Abuse</td>
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<td>NIMH</td>
<td>National Institute of Mental Health</td>
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<td>NISDI</td>
<td>NICHD Latin American/Caribbean International Site Development Initiative</td>
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<td>NTDs</td>
<td>Neural Tube Defects</td>
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<td>OGAC</td>
<td>Office of the Global AIDS Coordinator</td>
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<td>OVC</td>
<td>Orphans and Vulnerable Children</td>
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<tr>
<td>PA</td>
<td>Physical Activity</td>
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<td>PASS Network</td>
<td>Prenatal Alcohol in SIDS and Stillbirth Network</td>
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<tr>
<td>PEARL Study</td>
<td>Pregnancy and Early Life-Style Improvement Study</td>
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<tr>
<td>PEEP</td>
<td>Positive End-Expiratory Pressure</td>
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<tr>
<td>PEPFAR</td>
<td>U.S. President's Emergency Plan for AIDS Relief</td>
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<tr>
<td>PLP</td>
<td>Phantom Limb Pain</td>
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<tr>
<td>PMA</td>
<td>Post-Menstrual Age</td>
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<td>Acronym</td>
<td>Full Term</td>
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<tr>
<td>PMTCT</td>
<td>Prevention of Maternal-Child HIV Transmission</td>
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<td>PTD</td>
<td>Preterm Delivery</td>
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<td>PTN</td>
<td>Pediatric Trials Network</td>
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<tr>
<td>RFA</td>
<td>Request for Applications</td>
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<td>SAIL Study</td>
<td>Sustained Inflation for Lung Expansion Study</td>
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<tr>
<td>SBIR</td>
<td>Small Business Innovative Research</td>
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<tr>
<td>SCI</td>
<td>Spinal Cord Injury</td>
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<td>SGA</td>
<td>Small for Gestational Age</td>
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<tr>
<td>SI</td>
<td>Sustained Inflation</td>
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<td>Sudden Infant Death Syndrome</td>
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<td>Superb Microvascular Imaging</td>
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<td>Statens Serum Institut</td>
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<td>STAC</td>
<td>Scientific and Technical Advisory Committee</td>
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<td>Sexually Transmitted Infection</td>
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<td>Small Business technology Transfer</td>
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<td>T1DM</td>
<td>Type 1 Diabetes</td>
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<tr>
<td>TALEN</td>
<td>Transcriptional Activator Like Effector Nuclease</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>TBI</td>
<td>Traumatic Brain Injury</td>
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<tr>
<td>tDCS</td>
<td>Transcranial Direct Current Stimulation</td>
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<tr>
<td>TH</td>
<td>Thyroid Hormone</td>
</tr>
<tr>
<td>UNC</td>
<td>University of North Carolina</td>
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<tr>
<td>UNICEF</td>
<td>United Nations International Children's Emergency Fund</td>
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<td>USAID</td>
<td>U.S. Agency for International Development</td>
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<td>U.S. Pediatric Formulations Initiative</td>
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<td>UTI</td>
<td>Urinary Tract Infection</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Overview

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

OGH works in close collaboration with NICHD Divisions and Offices, as well as other National Institutes of Health (NIH) and U.S. Department of Health and Human Services (DHHS) entities, to improve the overall 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; and
- Assisting the Institute's components in enhancing their international research portfolios and other global health activities.

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

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

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

Mission

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

Major International Initiatives over the Past Year

World Health Organization (WHO) Nurturing Care Framework. 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 interventions aimed at enhancing health, nutrition, responsive caregiving, safety and security, and early learning. OGH was invited by the WHO's Department of Maternal, Newborn, Child and Adolescent Health to serve on an advisory group for the development of the WHO “Nurturing Care Framework for Early Childhood Development,” which was passed as a resolution at the May 2018 World Health Assembly (WHA) Meeting in Geneva, Switzerland. OGH participated in both the WHA launch of the WHO Nurturing Care Framework which included over 200 participants, and subsequent technical consultations aimed at developing plans for interagency implementation and guidelines for policy makers. The WHO Nurturing Care Framework was developed in response to growing international recognition of the importance of optimizing early childhood development toward later adult health outcomes as a means of reaching the United Nations Sustainable Development Goals.

NIH – Bill and Melinda Gates Foundation (BMGF) Collaboration. Since January 2014, a new phase of cooperation has been initiated between NIH and BMGF in the areas of maternal and infant nutrition, reduction of premature births, healthy cognitive development, point-of-care diagnostics, vaccine development, tuberculosis (TB) drug discovery, etc. This has included annual NIH-BMGF Global Health Meetings held on the NIH campus, with NICHD representatives in several working groups (i.e., Maternal and Child Health, Pediatric Pneumonia and Indoor Air Pollution, Contraceptive Research, and HIV/AIDS Working Groups). NICHD co-chairs the Maternal and Child Health Working Group which includes representation from NICHD, BMGF, the National Institute of Mental Health (NIMH), the National Institute of Drug Abuse (NIDA), and the National Institute of Neurological Disorders and Stroke (NINDS). This working group aims to identify new research collaborations in the areas of prematurity, child neurodevelopment, nutrition and growth, and neurocognitive assessment, among other areas. Joint activities have included secondary referral to BMGF of NICHD Small Business Innovative Research (SBIR)/Small Business technology Transfer (STTR) grants on neurodevelopmental assessment; NIH-BMGF data sharing; and possible collaborations with the NIMH Collaborative Hubs and/or on maternal depression research and the NIDA Adolescent Brain Cognitive Development (ABCD) longitudinal study.

WHO Consultation on Social, Behavioral and Community Engagement (SBCE) Interventions for Maternal, Newborn, and Child Health (July 24-25, 2018,
Geneva, Switzerland). OGH was invited by the WHO Department of Maternal, Newborn, Child and Adolescent Health to serve on this working group, which built on a WHO SBCE Evidence Map of related research evidence and gaps and results of a global research prioritization process. This WHO consultation is an extension of previous work and publications from an USAID-led interagency initiative that began with a review of related global health research, follow by an interagency Evidence Summit on Population-level Based Behavior Change that identified related research, program, and policy priorities, and led to several scientific publications and research funding announcements managed by the Foundation for NIH.

NICHD Menstruation: Science & Society Meeting (September 23-24, 2018, Bethesda, Maryland). OGH served on the planning group for this NICHD meeting which examined the state-of-the-science related to menstruation and the broader societal implications of that process, including the unique considerations necessary in menstrual health communications, population health research, and public health outreach. NICHD convened leaders in the field with expertise in endometrial biology, ‘omic analysis of the endometrium or menstrual effluent, new sampling or imaging modalities, smart technologies/apps and mHealth platforms, health literacy, and dissemination frameworks. OGH also moderated a scientific panel on global population health and was a financial sponsor of the meeting.

NIH-WHO Global Rehabilitation Meeting (January 14-15, 2018, Bethesda, Maryland). OGH serves on the planning group for a NIH-WHO Rehabilitation Meeting being led by the NICHD NCMRR with the objective of addressing the substantial gap between the need for rehabilitation research and assistive products and the capacity of countries to respond to those needs. To address global rehabilitation needs, WHO launched the Rehabilitation 2030 Initiative and established the Global Cooperation on Assistive Health Technology (GATE), which complement the NIH Research Plan for Rehabilitation (2016) in the areas of addressing rehabilitation needs across the lifespan, providing evidence for the efficacy and effectiveness of rehabilitation interventions, addressing the needs of the caregiver, integrating the individual back into the community, and advancing research methodologies including use of existing data and improved clinical trials. Consequently, NIH and WHO will convene stakeholders (researchers, clinicians, nongovernmental organizations, and policy makers) for a workshop to review critical considerations for prioritizing research questions and capacity-building in rehabilitation.

Trans-NIH Workshop on Conducting Health Research in Humanitarian Crises, (April 9-11, 2018). While substantial progress has been made in improving the health of people living in low- and middle-income countries (LMICs), the progress in countries with a history of humanitarian crises has been much slower. WHO defines disaster as “a serious disruption of the functioning of a community or a society causing widespread human, material, economic, or environmental losses which exceed the ability of the affected community or society to cope using its own resources.” OGH served on a trans-NIH planning committee for this workshop aimed at convening researchers, humanitarian organizations, and policymakers to share learning and strategies on conducting global
health research in the context of humanitarian crises, such as armed conflict, natural disasters, forced displacement, and disease outbreaks. As a follow up to the meeting, writing teams are preparing papers to identify research, program, and policy priorities and gap areas, and Fogarty is leading discussions with institutes across NIH about possible funding announcements to address knowledge gaps.

Global Child Development Panel at the American Academy of Pediatrics (AAP) Conference (November 2, 2018, Orlando, Florida). OGH was invited by the International Section of the AAP to organize and moderate a panel discussion on, “Placing Early Childhood Development on the Global Agenda: The Role of Pediatricians Within a Multidisciplinary Context.” This AAP panel will build on research priorities highlighted in the April 2017 NICHD Pediatrics global health journal supplement and the 2018 WHO Nurturing Care Framework with panelists being comprised of both NICHD/NIH researchers and WHO representatives.

U.S. Government (USG) “Children in Adversity” Initiative. In 2017, USAID announced the appointment of a new USG Senior Advisor of the Children in Adversity Initiative and implemented a progress review of past strategic goals and update of the USG Children in Adversity Framework to outline current roles of each participating USG agency. NICHD and other NIH representatives serve on the USG technical working group that developed an interagency strategy for next steps toward achieving the goals of the “Children in Adversity” Initiative that was launched at the White House in December 2012. A preliminary description of this initiative, aimed at developing a research agenda and whole-of-government strategy for work with children in adversity in LMICs, was published in the Lancet in December 2011, with the former NICHD Director serving as a co-author. An NICHD staff member served as co-editor of a special supplement in the journal Child Abuse and Neglect, and multiple NICHD and NIH staff members served as co-authors of several articles that described results of evidence review teams. NICHD hosted a Pre-Summit for this initiative at NIH in October 2011 and was a partner in the USG Evidence Summit held in December 2011 at USAID, which was supported by senior leadership of seven USG agencies, including NICHD.

NIH-World Bank (WB) Collaboration. In March 2018, an NIH- WB Meeting was held at NIH, led by Drs. Francis Collins (NIH) and Jim Yong Kim (WB), with a focus on identifying ways of further supporting implementation research, studies on stunting in child populations, and development of the Human Factor Index. This initial meeting was followed by a meeting at the WB between the NICHD Director and senior NICHD program staff and the WB Child Development Team led by Dr. Simeon Djankov. The follow-up meeting focused on NICHD staff providing scientific input toward a WB report on the current status of child development research, programs, and policy around the globe.
Recent Achievements in International Health

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

In collaboration with NICHD program staff, OGH prepared briefing materials and helped plan site visits for NICHD, NIH, DHHS, White House and Congressional senior leadership in Kenya, Malawi, Ghana, Ecuador, Romania, Bulgaria, & Thailand.

- **Coordination of Visits by Foreign Delegations.** Participated in the coordination of meetings and preparation of briefing materials for visits by foreign delegations (e.g., Qatar Foundation, British Research Council, Brazilian Ministry of Health).

- **Public Law (P.L.) 109-95 Congressional Report Data Call.** Serve as the lead NIH global health office for preparing the trans-NIH report on research projects studying the health and developmental outcomes of orphans and vulnerable children for the annual P.L.109-95 Congressional Report.

- **OGH Brown Bag Series.** Organize global health talks on diverse scientific topics in line with the NICHD mission.

- **Dissemination of Global Health Information Including Current NICHD Initiatives.** Regularly update the OGH webpage on the NICHD Insider and prepare the NICHD International Activities Catalog to facilitate information exchanges related to global health.

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

International Partnerships

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

**Examples of Staff Membership on Global Health Committees/Working Groups**

- NICHD Global Health Strategic Team. Representative: Vesna Kutlesic
- WHO Nurturing Care Framework Advisory Group. Representative: Vesna Kutlesic
- NIH-BMGF Child Health and Development Working Group. Representative: Vesna Kutlesic
- USG Children in Adversity Strategy Working Group. Representative: Vesna Kutlesic
• Trans-NIH Global Health Research Working Group. Representative: Vesna Kutlesic
• Trans-NIH International Clinical Research Subcommittee. Representative: Vesna Kutlesic
• Fogarty International Center (FIC) International Representatives Working Group. Representative: Vesna Kutlesic
• NICHD Zika Round-up Working Group. Representative: Vesna Kutlesic
• NICHD Reproductive Health Working Group. Representative: Vesna Kutlesic
• NICHD Maternal Mortality Working Group. Representative: Vesna Kutlesic
• NICHD-WHO Rehabilitation Planning Working Group. Representative: Vesna Kutlesic
• NICHD Pain/Opioid Working Group. Representative: Vesna Kutlesic
• NICHD Menstruation Meeting Planning Group. Representative: Vesna Kutlesic

**Point-of-Contact**

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Division of Extramural Research (DER)

The DER develops, implements, and coordinates cross-cutting, multidisciplinary research activities within the NICHD's mission, including efforts that focus on: demography, social sciences, and population dynamics; male and female fertility and infertility; developing and evaluating contraceptive methods; improving the safety and efficacy of pharmaceuticals for use in pregnant women, infants, and children; HIV infection and transmission, AIDS, and associated infections; pediatric growth and endocrine research; child development and behavior; developmental biology and typical and atypical development; intellectual and developmental disabilities; gynecologic health conditions, including pelvic floor disorders; and childhood injury and critical illness.

The DER also coordinates Institute research and training grant programs and advises the NICHD Director on extramural research and training policies and activities. The Division relies on its staff to represent the Institute on various trans-NIH and other collaborative workgroups and committees, to liaise with members of the Institute's federal advisory committees and boards, and to lead implementation of extramural policies and procedures for the NICHD.

The Division also performs grants management and scientific review functions, including conducting initial scientific merit review of grant applications and contract proposals for the NICHD. With a focus on scientific expertise, the DER also develops and supports extramural staff training while enhancing communication about standardized procedures, policies, methods, and approaches across the Institute.
Child Development and Behavior Branch (CDBB)

Mission

The CDBB develops scientific initiatives and supports research and research training relevant to the psychological, psychobiological, cognitive, behavioral, and educational development of children. The following theme characterizes all Branch programs: Development is best described and studied as a variable process in which individual differences in cognitive, social, affective, language, numeracy, neurobiological maturation, environment, life experiences, and genetics interact in complex ways.

Major International Activities over the Past Year

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

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

Integrated Early Childhood Development (ECD) Interventions. Recent neurobiological and psychological research has established that vital development occurs in language, cognitive, motor and socio-emotional development during the first few years of life, and early life outcomes are key determinants of adult outcomes such as educational achievement, labor market outcomes, and health. Yet more than 200 million children under age five who live in LMICs will fail to reach their developmental potential as adults, predominantly due to poverty, poor health and nutrition, and inadequate cognitive and psychosocial stimulation. ECD interventions that integrate nutrition and child stimulation activities have been shown to be effective in improving children's developmental and health outcomes, at least in the short-term. The Branch supports a multi-arm clustered randomized controlled trial across 60 villages and 1200 households in rural Kenya that tests different potentially cost-effective delivery models for an ECD intervention with a curriculum that integrates child psychosocial stimulation and nutrition education.

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

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

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

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

The Branch is supporting a collaboration with Norway to investigate the relationship of maternal and child infection, fever and immune disorders to Attention Deficit/Hyperactivity Disorder (ADHD) risk, the potential modulation of that risk by medications (antipyretics, analgesics, antibiotics), and micronutrients using prospective data about exposures in ADHD and control mother-child pairs. This study will also characterize immune signatures of mothers during pregnancy and their children at birth, determine their association with ADHD risk, as well as examine the role of specific infectious agents on the development of ADHD.
**Bilingualism and Cross-Linguistic Studies of Literacy and Language Development.** The Branch funds studies of infant perception, conceptual development, and early word learning in various languages. Some of these studies across languages are demonstrating which aspects of language development may be universal (the same for all languages) and which are language-specific. Published studies have indicated a cognitive advantage in some aspects of executive function in bilingual children, which supports the value of encouraging the development of bilingualism and the maintenance of first language in English learning children. Similarly, studies of reading and reading disability, including its neurobiological and genetic bases, are supported as domestic grants many of which have foreign subcomponents. Both cross-linguistic studies and those examining bilingual and second language learning populations are helping to describe the timing and trajectory of early language development and of literacy learning. Locations for some of the data collection and/or subcontracts for this work include Australia, Canada, China, France, Israel, Mexico, the Netherlands, Spain, and the United Kingdom (U.K.).

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

**Recent Achievements in International Health**
N/A

**International Partnerships**
N/A

**Staff Membership on Global Health Committees/Working Groups**
N/A

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Contraception Research Branch (CRB)

Mission
The CRB develops and supports research and research training programs in three areas:

- The effects of contraceptive use on human health
- The development of new and improved methods of contraception
- Targeted research to improve the development of new and improved methods of contraception

Major International Initiatives over the Past Year

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

Effects of Contraceptive Ring on Vaginal Microbiota, HIV Shedding, and Local Immunity. CRB continued support in Fiscal Year 18 of this study in Kenya to determine whether sustained vaginal delivery of estrogen promotes desirable vaginal bacteria and thus reduces the risk of bacterial vaginosis, which is a common cause of vaginitis and increases the risk of HIV, pelvic inflammatory disease, adverse pregnancy outcomes, and HIV acquisition.

Injectable Contraception and HIV/HSV-2 Incidence in Young South African Women. CRB continued supporting this project in Fiscal Year 18 which is one of the first studies of the relationship between the use of injectable contraceptives (DMPA and norethisterone enanthate) and the incidence of both HIV and HSV-2. It will also study their effects on other common sexually transmitted infections (STIs) and sexual risk behaviors in this vulnerable population, which has unusually high rates of HIV and unwanted pregnancies.

Promoting Effective Condom Use. CRB supported an SBIR grant that includes collaborating on design and manufacturing of an improved male condom with a condom manufacturing facility in Malaysia.
Pharmacological Strategies to use the Levonorgestrel (LGN) Implant in HIV-infected Women. CRB supported a research grant to study pharmacokinetics of samples collected over one year of combined use and compared to a control group of HIV-infected women on an LNG implant, but not yet on antiretroviral therapy (ART), which includes study sites in Uganda and England. The study will determine the LNG implant dosage required to ensure safe and effective combined use with ART regimens, spanning the continuum of HIV care. In turn, this work is strongly expected to improve the management of reproductive health in millions of HIV-infected women worldwide. Additionally, the models developed through this study represent a highly efficient and Food and Drug Administration (FDA)-recognized approach to predict drug-drug interactions and will guide future contraception studies. In doing so, the study addresses three important areas for research identified by the NIH Office of Research on Women's Health, including to: actualize personalized prevention methods, create strategic partnerships that maximize the global impact of women's health research, and build a vigorous women's health research workforce.

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

International Guidelines for Family Planning. Through an interagency agreement with the USAID that began 12 years ago, CRB continued in Fiscal Year 18 to provide both financial and technical support to the WHO's Department of Reproductive Health and Research for a series of technical documents on contraception. These documents are among the most highly respected guidelines for family planning personnel around the world and have had a significant impact on enabling family planning programs to provide evidence-based contraceptive services.

Collaboration with the BMGF. CRB staff continued to work with the BMGF and other organizations in Fiscal Year 18 to develop a clear picture of all the contraceptive products currently in the research pipeline worldwide and the current status of each. This effort has focused on identifying products that are particularly well-suited for South Asia and Sub-Saharan Africa.

Recent Achievements in International Health
N/A

International Partnerships
CRB continued its ongoing collaborations with the WHO throughout Fiscal Year 18. Through CRB’s interagency agreement (IAA) with USAID, the process of collecting and analyzing the world’s literature on contraception continued to provide the background for the
continuously revised WHO guidance documents. The *Medical Eligibility Criteria for Contraceptive Use*, the parent WHO family planning document, has been adapted and published for the United States by the Centers for Disease Control and Prevention (CDC).

**Staff Membership on Global Health Committees/Working Groups**

N/A

**Point-of-Contact**

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Developmental Biology and Structural Variation Branch (DBSVB)

Mission

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

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

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

Major International Initiatives over the Past Year

International Activities Involving Human Subjects

China

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

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

Multinational Collaborations

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

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

Japan, Sweden, and Hong Kong: Adolescent idiopathic scoliosis (AIS) is a twisting condition of the spine and is the most common pediatric musculoskeletal disorder, affecting 3% of children worldwide. Children with AIS risk severe disfigurement, back pain, and pulmonary dysfunction later in life at great economic costs. Girls requiring treatment
for AIS outnumber boys by more than five-fold, for reasons that are unknown. AIS is treated symptomatically rather than preventively because the underlying etiology is unknown. The overall purpose of this project is to understand the biologic causes of AIS as a means to early diagnosis, prevention and non-invasive biologic treatment. AIS is a complex genetic disease. Genome-wide association studies (GWAS) of common non-coding variants have identified AIS-associated DNA variations/polymorphisms, but the mechanistic basis of these associations remains to be defined. GWAS also require well-powered replication studies to validate the work being carried out. Presently, there are no U.S. research groups that have the necessary cohorts required to perform the validation studies. Consequently, the one investigator performing these studies in the United States interacts with investigators in Japan and Sweden through the International Consortium for Spine Genetics, Development, and Disease and electronically shares polymorphic markers found associated with scoliosis in the cohorts as well as summary statistics (allele frequencies, odds ratios, P values, etc.). In this way, investigators can test these markers in each other’s cohorts of scoliosis patients and controls and thus perform very powerful validation studies of each other’s GWAS data. The results of such collaborations can help to develop hypothesis-driven research aimed at early molecular diagnosis, prevention and potential therapeutic interventions. Recently, they added Hong Kong collaborators to improve validation studies.

**International Activities Involving Animal Models**

**Canada**

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

**Japan**

A major area of emphasis for the DBSVB is systems developmental biology because it offers a framework to provide a comprehensive understanding of embryonic development. This is particularly true for the elucidation of gene regulatory networks as a means of gaining a better understanding of normal developmental processes as well determining the
causes of structural birth defects. This method replaces the one-gene-at-a-time approach to development with a more holistic tactic to understanding embryonic development. It requires assimilating many levels of genomic, biochemical, and biophysical information into computational models of developmental processes that are quantitative, predictive, and experimentally verifiable. Such network models for embryonic development offer the potential to link isolated molecular and mechanistic descriptions of developmental processes into a foundational framework allowing important causal relationships to be identified and predictively understood.

One such project is generating a virtual model of the network of high-level genetic control mechanisms that result in formation of the digestive system. This work has direct relevance to understanding the corresponding processes occurring in human development, but it would be unfeasible and ethically unacceptable to conduct such studies in humans. *Xenopus* is the model animal used in this study because, unlike mammals, their early development is easily accessible, easily manipulated, and allows for testing the accuracy of the proposed genetic regulatory network models. The collaborator in Japan is heavily involved in developing and contributing reagents, generating gene expression data, and participating in the analyses of that data to generate the gene regulatory network models.

**Recent Achievements in International Health**
N/A

**International Partnerships**
N/A

**Staff Membership on Global Health Committees/Working Groups**
N/A

**Point-of-Contact**
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Fertility and Infertility Branch (FIB)

Mission
The mission of the FIB is to encourage, enable, and support scientific research aimed at alleviating human infertility, uncovering new contraceptive leads and expanding fundamental knowledge of processes that underlie human reproduction. To this end, the FIB provides funds for basic, clinical, and translational studies that will enable the development of more effective strategies for the diagnosis, management, and prevention of conditions that compromise reproductive health, with the goal of promoting a better quality of life for all individuals.

Major International Initiatives over the Past Year
There are no FIB international activities to report at this time.

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Gynecologic Health and Disease Branch (GHDB)

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

Major International Initiatives over the Past Year

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

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

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

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

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

**Recent Achievements in International Health**
N/A

**International Partnerships**
N/A

**Staff Membership on Global Health Committees/Working Groups**
N/A

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Intellectual and Developmental Disabilities Branch (IDDB)

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

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

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

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

Major International Initiatives over the Past Year

Gene and Variant Curation. The Branch support studies to identify the genetic causes underlying many IDDs. With advances in genomic sequencing technologies, clinical genetic testing is becoming increasingly routine in clinical practice both in the United States and
internationally. However, genome-scale sequencing is leading to the identification of many genomic variants with unknown significance, potentially leading to inappropriate medical interventions. In partnership with the Clinical Genome Resource (ClinGen) funded by the National Human Genome Research Institute, NICHD has initiated a program that brings together international panels of experts to identify the genes and genomic variants associated with the pathogenicity of conditions of high importance to NICHD. Three expert curation panels have been funded that include international experts from the United States, U.K., Italy, Germany, France, Australia, and the Netherlands.

**Down Syndrome Registry.** DS-Connect® is an online, secure registry to promote sharing of health information that will advance research to benefit individuals with Down syndrome and their families. Sponsored by the Down Syndrome Consortium, the registry was created by the NIH under NICHD leadership to connect families with researchers on projects of shared interest. DS-Connect® has attracted over 4,000 registrants in the United States and abroad and has supported recruitment for nearly two dozen research projects through its membership. International partners include Down Syndrome International, Jérôme Lejeune Foundation, and International Mosaic Down Syndrome Association (IMDSA), who are active members of the Down Syndrome Consortium and have promoted the registry worldwide. A Spanish translation of the website is available to increase the registry's outreach to Spanish-speaking families within the United States and in Latin America. The NIH is exploring translation of DS-Connect® into other languages and has developed a responsive web design to facilitate access on a wide variety of mobile platforms.

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

**Recent Achievements in International Health**

**Brain Disorders in the Developing World: Research across the Lifespan Initiative.** The IDD Branch participates in this FIC-led initiative to enhance research to ameliorate intellectual and developmental disabilities in low and middle-income countries. One of the grants funded under this initiative has evaluated the effectiveness of utilizing a computerized cognitive rehabilitation therapy (CCRT) training program for children in Uganda who have survived cerebral malaria. The CCRT program provides training for attention, memory and other neurocognitive executive skills. Cerebral malaria survivors receiving training showed significant improvements and the CCRT program has been
especially effective in improving neuropsychological performance in these children, though longitudinal studies indicate that there is a need for periodic booster training. CCRT and computerized cognitive tests are a viable method for treating brain injured children in resource-poor settings.

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

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

The Branch also supports the Wellstone Muscular Dystrophy Research Centers, one of which is collaborating with the University of Modena in Italy to identify and include patients with Facioscapulohumeral Muscular Dystrophy (FSHD). The goal of this Center is to identify genes and their modifiers, as well as biomarkers, to better understand the pathophysiology of FSHD muscle weakness. The researchers are also developing animal models and therapeutics for the treatment of FSHD.

The Branch supports an international collaboration on Wolfram Syndrome, a rare neurodegenerative disease first appearing in children with early onset diabetes, optic nerve atrophy, and deafness and death in early-mid adulthood. With the identification of the causative gene, the investigators have discovered a broader range of phenotypes. The research team has established a partnership with the U.K. to increase the number of children enrolled in the study to better understand both the neuropathophysiology of this disorder and to identify potential targets for brain-specific interventions.

**Autism research.** The Multigenerational Familial and Environmental Risk for Autism (MINERVa) Network, a component of the NIH Autism Centers of Excellence program, is an international partnership involving Australia, Denmark, Finland, Israel, Norway, Sweden, and the United States. The goal of this network is to conduct epidemiological studies examining relationships between the incidence of autism spectrum disorder and genetic and environmental factors. The Network has a specific focus on multigenerational familial relationships, immigration status, and use of medications during pregnancies.
Cookstove-Related Achievements

- NICHD is partnering with the National heart, Lung, and Blood Institute (NHLBI), National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), the NIH Common Fund, and the BMGF to support a randomized controlled trial of introducing liquefied petroleum gas (LPG) cookstoves in India, Guatemala, Peru, and Rwanda. Primary outcomes include low birth weight, pneumonia, and linear growth in children as well as blood pressure in the mothers. A biomarker study is being integrated with the clinical trial to explore the relationship of Household Air Pollution (HAP) exposures to health outcomes. Markers will include those relevant to HAP and second-hand smoke exposures and indicators of non-communicable disease. This study represents the first large-scale field trial utilizing clean LPG cookstoves. In addition, emphasis will be placed on behavioral and economic aspects of cookstove adoption in these countries (Branch: IDDB).

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

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

International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

N/A

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Maternal and Pediatric Infectious Disease Branch (MPIDB)

Mission

The MPIDB supports and conducts both domestic and international research related to the epidemiology, diagnosis, clinical manifestations, pathogenesis, transmission, treatment, and prevention of HIV infection and its complications, as well as other infectious diseases in infants, children, adolescents, pregnant women, mothers, women of childbearing age, and the family unit.

Currently, the Branch supports projects in about 50 countries through grants, cooperative agreements, and contracts.

Major International Initiatives over the Past Year

The NICHD International and Domestic Pediatric and Maternal HIV Clinical Trials Network (NICHD Network). With the goal of answering specific questions regarding the treatment, prevention, and persistence of HIV, the NICHD Network conducts clinical trials in infants, children, adolescents, and women including pregnant women. NICHD funds 15 domestic sites including Puerto Rico and 15 international sites in six countries: Argentina, Brazil, Kenya, South Africa, Tanzania, and Thailand. Through collaborations with the National Institute of Allergy and Infectious Diseases (NIAID), NIMH, CDC and other international partners, the NICHD Network has been able to conduct HIV-related trials including but not limited to the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT), AIDS Clinical Trials Group (ACTG), and the Tuberculosis Trials Consortium.

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

NICHD HIV Prevention Trials Network (HPTN) 040 Clinical Trial. The overall mission of the HPTN is dedicated to the discovery and development of new and innovative research strategies to reduce the acquisition and transmission of HIV. To identify optimal anti-HIV drug regimens to prevent mother-to-child transmission (MTCT) of HIV, this clinical trial included 17 sites in Argentina, Brazil, South Africa, and the United States with a specific focus on pregnant women in whom HIV infection was not diagnosed until delivery and did not receive anti-HIV drugs during pregnancy. The trial is complete, and additional
secondary analyses of the data and stored samples are ongoing. These resources are available through NICHD Data and Specimen Hub (DASH).

The NICHD Latin American/Caribbean International Site Development Initiative (NISDI). NISDI began in 1999 and was designed to provide capacity building and training for international sites and investigators through the conduct of two observational studies in pregnant women and children with HIV. These observational studies provided important data about the demographic, clinical, immunologic, and virologic characteristics of pregnant women and children in Latin America. Enrollment was completed, and study patient follow-up ended in 2012. As part of this initiative’s long-standing goal to provide training and capacity-building for sites with limited experience in conducting clinical trials, the majority of the NISDI sites and investigators subsequently graduated to the NICHD Network and are participating in clinical trials.

The NISDI perinatal protocol was a prospective study of pregnant women with HIV and their infants who receive care at participating clinical sites through 6 to 12 months postpartum. The NISDI pediatric protocol described the demographic, clinical, immunologic, and virologic characteristics of children and adolescents with HIV. There have been multiple international presentations and publications from the NISDI investigators, providing information on the long-term safety of exposure to antiretroviral (ARV) drugs in uninfected infants as well as issues regarding the long-term outcomes of treatment in infected children. NISDI involved 25 sites in six countries: Argentina, the Bahamas, Brazil, Jamaica, Mexico, and Peru; Brazil enrolled the majority of participants. Analyses of the databases and stored samples are ongoing, and data and specimens are now available via the NICHD DASH.

Identification of Birth Defects Possibly Related to Dolutegravir Treatment of Pregnant Women. In May 2018, a possible association was identified between neural tube defects involving the brain, spine, and spinal cord in babies born to women infected with HIV who were treated with dolutegravir, an antiretroviral drug of the integrase strand transfer inhibitor (INSTI) class. Preliminary results from an ongoing NICHD-funded observational study in Botswana indicated that women who received dolutegravir at the time of becoming pregnant appeared to be at higher risk for these defects. MPIDB helped to develop and coordinate some of the cautionary statements issued by the HHS Antiretroviral Treatment Guidelines Panels, FDA, European Medicines Agency, CDC, U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), and WHO while further investigation is pursued. Those efforts include the creation of an interagency workgroup to coordinate opportunities internationally for evaluating the possible association between dolutegravir and neural tube defects, and reproductive toxicity studies in animal models to rapidly evaluate dolutegravir potential to cause neural tube defects.

Other research grants. A number of grants are supporting research on the effects of HIV, its treatment, potential remission of HIV in children, and important co-infections such as malaria, hepatitis, and tuberculosis (TB) in children and pregnant women. These international studies are occurring in a number of countries including Botswana, China,
Congo, Cote d'Ivoire, Haiti, India, Kenya, Malawi, Mozambique, Namibia, Nigeria, South Africa, Thailand, Uganda, Zambia, and Zimbabwe. Examples of some of these studies include:

- **MPIDB/NICHD** in collaboration with FIC, other NIH institutes, and Office of the Global AIDS coordinator released an RFA entitled “Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA)” in fiscal year 2016. The RFA provided supplementary funding to existing NIH grants that could advance the effective use of evidence and help overcome implementation challenges related to prevention, screening, and treatment among adolescents with HIV in PEPFAR funded countries in sub-Saharan Africa. Grants were awarded to projects in the following sub-Saharan African countries: Kenya, Ghana, Nigeria, Malawi, Tanzania, Uganda, Zambia, Rwanda, Zimbabwe, South Africa, and Botswana.

- **MPIDB/NICHD** had several internationally-focused RFAs in fiscal year 2012 and fiscal year 2014 that are currently funding active or recently completed projects:
  - **U.S.-South Africa Program for Collaborative Biomedical Research (RFA AI-14-009, 14-010, and 14-018).** This series of RFAs solicited R01, R21, and U01 grants to establish this binational program for collaborative research in the areas of HIV/AIDS, TB, and cancer. Funding was also provided by the South African Medical Research Council. NICHD grants were awarded in maternal and pediatric HIV and in TB.
  - **Disclosure of HIV-Status to Children in LMIC Settings (RFA HD-12-197 and 12-205).** This RFA solicited R21 and R01 grants to assess intervention studies of the process of disclosure of HIV infection status to children infected and affected by HIV in low-resource settings and for the process of HIV-infected women (and other caretakers) disclosing their HIV status to their children, or both. This area of investigation is neglected, profoundly understudied, and of high importance to millions of children and their families in these settings. Three R21 grants were awarded for studies in China, Haiti/Dominican Republic, and Namibia, and four R01 grants were awarded for studies in China, Ghana, Uganda, and Zimbabwe.
  - **Perinatally HIV-Infected Youth in Africa and Asia (RFA HD-12-207).** This RFA solicited R01 grant applications for studies to evaluate the impact of HIV infection and its treatment on perinatally HIV-infected youth now surviving into adolescence and young adulthood in Africa and Asia. With the availability of treatment in low resource settings, these perinatally infected children are now expected to survive or are already surviving into adolescence, young adulthood, and beyond, and will face the potential consequences of prolonged HIV infection and long-term antiretroviral therapy (ART), which may be exacerbated by endemic diseases and co-morbidities not seen in resource-rich countries such as the United States. Five R01 grants were awarded for studies in Thailand and South Africa.
NIH/PEPFAR Collaboration for Advancing Implementation Science in Prevention of Maternal-Child HIV Transmission (RFA HD-12-210). MPIDB/NICHD, together with the Office of the Global AIDS Coordinator (OGAC), developed this RFA for implementation science projects that will inform PEPFAR as it develops more efficient and cost-effective methods to deliver proven interventions for prevention of (MTCT). This NICHD-led initiative represents a multi-agency (OGAC, CDC, and USAID PEPFAR partners) and multi-institute (NICHD, FIC, NIMH, Office of Research on Women’s Health, NIAID, Office of Behavioral and Social Sciences Research) collaboration in both its scientific development and funding. This RFA aimed to stimulate implementation science research to determine how to optimize effective delivery of infant and maternal interventions at each step of the prevention of MTCT cascade. Nine R01 grants were awarded for research in seven countries: Congo, Cote d’Ivoire, Kenya, Mozambique, Nigeria, South Africa, and Zambia.

Safety and Effectiveness of Triple Antiretroviral Drug Strategies for Prevention of MTCT (RFA HD-14-027). This RFA solicited R01 grant applications to evaluate the safety and overall population-based effectiveness of implementation of triple ARV drug strategies for prevention of MTCT in resource-constrained settings. This includes a range of research issues, including overall long-term transmission and HIV-free survival rates for infants and long-term health of the mother; acceptability and adherence to the regimens; linkage to care and retention of the mothers and infants; optimal service organization and comparison of models of ARV drug delivery and monitoring; issues of adverse pregnancy outcome including birth defects, preterm delivery, stillbirth, low birth weight; surveillance for drug resistance; and cost-benefit analysis and impact on overall country ARV programs. With PEPFAR providing additional funding for one grant, eight grants were awarded for research in six African countries: Botswana, Kenya, Malawi, South Africa, Uganda, and Zimbabwe. The grantees will address the full range of research priority areas in the RFA, from evaluating birth outcomes with in utero ARV exposure, several different innovative methods to promote maternal ART adherence and retention of mothers/infants in care, and population-based studies to look at long term effectiveness of maternal ART strategies for prevention of MTCT and maternal health.

Evaluation of the Latent Reservoir in HIV-Infected Infants and Children with Early Antiretroviral Therapy and Virologic Control (RFA HD-14-026). In support of the Office of AIDS Research (OAR) 2015 scientific research priority that targets cure (elimination or functional cure) of HIV infection, this RFA solicited studies of the latent reservoir in HIV infected children who have had early treatment (ART initiated before 6 months of age) and have had continuous viral suppression. One of the grants through this RFA is an international clinical trial of very early treatment (within 48 hours of birth) of
HIV-infected infants in Johannesburg, South Africa, will assess whether this early treatment initiation results in remission of HIV. The trial will include careful and sophisticated evaluations of immunological responses.

- **Increasing Access and Uptake of HIV Testing and Counseling and Appropriate HIV-Related Services for Adolescents in LMIC (RFA HD-15-17).** MPIDB/NICHD in collaboration with NIAID, the National Institute on Drug Abuse, and NIMH issued this internationally focused RFA in fiscal year 2015 to solicit R01 grant applications for implementation science projects that will provide results to directly inform HIV prevention and care service delivery programs for HIV-infected and at-risk, uninfected adolescents in resource-limited settings, in order to increase their impact, efficiency, and sustainability. Grants were awarded for studies in Bulgaria, Kenya, Tanzania, and Zimbabwe.

- **HIV-Infected Adolescents: Transitioning from Pediatric to the Adult Care Settings (RFA-HD-033/034).** MPIDB/NICHD issued this fiscal year 16 RFA that is currently funding active projects. The four awarded grants offer a range of approaches and geographical locations (Kenya, Thailand, Malawi, South Africa, United States) on transition of HIV-infected youth to adult care with the goal of developing an evidence base to support guidelines applicable to low, middle and high-income countries.

- **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-17-550/555).** MPIDB/NICHD issued this RFA for fiscal year 2017, in collaboration with NIMH. The goals are to: 1) enhance our understanding of the multilevel factors that influence HIV prevention strategy use; and 2) develop and test novel interventions to address these factors and enhance the uptake and adherence to HIV prevention strategies, both among AGYW in sub-Saharan Africa. In 2017, the NIH funded 11 grants in response to the 3 companion RFAs, with the research taking place in Kenya, South Africa, Tanzania, Uganda, and Zimbabwe. The investigative, multidisciplinary teams on the grants are addressing a wide range of issues affecting AGYW including involvement in sex work, gender-based violence, and stigma by health care professionals. Different approaches are being evaluated to determine how to increase uptake and adherence to HIV prevention strategies including the evaluation of a risk screening tool, counseling using behavioral economic principles, pre-exposure prophylaxis (PrEP) knowledge, and peer-networks.

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

- **Prevention and Treatment through a Comprehensive Care Continuum for HIV-affected Adolescents in Resource Constrained Settings (PATC³H) (RFA-HD-18-032).** MPIDB/NICHD issued this RFA for fiscal year 2018, in collaboration with NIMHD, NIAAA and OBSSR. These eight newly funded large cooperative agreements will support research projects in South Africa, Kenya, Nigeria, Uganda, Zambia, Mozambique, and Brazil aimed at preventing HIV infection among youth at risk and maintaining their HIV negative status. They also will seek to enroll youth with HIV into treatment studies to improve their health and prevent transmission to others. As a collective, the projects in PATC³H aim to improve the numbers of adolescents in resource-limited settings who achieve successful outcomes across the entire HIV prevention and care continuum. Investigators have established relationships with clinical sites and national programs that have expertise in conducting research studies and in providing care for these vulnerable adolescents. Through the engagement and leveraging of multilateral relationships with local and national stakeholders, the foundation is in place for possible scale-up and sustainment of rolling out interventions in these regions should they be found effective and will maximize the impact on public health.

**TB in Children and Pregnant Women**

The MPIDB has a special focus on TB in children and pregnant women and has had several RFAs addressing this area in addition to a number of investigator-initiated grants. These studies are conducted internationally in settings of high TB incidence. Past RFAs and projects include:

- Several grants and other projects in South Africa are evaluating the pharmacokinetics of first- and second-line TB treatment, including treatment for multi-drug resistant TB, in HIV-infected children. These studies include children with malnutrition as well as HIV and interactions of anti-TB drugs with ARV drugs. Drug interactions could lead to sub-therapeutic drug levels for the anti-HIV drugs, anti-TB drugs, or both.

- A clinical trial to assess optimal treatment of TB meningitis in children is enrolling in Malawi and India.

- **NIH/PEPFAR Collaboration on Implementation Science for HIV: Toward an AIDS-free Generation RFA-AI-15-020 (R01).** NIH, in collaboration with the OGAC, funded applications for implementation science research that will inform the delivery and scale-up of efficacious interventions to improve HIV prevention, care, and treatment in Africa. MPIDB/NICHD funded investigators in the Democratic Republic of Congo that are evaluating strategies to improve long-term therapy in maternal and child health clinics and investigators in Nigeria that are evaluating strategies for HIV testing and supporting breastfeeding practices.
A study in South Africa looks at replisome dynamics in TB linking persistence to genetic resistance. This study was extended to include work on the assessment of *Sutherlandia frutescens*, a botanical, in multidrug-resistant tuberculosis. This work includes a collaboration with intramural scientists at the NICHD. Students from South African from under represented universities have the opportunity to work in NIH laboratories to advance their science.

**Malaria**

- A large program project in Uganda is evaluating the interaction of HIV, HIV treatment, and malaria in HIV-infected children and pregnant women. The study is also evaluating several different malarial prophylaxis regimens for children to determine an optimal anti-malaria preventive regimen. An associated R01 grant is evaluating pharmacokinetics of anti-malarial drugs in combination with ARV drugs in pregnant women. A separate R01 grant is investigating the effects of maternal and child malaria prevention on child neurodevelopment and will form the basis for interventions to improve child neurodevelopment.

- In Ghana and Malawi, a study of children with retinopathy-negative cerebral malaria identified viral co-infecting pathogens, determined if the presence of a viral co-infecting pathogen changed rates of morbidity or mortality, and investigated whether children with viral co-infection can be identified using routine laboratory or clinical parameters.

**Hepatitis B**

- In Thailand and Laos, a study will evaluate antiviral prophylaxis using tenofovir in mothers with hepatitis B infection and infant vaccination without immune globulin to prevent perinatal hepatitis B infection

**Zika**

- **Rapid Assessment of Zika Virus Complications (R21) PAR-16-106.** The purpose of this RFA was to provide an expedited funding mechanism for research on Zika virus and its complications. This rapid RFA, in conjunction with several other participating NIH institutes, was a targeted effort to address the growing concerns of transmission and outcomes in at risk populations such as women who are pregnant. In response to this public health emergency, MPIDB/NICHD funded grants on the natural history and pathogenesis of Zika in reproductive age women and the fetus, whether in-utero, postpartum, or through breastfeeding.

- MPIDB led efforts to develop the **ZIP Study (Zika in Infants and Pregnancy)**, which will enroll up to 10,000 pregnant women in the first or early second trimester in multiple sites throughout South America and the Caribbean. This study will help guide medical and public health responses to Zika as discoveries regarding the virus and the full scope of its impact on at risk populations continues to unfold. At the forefront of the epidemic, investigators are working to better understand the
underlying complications of Zika to protect the health of women and their children throughout the world. A prospective case-control observational cohort study of growth and development in children born to women infected with Zika during pregnancy to evaluate longer term impact on exposed children is currently in development.

- **Zika and HIV co-infection.** This is a two-phase prospective international cohort study of pregnant women and their infants from those pregnancies whose goals are to compare the incidence of Zika virus infection among pregnant women with and without HIV infection and to determine the risk of adverse maternal and child outcomes associated with Zika virus/HIV co-infection across clinical sites in the continental United States, Puerto Rico, and Brazil. Phase I will enroll pregnant women/infant pairs who are: (1) infected with HIV only; (2) infected with ZIKV only; (3) infected with HIV and ZIKV; and (4) not infected with HIV or ZIKV. Phase I will assess the feasibility of enrolling a total of 200 pregnant women/infant pairs within a year, with a target of 150 HIV-infected women, 50 HIV-uninfected women from the continental U.S. sites only, and a minimum of 20 who are co-infected with HIV and ZIKV by the end of pregnancy. Should the feasibility of Phase I prove successful, Phase II will commence by enrolling up to 1,800 additional pregnant women/infant pairs to the 4 groups described above. The comparison group of HIV-uninfected pregnant women/infant pairs from Puerto Rico and Brazil (ZIKV-infected and uninfected) will be obtained from data collected in the concurrent International Prospective Observational Cohort Study of Zika in Infants and Pregnancy (ZIP study). All HIV-infected and uninfected study participants will be tested for ZIKV. Enrolled women will be followed throughout their pregnancy and up to 6 weeks postpartum. Infants born to enrolled women will be followed for a full year after birth.

**HIV Prevention and Treatment in Children**

- In the Bahamas, a research project will support the efforts of the entire nation of the Commonwealth of The Bahamas and serve as a prototype for other nations in the quest for elimination of the HIV/AIDS epidemic by 2030. It employs a theory-based, practical, data-driven implementation process to deliver an evidence-based HIV prevention curriculum through the government school system to all students throughout the nation enrolled in grades 6 to 9 and their parents.

- In Botswana, over 3,000 HIV-exposed but uninfected infants were randomized to receive either cotrimoxazole or placebo from four weeks through 15 months to determine if the use of the antibiotic cotrimoxazole may improve survival in infants who are formula fed or after weaning. In addition, breastfeeding infants will be randomized to either breastfeed until 6 or 12 months of age. Children will be followed prospectively until 18 months of age. The primary endpoint is survival at 18 months comparing all infants in the cotrimoxazole vs. placebo arms, and by randomized duration of breastfeeding. Results were presented at Conference on Retroviruses and Opportunistic Infections (CROI) in 2016.
• In Malawi and Uganda, a 60-month longitudinal study is evaluating neurodevelopmental, neurocognitive, hematologic and growth outcomes of HIV- and ARV drug-exposed infants compared to a control group of children not exposed to HIV or ARV drugs from similar socioeconomic and cultural backgrounds. This project will evaluate the potential for adverse late effects of in utero ARV exposure on these parameters in HIV-exposed but uninfected children.

• A clinical trial in Kenya evaluated the optimal time (emergent within 48 hours vs. post-stabilization at 2 weeks) to start anti-HIV treatment in HIV-infected children who are diagnosed at the time of presentation in the hospital with a severe co-infection such as pneumonia or meningitis.

• Also in Kenya, a study of HIV Counseling and Testing for Children at Home (CATCH) is being conducted to optimize strategies to identify undiagnosed, asymptomatic HIV-infected children in Kenya, a population that is typically excluded from testing, and link them to HIV care.

• Another study in Kenya will evaluate the impact and cost-effectiveness of the HIV Infant Tracking System (HITSystem©), an online, automated intervention designed to overcome current early infant diagnosis barriers by prospectively tracking HIV-exposed infants, improving the communication of polymerase chain reaction results from laboratories to both clinics and mothers, and supporting existing networks to facilitate quality HIV pediatric care.

• A study in South Africa proposes to examine the effectiveness of an intervention to increase the uptake of a comprehensive prevention of MTCT program that includes risk reduction and medication adherence by HIV-positive pregnant women in Phase I. The male partners are included in the intervention in Phase 2.

• An R21 study in South Africa seeks to adapt the mobile phone-based NeuroScreen application for use by Xhosa-speaking lay counselors. This study will explore the association between NeuroScreen results and medical health outcomes in South African HIV patients with neurocognitive impairment.

• A study in Uganda will implement a randomized-controlled trial to evaluate the effectiveness of an adherence-related messaging system to maintain medication adherence among 15- to 24-year-olds in two large urban HIV-clinics, as well as the cost-effectiveness of the intervention.

• HIV programs focusing on orphans and vulnerable children are a vital strategy for reducing vulnerability to HIV in children. Two separate grants in China and Uganda are researching the effects of care setting on children affected by HIV/AIDS, including an innovative family-based economic empowerment intervention. Investigators are conducting research in China to apply cognitive and behavioral assessments and advanced imaging techniques to identify the functional and structural neural alterations that are associated with history of adversity and subsequent exposure to different care settings in Chinese children who have been orphaned by AIDS.
• A study in Uganda will investigate whether surrogate markers of cardiovascular disease are able to identify HIV-infected children and adolescents at risk of early heart disease and to understand the mechanisms of such changes, so that risk-reduction therapist can be appropriately implemented.

• A new study that is part of the H3Africa Program is looking at the influence of breast milk microbiota on infant immunity and growth. This collaborative effort between Nigeria and South Africa may show differences in the health outcomes of breastfed infants.

• Another study in South Africa will look at the contribution of zinc deficiency to infections with perinatal Group B Streptococcus in infants. Zinc deficiency has been shown to contribute to disruption of mucosal the biofilm providing an opportunity for colonization by Group B streptococcus in pregnant women and transmission during birth.

• Two studies are using neuroimaging as a marker of neurodevelopment and predictor of cognitive performance in infants exposed to HIV and ART in utero and perinatally. This group will also correlate their neuroimaging findings with an assessment of microbiome markers of development in these HIV exposed but uninfected infants.

• A study in Uganda will look at the stress and long-term functional survival of Ugandan adolescents perinatally infected with or exposed to HIV. This study will also measure the effect of stress and neurocognitive decline in HIV infected caregivers of these HIV exposed/infected children to measure the rapidity of cognitive decline.

• A study in Malawi will dissect the in-utero effect of HIV exposure on infant T and B cell responses. This work will also employ neuroimaging of the infant to correlate changes in brain development with changes in the immune response.

• A study in Kenya will evaluate post discharge morbidity and mortality in HIV infected and HIV exposed but not infected and HIV non-infected Kenyan children who have been treated with Azithromycin.

• In Uganda a series of studies have examined the microbial cause of infant hydrocephalus by evaluating and control of the neonatal septisome.

**HIV in Women**

• In Uganda, a study is evaluating the hypothesis that extended repeat HIV Testing and Enhanced Counseling (HTEC) in 1,230 HIV-uninfected women during late pregnancy and breastfeeding can increase and/or sustain risk reduction behaviors and prevent incident sexually transmitted infections and HIV infections among HIV-uninfected pregnant women and that couple HTEC can further enhance this effect. Enhanced counseling will emphasize the concept of a HIV-free and healthy baby and family based on primary prevention, adequate infant feeding, and family planning.
• In Lilongwe, Malawi, a study is being conducted that will characterize the safety, durability, ART resistance, and clinical outcomes for mothers and infants exposed to efavirenz-based Option B+ for prevention of MTCT and HIV treatment.

• In South Africa, researchers are evaluating three contraceptive methods in adolescents in terms of their influence on the vaginal immunology and microbiome and potential increased risk of HIV acquisition in adolescent girls.

• In South Africa, researchers are conducting a randomized trial to evaluate the safety and acceptability of the levonorgestrel intrauterine device (IUD) compared to the copper IUD in HIV-infected women.

• In India, researchers are evaluating maternal inflammation, diet, and the gut microbiome in mothers infected with HIV and the impact on infant outcomes.

• In Nigeria, a study to increase HIV testing among pregnant women incorporates community and clinic integration. Male partners of the women are included to support prevention of MTCT and breastfeeding efforts.

• In Democratic Republic of Congo, researchers are conducting cluster randomized trials of health district maternal and child health HIV clinics to identify modifiable delivery system factors with the aim to improve long-term retention in care and viral suppression in women who start lifelong therapy.

• In Kenya, researchers will compare baseline inflammation and vaginal bacteria in a group of virgin adolescent girls who go on to acquire sexually-transmitted infections (STIs) compared with adolescent girls who do not get STIs. By studying biological characteristics of adolescent girls prior to sexual debut, they can uncover risk factors for STIs and help develop prevention strategies to reduce HIV and STI risk among adolescent girls.

• In Zambia, preterm birth and perinatal HIV are among the two biggest risks faced by neonates. Researchers have initiated a trial of the FDA-approved drug 17-hydroxyprogesterone caproate (17P) to prevent preterm birth among 800 HIV-infected pregnant women. The aims are a randomized clinical trial of 17P to prevent preterm birth among HIV-infected pregnant women initiating or continuing ART, and to study the relationship between timing of ART initiation and the risk of preterm birth. The hypothesis is that HIV-infected women who start ART during pregnancy will have higher rates of preterm birth compared to women who enter antenatal care on ART started prior to conception.

• In South Africa a study to optimize routine HIV viral load monitoring in pregnant and postpartum women will clarify the appropriate time points to test for fluctuations in viral load in HIV positive women. This may inform guidelines for HIV testing in pregnancy and postpartum.

• In Kenya, a study has shown that a difference in the periconceptual vaginal microbiota may impact a woman's risk of preterm birth especially in high risk and HIV positive women. Another study examines an implementation tool for the
integration of HIV testing into family planning services provided to these high-risk women.

- Two studies in sub-Saharan Africa are looking at the effects of hormonal contraception on genital immunity and susceptibility to HIV.
- In another study in Uganda work is being done to evaluate the impact of concurrent use of DMPA a hormonal contraceptive and PrEP, tenofovir an ARV, on bone loss in young women.
- In Haiti, a study called FANMI, which is a community-based cohort of care for HIV infected girls, will ask young girls to assemble in community settings that are familiar and welcoming to deliver positive HIV message and encourage engagement and retention in care.

Recent Achievements in International Health

- Researchers in Botswana identified a potential early signal of increased neural tube defects in infants born to pregnant women living with HIV who were on dolutegravir around the time of conception. (letter to editor *N Engl J Med* 2018; July 24)
- A clinical trial in Kenya found that mortality was very high among hospitalized children with HIV but that starting HIV treatment within 48 hours did not improve survival. (*Lancet HIV* 2018;5:e12-22)
- A clinical trial in Thailand showed that tenofovir disoproxil fumarate added to standard of care did not result in a significantly lower rate of hepatitis B perinatal transmission but did show that it was safe and well tolerated. The data from this study are available in NICHD's DASH. (*N Engl J Med* 2018;378:911-23).
- A neurosurgery clinical trial in Uganda showed that endoscopic treatment with choroid plexus cauterization was comparable to the more intensive ventriculoperitoneal shunting in infants with hydrocephalus. (*N Engl J Med* 2017;377:2456-64)
- Researchers found that early HIV treatment was neuroprotective in children based on neuroimaging findings in a study from South Africa. (*Frontiers in Neuroanatomy* 2017)
- A cost-effectiveness analysis showed the value of confirmatory HIV testing in infants in South Africa. (*PLoS Medicine* 2017;14:e1002446)
- MPIDB/NICHD-funded research through the U.S. Adolescent Medicine Trials Network for HIV/AIDS Interventions informed FDA and EMA decisions in 2018 to extend approvals of the antiretroviral combination tenofovir/emtricitabine as HIV PrEP for at-risk adolescents weighing at least 35 kg. This has facilitated PrEP implementation guidance for adolescents to be incorporated in to the WHO implementation tool for pre-exposure prophylaxis of HIV infection as a separate module on Adolescents and Young Adults (module 12).
International Partnerships

N/A

Staff Membership on Global Health Committees/Working Groups

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

Point-of-Contact

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301-435-6868
Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB)

Mission

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

Major International Initiatives over the Past Year

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

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

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

**Collaboration with the European Pediatric Formulations Initiative (EU PFI) and U.S. Pediatric Formulations Initiative (U.S. PFI).** There is a need to improve the availability of pediatric formulations. Collaboration has been formed between the EU PFI and the U.S. PFI to discuss needs and potential solutions to this unmet need.

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

International Partnerships
N/A

Staff Membership on Global Health Committees/Working Groups
- European Medicines Agency. Dr. George Giacoia, OPPT Branch, developed collaborations with the European Medicines Agency to develop a safety database for excipients used in pediatric formulations
- Steering Committee of the International Neonatal Consortia. Member: PENDING
- Therapies Scientific Committee, International Rare Diseases Research Consortium (IRDiRC). Member: Dr. Katerina Tsilou

Point-of-Contact
Dr. Rohan Hazra
Acting Branch Chief, OPPTB
hazrar@mail.nih.gov
301-435-6868
Pediatric Growth and Nutrition Branch (PGNB)

Mission

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

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

Areas of coverage include:

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

Major International Initiatives over the Past Year

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

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

**Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study.** The goal of this study is to better understand the pathologic effects of levels of glycemia within what is generally considered to be the normal range in pregnant women: fasting plasma glucose levels of 70-104 mg/dL. The study examines the relationship between the glycemic state of women and their rates of cesarean section when both the women and their caregivers are blinded to the women’s level of glycemia. This international study in eight countries in addition to the United States has enrolled more than 25,000 pregnant women and administered oral glucose tolerance tests to them during their second trimesters. Other outcomes of interest are macrosomia of the infants, hyperinsulinemia in the cord blood of the infants, pre-eclampsia in the mothers, and infant hypoglycemia. An important finding of HAPO is that the rate of preeclampsia quintuples, from 3 percent to 15 percent over the range of fasting plasma glucose noted above. The rates of operative delivery doubled from 13 percent to 26 percent over the same range of glycemia, despite the blinding. NICHD and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are collaborating on a follow-up study of the offspring of the women in this study to ascertain rates of obesity, beta cell failure, type 2 diabetes, and metabolic syndrome.
Genetic and Environmental Influences on the Metabolic Syndrome. Two thousand twin pairs are being followed in Anqing, China, to ascertain genetic vs. environmental factors that may impact body composition and the development of metabolic risk factors. The twins were initially assessed at 6 to 21 years of age and are being examined again at 12 to 27 years of age. The large sample size and twin study design will yield significant information on the epidemiology of the metabolic syndrome.

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

International Partnerships

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

Staff Membership on Global Health Committees/Working Groups

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

Point-of-Contact

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301-435-7568
Pediatric Trauma and Critical Illness Branch (PTCIB)

Mission

PTCIB was established as a result of the Institute's re-organization in 2012. This Branch develops and supports research and research training in pediatric trauma and critical illness. Priority areas of research include:

- Care and Treatment of Trauma and Critical Illness for Pediatric Populations
- Collaborative Multidisciplinary Research across the Continuum of Care
- Ethical Issues Related to the Care of Critically Ill Children and Their Families
- Interplay of Physical and Psychological Trauma in Children
- Multiple Organ Dysfunction Syndrome (MODS) in Critically Ill Children
- Prevention and Treatment of Life-Threatening Traumatic Injuries in Children

Major International Initiatives over the Past Year

Biological Pathways of Risk and Resilience in Syrian Refugee Children

Principal Investigators: Dr. Michael Pluess: Queen Mary University of London; Dr. Elie Georges Karam

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

Collaborative for Enhancing Emergency Care Research in LMICs (CLEER)

FIC's Center for Global Health Studies is leading a project to address barriers and solutions to conducting research in emergency or acute care settings in LMICs. Emergency or acute care is the common final endpoint for many health challenges in LMICs and therefore strengthening acute care is critical to improving public health in LMICs. However, research in the acute care context in LMICs remains difficult due to a variety of challenges related to data collection, data analysis, comparability of research findings, and research ethics.

The goal of the project is to promote research that improves immediate and long-term outcomes for patients and populations with acute, potentially life- or limb-threatening
conditions by focusing on the care provided in the first minutes to hours of illness or injury. Care consists of diagnosis, resuscitation, symptom relief, and health promotion activities and often delivered health care facilities with variable resources. Through identifying unique challenges, exploring lessons learned and articulating new strategies, methods and tools, we hope to facilitate more research and inform research designs specific to these settings. Deliverables include peer-reviewed publications addressing challenges and strategies for conducting research in the acute care setting in LMICs, and active dissemination and outreach to stimulate the field using final publications.

**Recent Achievements in International Health**

N/A

**International Partnerships**

N/A

**Staff Membership on Global Health Committees/Working Groups**

- USAID Children in Adversity (P.L. 109-95) Working Group. Representative: Dr. Valerie Maholmes
- CLEER Working Group. Representative: Dr. Valerie Maholmes

**Point-of-Contact**

Dr. Valerie Maholmes

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301-496-1514
Population Dynamics Branch (PDB)

Mission

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

Data and Methods for Global Health

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

Data Archiving

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

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

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

The 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 (LIC) and LMICs that lack adequate vital registration systems and health information systems.

<table>
<thead>
<tr>
<th>Purpose of Methodology</th>
<th>Countries</th>
<th>Grant</th>
<th>PI/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population projection—Estimating how population size and composition will change in the future</td>
<td>All countries</td>
<td>R01HD070936</td>
<td>Raftery, Adrian University of Washington</td>
</tr>
<tr>
<td>Estimating and addressing non-sampling error in fertility rates</td>
<td>LMIC</td>
<td>K01HD078452</td>
<td>McCormick, Tyler University of Washington</td>
</tr>
<tr>
<td>Developing a standard, automated method to assign causes of death using verbal autopsy data</td>
<td>LMIC</td>
<td>R01HD086227</td>
<td>Clark, Samuel Ohio State University</td>
</tr>
<tr>
<td>Developing data collection tools to improve the quality of survey data on neonatal mortality</td>
<td>LIC in sub-Saharan Africa, South Asia, Elsewhere Validated in Guinea-Bissau</td>
<td>R21HD087811</td>
<td>Helleringer, Stephane Johns Hopkins University</td>
</tr>
<tr>
<td>Improving the measurement of adolescent and adult mortality in low-income countries</td>
<td>Bangladesh, Malawi, Uganda, Guinea-Bissau</td>
<td>R01HD088516</td>
<td>Helleringer, Stephane Johns Hopkins University</td>
</tr>
<tr>
<td>Identifying disparities in early-life mortality among population subgroups, examining impact of practices aimed at reducing child mortality</td>
<td>LMIC</td>
<td>K99HD088727</td>
<td>Ramos, Antonio UCLA</td>
</tr>
<tr>
<td>Purpose of Methodology</td>
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<td>Grant</td>
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</tr>
<tr>
<td>Improving understanding of age patterns of under-5 mortality</td>
<td>LMIC</td>
<td>R01HD090082</td>
<td>Guillot, Michel University of Pennsylvania</td>
</tr>
<tr>
<td>Estimating age- and cause-specific child mortality</td>
<td>LMIC</td>
<td>R21HD095451</td>
<td>Li, Liu University of Washington</td>
</tr>
</tbody>
</table>

*Validated in Guinea-Bissau; LMIC=Low- and middle-income countries; LIC=Low-income countries

**Global Partnerships**

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

<table>
<thead>
<tr>
<th>Country/Major Foreign Institution</th>
<th>Grant</th>
<th>PI/U.S. Institution</th>
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</thead>
<tbody>
<tr>
<td>Vietnam Hanoi Medical University</td>
<td>R24HD056691</td>
<td>Hirsch, Jennifer Columbia University Health Sciences</td>
</tr>
<tr>
<td>South Africa University of Cape Town</td>
<td>R24HD077976</td>
<td>Lurie, Mark Brown University</td>
</tr>
</tbody>
</table>

**Scientific Pipeline**

The PDB supports the training and mentorship of young scientists interested in research in global health through its individual fellowships and individual career development awards.
<table>
<thead>
<tr>
<th>Topic</th>
<th>Country studied /Applicable to</th>
<th>Grant</th>
<th>PI/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early menarche and reproductive health</td>
<td>Ghana</td>
<td>F31HD089592</td>
<td>Ibitoye, Mobolaji Columbia University Health Sciences</td>
</tr>
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<td>Effects of a national vaccination campaign on reducing disparities in urban-rural child mortality</td>
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<td>Effects of introduction of antibiotics to reducing SES disparities infectious-disease mortality</td>
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<td>Effect of economic and environmental factors on households’ adoption of hygienic practices</td>
<td>India</td>
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<td>Effects of co-resident and non-coresident fathers and grandparents on child growth and cognitive development</td>
<td>Chile</td>
<td>K99HD088751</td>
<td>Reynolds, Sarah University of California, Berkeley</td>
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<td>Measuring and identifying disparities in early-life mortality among population subgroups, examining impact of practices aimed at reducing child mortality</td>
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<td>Adolescent fertility and social networks</td>
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<td>Intervention research addressing reproductive coercion among medically underserved female adolescents</td>
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<td>Role of gender inequality and food insecurity on maternal and child health</td>
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<td>K01HD086281</td>
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<td>Influence of service delivery factors on contraceptive use</td>
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<td>Estimating and addressing non-sampling error in fertility rates</td>
<td>LMIC</td>
<td>K01HD078452</td>
<td>McCormick, Tyler University of Washington**</td>
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</tbody>
</table>

**See also Developing Methodology section; LMIC=Low- and middle-income countries**
Supporting Offices of Research and Sponsored Programs

The 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 (BRAD) Award (G11) program (PAR-14-333). Institutions in sub-Saharan Africa, India, and LMICs in the Caribbean and South America are eligible to apply. The Branch currently supports programs in Zimbabwe, Peru, and Zimbabwe.

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<thead>
<tr>
<th>Country</th>
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<td>Zimbabwe</td>
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Additional International Research Projects

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

<table>
<thead>
<tr>
<th>Topic</th>
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<td>Enhanced STI/HIV Partner Notification in South Africa</td>
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<td>Causal Pathways to population health impact of HIV antiretroviral treatment</td>
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<td>Health Needs of First Generation-HIV Infected Adolescents</td>
<td>South Africa</td>
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<td>Young Africans’ Changing Understandings of HIV/AIDS Risk</td>
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<td>Integrating Counseling to Transform HIV Family Planning Services</td>
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<td>Addressing Disparities in HIV Testing and Care among Displaced MSM</td>
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<td>Enhancing male participation in interventions to prevent unintended pregnancy</td>
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<td>Fathers' Time Spent with Sons and Daughters</td>
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<td>India Human Development Survey</td>
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<td>Promoting Condom Use among Women in Established Relationships</td>
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<td>Improving the Reproductive Health of Families</td>
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<td>Intimate Partner Coercion and Implications for Women's Health and Well-being</td>
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<td>Multilevel Protective Factors for LGB Youth in North America</td>
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**International Partnerships**
N/A

**Staff Membership on Global Health Committees/Working Groups**
N/A

**Point-of-Contact**
Dr. Rebecca L. Clark
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301-496-1175
Pregnancy and Perinatology Branch (PPB)

Mission
The mission of PPB is to improve the health of mothers and children with a focus on maternal health, pregnancy, fetal wellbeing, labor and delivery, and the developing child with particular interest in high risk pregnancies, fetal pathophysiology, premature labor and birth, newborn disorders, and sudden infant death syndrome (SIDS).

Major International Initiatives over the Past Year

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

Maternal Newborn Health Registry. The Maternal Newborn Health Registry is a prospective, population-based study of pregnancies and their outcomes in seven sites in six LMICs, including the Democratic Republic of the Congo, Guatemala, India, Kenya, Pakistan, and Zambia. With the addition of a new site in Bangladesh, it is anticipated that all pregnant women in participating sites are being registered and their outcomes tracked for 6 weeks post-delivery. The primary purpose of this prospective, population-based observational study of approximately 60,000 women per year is to quantify and understand the trends in pregnancy services and outcomes over time in defined, low-resource geographic clusters. The goal is to provide population-based statistics on stillbirths and neonatal and maternal mortality that can help inform health care policy. The data from the registry also provide the mortality and morbidity outcomes for Global Network trials and help investigators plan future studies for the Global Network. Data collection began in 2008 and is ongoing. To date, the Registry has collected data from more than 600,000 mother-baby dyads.
Women First: Preconception Maternal Nutrition Study. The primary hypothesis of this project is that for women in low resource communities, a comprehensive maternal nutrition intervention (i.e., commencing at least three months prior to conception and continuing throughout pregnancy) will be associated with a significantly greater newborn length than for offspring whose mothers start to receive the same intervention at 12 weeks gestation or who do not receive the intervention at all. The trial is complete and the primary paper by Krebs, et al, titled “A multi-country randomized controlled trial of comprehensive maternal nutrition supplementation initiated prior to conception: The Women First Trial” will be published by the American Journal of Clinical Nutrition this year. Infants were followed through age 2 years to assess growth and neurodevelopmental outcomes, and the data from this component of the study are being analyzed.

Ultrasound Study. This multicountry cluster randomized trial will assess the impact of antenatal ultrasound screening performed by community physician and non-physician health care staff in low-resource community settings. The first hypothesis to be assessed is that ultrasound will increase the rate of prenatal care and appropriate utilization of delivery facilities for women with complicated pregnancies. The second hypothesis is that antenatal ultrasound screening performed by community physician and non-physician health care staff will improve a composite outcome of maternal mortality, maternal near miss mortality, stillbirth, and neonatal mortality. Specifically, the investigators hypothesize that introduction of ultrasound will decrease the composite outcome, including near miss maternal mortality events and stillbirths plus early neonatal mortality. The trial was completed in June 2016. The study found no improvement in performing "routine" ultrasound examinations to improve outcomes.

This is the first randomized clinical trial anywhere in the world to test the value of routine antenatal ultrasound screening to improve pregnancy outcomes. Results of the trial have been published in the British Journal of Obstetrics and Gynecology.
http://dx.doi.org/10.1111/1471-0528.15287

Aspirin Supplementation for Pregnancy Indicated Risk Reduction in Nulliparas (ASPIRIN). This multicountry individual randomized trial will assess the impact of first trimester administration of aspirin on the risk of preterm birth among nulliparous women with a singleton pregnancy. The trial has two treatment arms: daily administration of low-dose (81 mg) aspirin (LDA) also known as acetylsalicylic acid, initiated between 6 0/7 weeks and 13 6/7 weeks gestational age and continued to 36 0/7 weeks gestational age; compared to an identical-appearing placebo. The primary objective is to determine whether daily LDA initiated between 6 0/7 -13 6/7 weeks gestational age and continued to 36 0/7 weeks gestational age reduces the risk of preterm birth. Secondary outcomes of interest are the rate of preeclampsia/eclampsia, small for gestational age, perinatal mortality, and the impact of malaria on pregnancy. Enrollment was initiated in February 2016 and was completed in June 2018. A total of 11,960 women were enrolled. The results will be available in early 2019.
**Studies in Other Networks and Researcher-Initiated Activities**

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

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

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

The T32 program will:

- Provide a sustained training opportunity for obstetrician/gynecologists pursuing academic careers in global women’s health;
- Allow trainees to complete degree requirements for a master of science degree in clinical research, providing the necessary theoretical framework for later practical training;
• Leverage the vast global health expertise at the University of North Carolina School of Medicine and Gillings School of Global Public Health to expand the scope and depth of academic mentorship; and

• Introduce the University of North Carolina Project-Malawi in Lilongwe, Malawi, as a second training site for women's health research, in addition to the established obstetrics/gynecology post-residency training in Lusaka, Zambia. Trainees will thus have access to two established, internationally renowned institutions where they can gain valuable field experience and mentored research training. By the end of the 3-year fellowship, graduates will obtain the necessary skills and experience to become independent investigators, and leaders, in the field of global women's health.

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

**Triggers of Abruptio Placentae (AP): A Case-Crossover Study of an Ischemic Placental Disease (Peru).** AP is a life-threatening obstetric condition that complicates roughly 1-2 percent of all pregnancies. Results from previous studies suggest a significant genetic component in the pathogenesis of AP. The investigators are conducting a large multicenter epidemiologic study of AP in Lima, Peru. A self-matched case-crossover design will be used to evaluate the acute effects of: 1) maternal smoking and alcohol consumption; 2) physical exertion; 3) sexual activity; 4) abdominal trauma secondary to falls or motor vehicle crashes; and 5) exposure to intimate partner violence as potential "triggers" of AP. They will also study genetic variants that influence the pathogenesis of AP in well-characterized 900 mother-infant abruption case pairs and 900 mother-infant control pairs. Collectively, these new insights may facilitate the development of new approaches for the primary prevention of AP at the public health level and may also facilitate the development of new therapies and methods for diagnosis.

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

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

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

Mechanisms of Fetal Inflammatory Response Syndrome Induced by Chorioamnionitis: University of Cincinnati, with subcontract to University of Western Australia, Perth, Australia. Investigators are testing how chorioamnionitis, or inflammation, in the fetal membranes present in about 70 percent of preterm infants born before 30 weeks gestation, becomes a major contributor to morbidity and mortality in this population. Since fetal inflammatory response syndrome (FIRS) is present in about 50 percent of preterm infants exposed to chorioamnionitis, the study will try to decipher the mechanisms behind FIRS. They will use the sheep lab facilities at the University of Western Australia, Perth, for these studies.

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

**Human Placenta Project (HPP).** HPP is an initiative aimed at developing tools and technologies that will enable safe, non-invasive, real time assessment of placenta development and function across pregnancy. Multiple initiatives have been funded since the project’s inception in 2014. Translation of technologies globally, especially into low resource settings, is a major goal for the project. The upcoming 5th annual meeting of this project on November 13-14, 2018, will include talks and panel discussion focused on the opportunities and challenges of making this goal a reality. The following newly awarded HPP grants to U.S. entities, had international components.

- **HD086313-01 Novel Tools for the Noninvasive Evaluation of the Human Placenta: Award to University of Virginia, and the Foreign component, Cambridge University, U.K.**
  Mounting evidence suggests that abnormal placental development in early gestation is highly associated with many maternal and fetal pathologic conditions, which can manifest later in pregnancy. The ability to evaluate in real time human placental structure and function in early gestation by using novel ultrasound tools will allow for the identification of early markers of placental dysfunction with the ultimate long-term goal of prevention of adverse pregnancy outcomes. As initial steps in accomplishing this long-term goal, this study was designed to find which of the novel ultrasound tools are best at discriminating between women who will develop adverse pregnancy outcomes and those who will not. To date, 420 pregnant women have been enrolled, and 282 patients have completed the study with delivery. It is anticipated that in the coming months it will be possible to develop normograms for the novel ultrasound tools and begin interim analysis of blood sample and imaging data.

- **HD089660-01: Lipidomics: A Novel Tool to Define Human Placental Development and Function Across Pregnancy**
  Among the most intractable pregnancy pathologies are preeclampsia, intrauterine growth restriction (IUGR) and gestational diabetes (GDM), all of which are associated with placental dysfunction. The onset of these disorders occurs likely in late first and
early second trimester before the onset of the clinical manifestations. Currently no tools to assess placental health/function in these crucial trimester periods have been developed that could be utilized for routine clinical diagnosis. This study applies cutting-edge high throughput lipidomic technologies that provide measurements of the lipidome in exosomes of placental origin in the circulation of pregnant mothers. To date, it has been determined that some lipid classes change markedly across gestation. Preeclamptic pregnancy profiles are revealing differences from control pregnancy profiles and this is being explored for potential diagnostic value.

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

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

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

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

**Recent Achievements in International Health**

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

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

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

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

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

The Antenatal Corticosteroids Trial (ACT) in Preterm Births to Increase Neonatal Survival in Developing Countries is a randomized controlled trial testing an intervention aimed at reducing neonatal mortality by improving the identification of women at high risk of preterm delivery and administering antenatal corticosteroids. The four components of the intervention include: (1) diffusing recommendations to healthcare providers for antenatal corticosteroids use, (2) training healthcare providers to identify the signs of preterm labor and eligibility criteria for antenatal corticosteroid use among pregnant women, (3) providing birth attendants with preassembled kits containing supplies necessary for a full course of antenatal steroids and reminders to healthcare providers on the use of the kits, and (4) using a color-coded tape to measure uterine height in order to estimate gestational age in women at risk for preterm delivery with unknown gestational age. The study enrolled over 100,000 women and their infants and has been published in the Lancet. The primary findings showed that the intervention effectively increased antenatal corticosteroids administration in <5th percentile infants (45% vs 10%); however, among all births, the intervention resulted in a 3.5 per 1000 absolute increase in neonatal deaths and a 5.1 per 1000 increase in perinatal deaths. These results have generated extensive interest regarding the current practice and guidelines around the use of antenatal corticosteroids in community settings.

Zika Virus

- **Rapid Assessment of Zika Virus Complications (R21) PAR-16-106**
  The purpose of this RFA was to provide an expedited funding mechanism for research on Zika virus and its complications. This rapid RFA, in conjunction with several other participating NIH institutes, was a targeted effort to address the growing concerns of transmission and outcomes in at risk populations such as women who are pregnant. In response to this public health emergency, PPB participated in a MPIDB funded grants on the natural history and pathogenesis of Zika in reproductive age women and the fetus, whether in-utero, postpartum, or through breastfeeding.

- PPB was part of a MPIDB-led effort to develop the ZIP Study (Zika in Infants and Pregnancy), which will enroll up to 10,000 pregnant women in the first or early second trimester in multiple sites throughout South America and the Caribbean. This study will help guide medical and public health responses to Zika as discoveries regarding the virus and the full scope of its impact on at risk populations continues to unfold. At the forefront of the epidemic, investigators are working to better understand the underlying complications of Zika to protect the health of women and their children throughout the world.
Individual Studies Utilizing International Collaboration

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

**Sustained Inflation for Lung Expansion (SAIL) Study.** This is a multi-Principal Investigator project to investigators from the Community Health Advocacy Program (CHAP) and Brown University and has international collaborations from: Australia, Canada, England, Germany, and the Netherlands. Investigators will perform a randomized controlled trial in preterm infants to determine which of two strategies at birth are best to optimally aerate the lung. The study will address the question: in 600 infants of 23 to 26 weeks gestational age needing respiratory support at birth, which of two lung opening strategies, either a standard positive end-expiratory pressure/continuous positive airway pressure (PEEP/CPAP) of 5-7 cm H2O in the delivery room, as compared to early lung recruitment using sustained inflation (SI) in the delivery room, will result in a lower rate of the combined endpoint of death or bronchopulmonary dysplasia (BPD) (using a standardized oxygen reduction test) at 36 weeks post-menstrual age. At about the midpoint of the trial, the NICHD Director accepted the Data Safety and Monitoring Committee recommendations to stop the study because there was no difference in the primary outcomes; however, there was a statistically significant increase in early neonatal deaths. The investigators continue to follow-up enrolled participants.

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

**Premature Infants Receiving Cord Milking or Delayed Cord Clamping: R01HD088646.** Preterm brain injury from intraventricular hemorrhage (IVH) is a pressing worldwide public health problem. Delaying clamping of the umbilical cord at birth for 30 to 60 seconds provides the newborn with a significant autologous transfusion of blood from the placenta and has been shown to reduce IVH. Delayed cord clamping (DCC) has been shown to reduce overall IVH (mainly lower grades 1 and 2) by 50 percent but has not reduced the incidence of severe IVH or death. This study is being done to find out whether umbilical cord milking (UCM) is at least as good as or better than DCC in reducing bleeding in the brain or preventing death in premature newborns. The investigators will study short- and long-term outcomes of infants delivered before 32 weeks gestation that receive either UCM or DCC. In addition to six U.S. sites, University of Alberta, Canada, University College Cork, Ireland, and University of Ulm Germany are participants. The specific aims of this trial are: To compare the incidence of severe IVH and/or death in premature newborns <32 weeks...
gestational age delivered by caesarean section receiving UCM to those receiving DCC; to compare the safety and efficacy profiles of premature newborns <32 weeks gestational age delivered by caesarean section receiving UCM vs. DCC during their hospitalization and at 24 months corrected age; 3) to compare the outcomes of premature newborns <32 weeks gestational age delivered by caesarean section (from Aims 1 and 2);

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

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

**Group Antenatal Care to Promote a Healthy Pregnancy and Optimize Maternal and Newborn Outcomes: A Cluster Randomized Controlled Trial: R01HD096277-01.** The goal of this project is to improve health literacy and reduce preventable maternal and newborn morbidities and mortality with a focus on preparing for birth, identifying complications, and care-seeking patterns. The research team will test the efficacy of providing antenatal care in groups of 8 to 12 women of similar gestational age. Women will meet with the same group and the same provider over the course of their pregnancy for a 60-minute facilitated discussion in addition to their individual assessment. The research team will recruit 845 women less than 24 weeks’ gestation, over the age of 15 years at their first antenatal care visit from health facilities in rural Ghana. Participants will be surveyed in person at the health facility or by cellphone at six time points: (1) initial enrollment in antenatal care, (2) third trimester (prior to delivery), (3) immediately postpartum, (4) 6-weeks postpartum, (5) 6-months postpartum, and (6) 1 year postpartum. Additional data will be collected from antenatal care and hospital medical records.
Addressing Provider Stress and Unconscious Bias to Improve Quality of Maternal Health Care: K99HD093798-01A1. The goal of this project is to improve quality of maternal health care, particularly person-centered maternal health care (PCMHC), and reduce disparities in PCMHC—focusing on the role of health care provider stress and unconscious bias. In the K99 phase we will: (1) conduct secondary data analysis using existing data from about 1000 women, 50 providers, and facility level data to examine factors associated with PCMHC, focusing on the role of provider stress; and (2) conduct structured and in-depth interviews with 100 and 20 to 40 providers respectively, to examine the levels of provider stress and unconscious bias, and the types of stressors and biases in Kenya. In the R00 phase we will: (1) design an intervention that enables providers to identify and manage their stress and unconscious bias; (2) pilot the intervention to assess its feasibility and acceptability; and (3) assess preliminary effect of the intervention. We will recruit 80 providers for the pilot and its evaluation. All study participants (providers) will be older than 18 years, and recruited from health facilities in Migori County, Kenya. They will participate in surveys at one time point in the K99 phase and two time points in the R00 phase. They will also provide hair samples for cortisol levels to measure stress in the R00 phase.

International Partnerships
N/A

Staff Membership on Global Health Committees/Working Groups
N/A

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National Center for Medical Rehabilitation Research (NCMRR)

Mission

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

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

Major International Initiatives over the Past Year

NCMRR is working with the WHO during the planning stages of the Rehabilitation 2030 initiative, led by the Rehabilitation and Disability component of WHO. This includes working to facilitate a research agenda for the initiative and identifying the priority package of interventions that would be included in the launch of this work.

Recent Achievements in International Health

N/A

International Partnerships

**Big Data Neuroimaging to Predict Motor Behavior after Stroke.** Stroke is a leading cause of serious long-term adult disability around the world. There is huge variability among stroke survivors in terms of lesion location, age, gender, and time since stroke that may affect a person's likelihood of recovery and response to different types of rehabilitation treatments. This research seeks to combine the best neuroimaging techniques with functional assessments from stroke survivors from across the globe to identify neural and behavioral biomarkers that predict recovery of motor impairment
(ENIGMA Center for Worldwide Medicine, Imaging, and Genomics). This approach has the potential to revolutionize the way that rehabilitation research is validated, to ensure robust, reliable, and reproducible results.

**Comorbidity in Traumatic Brain Injury (TBI) and Risk of All-Cause Mortality, Functional, and Financial Burden: A Decade-Long Population Based Cohort Study.**

Comorbidity is prevalent after TBI and across the spectrum of injury severity. It can be present at the time of injury, arise early after injury, or during hospitalization or inpatient rehabilitation. This study, at the University Health Network in Toronto, Canada, involves at least 35,000 acute care cases over a 10-year period. It will utilize linked data of all patients with TBI diagnostic codes, derived from emergency departments (National Ambulatory Care Reporting System), acute care (Discharge Abstract Database), inpatient rehabilitation (National Rehabilitation System), community services and long-term care (Home Care Database), continuing care (Continuing Care Reporting System), and prescription data (Ontario Health Insurance Plan Claims Database) over a 10-year period. It is hypothesized that acutely derived variables (i.e., age, intracranial injury, injury mechanism, injury severity, length of stay) are not by themselves sufficient to accurately predict resource consumption, all-cause mortality, and functional outcomes in individuals with TBI, stratified by age and sex. It is also hypothesized that an expanded set of factors and factor clusters including patient demographics, certain clinical (i.e., comorbid) disorders and social indices, will provide greater accuracy in predicting resource consumption, all-cause mortality and functional outcomes of TBI, and these clusters will be subject to change over time.

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

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

**High-performance, Low-Cost, Passive Prosthetic Knees Optimized to Replicate Physiological Gait in Multiple Mobility Scenarios.** The focus of this program is to create high-performance, low-cost, passive prosthetic knees that can accurately replicate physiological gait in multiple mobility scenarios. The product of this work will be knee technology that drastically enhances the mobility and quality of life for lower leg amputees in the developing world, while also providing a cost-effective option with enhanced performance to developed world users. The foundation of this research is our novel method for determining the knee torque profile required for a low-mass prosthesis to replicate a given gait behavior, calculated from able-bodied kinematic and kinetic data for the same behavior. Adjusted prosthesis torque profiles can be produced using only simple, low-cost, passive mechanical elements such as linear springs and friction dampers. This research program will entail measuring kinematic and kinetic data of able-bodied individuals performing activities of daily living. These data will be used to calculate the adjusted torque profiles required for a prosthetic knee to perform the same activities and then they will optimize knee architecture to use only simple, passive mechanical elements that can most accurately replicate all of the gait activities. An updated version of the knee design will be tested in a gait lab at Northwestern University, to correlate experiments with our theoretical model and refine its accuracy. The knee will then be field tested in India with BMVSS Jaipur Foot. The project will culminate in a refined knee technology that is ready for larger-scale clinical testing and progression towards commercialization.

**Machine-Learning Algorithms to Measure Physical Activity in Children with Cerebral Palsy (CP).** The purpose of this project is to improve physical activity measures in children with CP through machine learning in accelerometer data processing. This collaboration with Queensland University of Technology in Australia is the first to develop, evaluate, and deploy machine learning algorithms to measure activity type and energy expenditure in children with CP. The specific aims of this project are to: 1) Develop and test machine learning algorithms to predict physical activity type, walking speed, and energy expenditure in ambulant children and adolescents with CP; 2) compare the accuracy of physical activity intensity estimates provided by machine learning algorithms to those provided by conventional cut-point methods; and 3) evaluate the performance of the resultant CP prediction models in an independent sample of children with Acquired Brain Injury (ABI). This project will result in prediction models that will enable clinicians and rehabilitation professionals to more effectively monitor the physical activity levels of their patients to improve health and function. Improved objective measures of physical activity will also enable health researchers to better understand the short-and long-term health benefits of regular physical activity and impact of physical activity on adverse health conditions associated with CP.

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

**Multidiscipline Design Projects with Outreach to Persons with Disability.** The overall goal of this program, a collaboration with Ohio State University and Nanjing University in China, is to build a dynamic senior design program that fosters multi-disciplinary efforts at the student, mentor and university level, and promotes outreach to the disabled community. These goals will be met through the following specific objectives: 1) require multidisciplinary teams that will design, build and test a device; 2) expand university and community collaborations to include expertise in electrical and computer engineering; and 3) encourage early participation of biomedical engineering juniors through a summer design program. From this new collaboration, students will gain valuable skills from areas outside of their primary field, and it is expected that the level of project design will improve.

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

**Novel Gene Targets for Central Nervous System (CNS) Axonal Regeneration.** This research, a collaboration with Imperial College London, will use high throughput technologies to identify genes regulating CNS regeneration by examining two related hypotheses about intrinsic factors. The first will examine whether Dorsal Root Ganglion (DRG) neurons display ribonucleic acid sequences (RNAs) that are expressed at significantly lower levels in CNS neurons and allow DRG axon regeneration. The second is that DRG neurons that have experienced a conditioning peripheral lesion express RNAs that allow regeneration and are missing (or very lowly expressed) in lesioned CNS neurons, such as the corticospinal neurons. A major impediment to recovery after CNS injury is the failure of axons to regrow effectively. A variety of extrinsic and intrinsic factors contribute to this problem. Extrinsic factors include inhibitory proteins found in and around the injury site such as those from the glial scar as well as those associated with intact or damaged myelin. Regarding intrinsic factors, a key finding motivating this work is that DRG neurons can respond to peripheral injury with changes in gene expression that promote CNS
regeneration, even in the inhibitory environment around the injury site. In contrast, CNS neurons typically fail to regenerate axons through such inhibitory regions. This implies that CNS neurons have inherent molecular differences that limit CNS regenerative capacity. The recent discovery of PTEN, SOC3S3, KLF4 and KLF7 as important intrinsic regulators of CNS axon regeneration validates this hypothesis. However, the small fraction of CNS axons able to regenerate after injury, even in animals in which these genes have been manipulated, indicates that additional regulators remain to be discovered.

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

**Postnatal Neuronal Precursors and Brain Repair.** Precursors of cortical interneurons, a collection of local-circuit inhibitory nerve cells essential to proper brain function, have a unique potential for brain repair. When grafted into the juvenile brain, these young neurons migrate and integrate into host circuitry inducing a new period of cortical plasticity. Through a partnership with University of Valencia in Spain, this research seeks to identify which type(s) of interneurons are responsible for the induction of cortical plasticity in mice, and to determine if these cells can induce similar plasticity and functional recovery when grafted into fully mature adult brains. This work will help identify key neuronal cell types required for the induction of cortical plasticity, essential information for the further development of interneuron transplantation for brain repair.

**Subject-Specific Diffusion Magnetic Resonance Imaging Profiles of Injury in TBI and Post Traumatic Stress Disorder.** While mild TBI (mTBI) has become the focus of many neuroimaging studies, the understanding of mTBI, particularly in patients who exhibit no radiological evidence of injury and yet experience clinical and cognitive symptoms, has remained a complex challenge. Sophisticated imaging tools are needed to delineate the kind of subtle brain injury that is extant in these patients, as existing tools are often ill-suited for the diagnosis of mTBI. The goal of this study, in collaboration with the French Institute for Research in Computer Science and Automation (INRIA), is to develop a robust framework to perform subject-specific neuroimaging analyses of diffusion MRI (dMRI), as this modality has shown excellent sensitivity to brain injuries and can locate subtle brain abnormalities that are not detected using routine clinical neuroradiological readings.

**Training-Induced Plasticity in Human Motor and Sensory Systems.** The focus of this research is on the sensorimotor system and exploring whether training induced changes to the brain spread from the motor to somatosensory areas of the brain and vice versa. This research will address the effects of motor learning on sensory systems and of somatosensory perceptual training on motor systems by using an approach that combines
psychophysical, neurophysiological and neuroimaging techniques. The ability to quantify changes to brain plasticity that accompany both somatosensory training and motor learning may permit a better understanding of the broader effects of neurological rehabilitation on sensorimotor disorders. Imaging the sensory and motor networks of the brain that are associated with both somatosensory and motor learning may also lead to better diagnoses and tracking of brain neuroplasticity during therapy. This approach may aid in the development of neuroscience-based strategies for training and rehabilitation. This study is in collaboration with McGill University and Western University in Canada.

**Diaphragm Pacing and Rehabilitation in Pompe Disease.** Pompe disease is a relatively rare disorder that affects 1/40-50,000 births. This project is aimed at developing a rehabilitative strategy to help promote breathing capacity and wean adult patients off of ventilators. They are using a 12-week diaphragm-pacing program to promote phrenic neuromuscular plasticity, support independence, and prolong recovery. During the course of the study, patients on full ventilator support and with reduced assistance, will be followed for breath timing during spontaneous breathing, changes in motor unit activity, capacity to voluntarily increase diaphragm/phrenic activity, and improved tidal volume capacity. Because Pompe disease is such a rare condition, these researchers will be traveling out to Italy to consult with Dr. Rossella Parini at the Universita degli Studi di Milano-Bicocca and Dr. Matteo Giacomini at the Niguarda Hospital, Milan, although no NIH grant funds go directly to these Italian collaborators. In addition, Dr. Darlene Reid, a physiotherapist at the University of Toronto, Canada, serves as a consultant on the data and safety monitoring board for this research study.

**Staff Membership on Global Health Committees/Working Groups**
Priority Package of Interventions Working Group, Rehabilitation 2030, Disability Component, WHO. Representative: Dr. Alison Cernich

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Division of Intramural Population Health Research (DIPHR)

Mission

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

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

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

Major International Initiatives over the Past Year

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

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

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

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

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

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

**Recent Achievements in International Health**

- **Tryptophan and Inflammation.** In collaboration with Trinity College, Dublin, it has been shown that the markers for inflammation neopterin and interleukin 10 are strongly related to tryptophan metabolism in healthy adults. This study also reported that tryptophan and vitamin B6 in young adults are affected by gender and alcohol consumption.

- **In Utero Glycemia Levels & Risk of Childhood Obesity.** Maternal fasting plasma glucose concentrations were significantly and positively associated with birth size and overweight/obesity risk at seven years.

**International Partnerships**

- **Neural Tube Defects: Biochemistry related to birth defects and genome wide association studies with Trinity College in Dublin, Ireland.** Principal Investigator: Dr. J. Mills.

- **Formate metabolism and genetic factors with Memorial University in Newfoundland, Canada.** Co-investigator: Dr. J. Mills.

- **Tryptophan metabolism and its role in immune response with University of Bergen in Bergen, Norway.** Co-investigator: Dr. J. Mills.

- **In collaboration with investigators at SSI in Copenhagen, Denmark, NICHD investigators are working to investigate congenital hydrocephalus genetics and are conducting a genome wide association study.** Co-investigator: Dr. J. Mills.

- **In collaboration with SSI, Copenhagen, Denmark, NICHD genetic determinants for the progression from gestational diabetes to type 2 diabetes.** Principal Investigator: Dr. C. Zhang; co-investigators: E. Schisterman, G. Buck Louis, J. Mills, E. Yeung, A. Liu.

- **In collaboration with the SSI, Copenhagen, Denmark, NICHD investigators are working on the Danish National Birth Cohort to investigate the intergenerational impact of gestational diabetes and maternal obesity.** Principal Investigators: Drs. C. Zhang, S. Mumford, E. Yeung; co-investigators: P. Mendola, J. Mills, A. Liu.
- International consortium project on angiogenesis factors and preeclampsia. Investigators: Drs. C. Zhang, E. Schisterman.
- Reproductive effects of in utero exposure to Chernobyl fallout in an iodine deficient region of Ukraine. Investigators: Dr. K. Grantz, Dr. J. Mills, Dr. Maureen Hatch (NCI).
- In collaboration with investigators at SSI in Copenhagen, Denmark, NICHD investigators are working to investigate pyloric stenosis genetics and are conducting a genome wide association study. Co-investigator: Dr. J. Mills.

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

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Division of Intramural Research (DIR)

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

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

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

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

- How do cells transmit signals from the outside environment to the nucleus, initiate gene expression and replication, and then translate molecular responses into changes in function, differentiation, and communication with the cells' neighbors and environment?

- How do cells talk to one another, identifying their properties and location to give rise to tissues and organs?

- How are these processes integrated during embryonic, fetal, and postnatal development?

- When these processes go awry and disease ensues, how may we intervene in this pathologic sequence and treat the disease?
Section on Clinical Neuroendocrinology (SCN)

Investigator: Karel Pacak, M.D., Ph.D., D.Sc.
Affinity Group: Developmental Endocrine Oncology and Genetics

Mission
Focus in on endocrine tumors

Major International Initiatives
WHO Classification of Tumours: Tumours of Endocrine Organs

Publications with International Collaborators


Recent Achievements in International Health
N/A

International Trainees
N/A

International Partnerships
N/A

Staff Membership on Global Health Committees/Working Groups
Working Group on Endocrine Hypertension, PRESSOR: Pheochromocytoma Research and Support Organization
Point-of-Contact
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301-402-4594
Section on Endocrinology and Genetics (SEGEN)

Investigator: Constantine A. Stratakis, M.D., M. (Med) Sci. – Scientific Director
Affinity Group: Developmental Endocrine Oncology and Genetics

Mission

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

Major International Initiatives

- Dr. Jerome Bertherat and colleagues: Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France: Cloning of new genes for Carney complex, 06/2003-2013 (approx. $400K/year); and others in France
- Prof. A. Beckers and colleagues: Department of Endocrinology, Chu de Liège, Domaine Universitaire du Sart-Tilman, Liege, Belgium; and others in Belgium
- Prof. Stefan Bornstein and colleagues: Medizinischen Klinik und Poliklinik III und des Zentrums für Innere Medizin Universitätsklinikum Carl Gustav Carus an der TU Dresden, Germany; and others in Germany
- Dr. Jan Maarten Wit and colleagues: Leiden University Medical Center, The Hague Area, Netherlands; and others in Netherlands
- Dr. Annalisa Vetro and colleagues: Università degli Studi di Pavia: Dipartimento di Medicina Molecolare, Genetica Medica, Pavia, Italy
- Prof. Massimo Mannelli and colleagues: Dept. Experimental and Clinical Biomedical Sciences, Sez. Endocrinologia, Universita Degli Studi – Firenze, Italy
- Prof Francesco Brancati and colleagues: Ambulatori Genetica Clinica – Genetica Medica, Policlinico Universitario Tor Vergata – Rome, Italy
- Dr. Maria Candida Fragoso and colleagues: Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Unidade de Endocrinologia do Desenvolvimento, Unidade de Neuroendocrinologia, Laboratório de Hormônios e Genética Molecular/LIM42, Sao Paulo, Brazil
- Prof. Amilcar Tanuri and colleagues: Laboratório de Virologia Molecular, Instituto de Biologia - Departamento de Genética, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil; and others in Brazil
Selected Publications with International Collaborators in the Past 5 years


**Recent Achievements in International Health**

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

**International Trainees**

- Annabel Berthon, Ph.D.
  Postdoctoral Visiting Fellow
  University of Clermont Ferrand, France
  Issoire, France

- Laura Cristina Hernández Ramírez, Ph.D.
  Postdoctoral Visiting Fellow
  Queen Mary University of London
  Barts and The London School of Medicine Centre for Endocrinology
  William Harvey Research Institute

- Giampaolo Trivellin, Ph.D.
  Postdoctoral Visiting Fellow
  University of Padova
  Bassano Del Grappa, Italy

- Nikolaos Settas, Ph.D.
  Postdoctoral Visiting Fellow
  National and Kapodistrian University of Athens, School of Medicine Department of Genetics
  Athens, Greece
• Christina Tatsi, M.D., Ph.D.
  Clinical and Research Fellow in Pediatric Endocrinology
  National and Kapodistrian University of Athens, School of Medicine
  Department of Pediatrics
  Athens, Greece

• Ludivine Drougat Charlier, Ph.D.
  Postdoctoral Visiting Fellow
  Institut Cochin
  Paris, France

• Andrea Gutierrez Maria, Ph.D.
  Special Volunteer
  Universidade de Sao Paulo
  Department of Pediatrics
  Sao Paulo, Brazil

• Atila Rossi, M.Sc.
  Special Volunteer
  Universidade Federal do Rio de Janeiro
  Department of Genetics
  Rio de Janeiro, Brazil

**International Partnerships**

Memoranda of Understanding with:

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

**Staff Membership on Global Health Committees/Working Groups**

N/A

**Point-of-Contact**

Dr. Fabio Rueda Faucz
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Section on Environmental Gene Regulation (SEGR)

Investigator: Gisela Storz, Ph.D.
Affinity Group: Cell and Structural Biology

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

Major International Initiatives
N/A

Publications with International Collaborators

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

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

International Partnerships
N/A

Staff Membership on Global Health Committees/Working Groups
N/A

Point-of-Contact
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301-402-0968
Section on Intercellular Interactions (SII)

Investigator: Leonid Margolis, Ph.D.
Affinity Group: Maternal-Fetal Medicine, Imaging, & Behavioral Determinants

Mission
To identify basic mechanisms of cell interactions in norm and pathologies

Major International Initiatives
1. Identification of antigenic spectra of individual HIV-1 virions: A collaborative project with the Imperial College London, U.K. (PI: Dr. Robin Shattock)
2. Development of ex vivo models of atherosclerotic plaques: A collaborative project with Moscow University of Medicine and Dentistry, Moscow, Russia (PIs: Dr. Elena Vasilyeva and Alexander Shpektor)
3. Morphological analysis of extracellular vesicles generated by CMV-infected cells and their role in HIV infection: A collaborative project with Cochin Institute, Paris, France (PIs: Dr. Morgan Bomsel)
4. Investigation of the role of Lactobacillus-generated of extracellular vesicles in protection against vaginal HIV transmission: A collaborative project with the University of Bologna, Bologna, Italy (PIs: Dr. Beatrice Vitali)
5. Development of Anti-HIV/ anti-EB dual-targeted antivirals: A collaborative project with the Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russia (PIs: Dr. Sergey Kochetkov)

Publications with International Collaborators
N/A

Recent Achievements in International Health
N/A

International Trainees
- Mr. Rogers Palomina
  International trainee
  University of Bologna, Italy
- Dr. Sonia Zicari
  International trainee
  University of Brescia, Italy
- Ms. Daria Vorobyeva
  Ph.D. Student
  Moscow Medical University
• Mr. Ezequiel Dantas  
Recipient of the Fulbright Award  
Argentina

International Partnerships
The Section is an international partner in the framework of the OAR Intramural-to-Russia Program.

Staff Membership on Global Health Committees/Working Groups
N/A

Point-of-Contact
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301-594-2476
Section on Molecular Morphogenesis (SMM)

Investigator: Yun-Bo Shi, Ph.D.
Affinity Group: Cell Regulation and Development

Mission

The Section on Molecular Morphogenesis studies the gene-regulatory mechanisms controlled by thyroid hormone (TH) receptor (TR) that establish the developmental program of metamorphosis. The laboratory recently showed that the level of TR-binding coactivators regulates the rate of metamorphosis progression, and revealed the origin of the TH-induced adult intestinal epithelial stem cells. The laboratory also showed that a TH-induced matrix metalloproteinase regulates apoptosis via two different mechanisms in different organs during metamorphosis.

Major International Initiatives

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

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

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

Through collaboration with researchers at the University of Dundee in the United Kingdom, a conditional knockout mouse line has been generated to investigate the role of a transporter for thyroid hormone and amino acids that has been previously shown to be induced by thyroid hormone during frog intestinal metamorphosis. Analysis of the mouse knock-out line indicates that control of the transporter expression and amino-acid uptake by antigen receptors and pathogens is critical for metabolic reprogramming that allows immunologically activated T-cells to mediate adaptive immune responses, thus suggesting potential avenues for immunotherapy and disease prevention.
In addition, the collaboration with Wuhan University on the global developmental expression profiles has revealed genetic programs underlying the developmental divergence between mouse and human embryogenesis. Though this collaboration formally came to a conclusion earlier, continued data analysis resulted in recent publications listed below.

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

Publications with International Collaborators


**Recent Achievements in International Health**

N/A
**International Trainees**
N/A

**International Partnerships**
N/A

**Staff Membership on Global Health Committees/Working Groups**
N/A

**Point-of-Contact**
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301-402-1004
Section on Molecular Neurobiology (SMN)

Investigator: Andres Buonanno, Ph.D.
Affinity Group: Cell and Structural Biology

Mission

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

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

Major International Initiatives

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

Project B) The major initiative of this project, in collaboration with Dr. Kristian Gundersen's group at Oslo University, Norway, is to identify transcription factors that are differentially modulated by slow (10 Hz) and fast (100 Hz) patterns of motorneuron activity and that, in turn, regulate genes encoding the contractile properties that determine the slow- and fast-twitch properties of skeletal muscles.
Publications with International Collaborators

Project A


Project B


Recent Achievements in International Health

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

International Trainees (alphabetical order)

- Tanveer Ahmed, Ph.D.
  Assistant Professor, Department of Biochemistry, University Grants Commission
  New Delhi, India

- Sharmila Basu, Ph.D.
  President and Chief Scientific Officer, MindSpec
  McLean, Virginia

- Swagata Roychowdhury-Basu, Ph.D.
  Technical writer for neuroscience advances
  Inscopix, Inc.
• Soledad Calvo, M.D., Ph.D.
  Assistant Professor, Facultad de Medicina at Alicante University
  Spain
• Claudia Colina-Prisco, Ph.D.
  Postdoctoral Fellow
  National Institute of Alcohol Abuse and Alcoholism, NIH
• Rolando Garcia, Ph.D.
  Senior Scientist
  Wellstat Therapeutics
  Gaithersburg, Maryland
• Carmen M. Gonzalez, Ph.D.
  Department of Pathology and Exp Therapy
  University of Barcelona, Spain
• Ryoichi Kimura, Ph.D.
  Assistant Professor, Department of Physiology, Hyogo College of Medicine
  Nishinomiya, Japan
• Oh-Bin Kwon, Ph.D.
  Assistant Professor, Molecular NeuroScience Lab
  Department of Life Science, POSTECH
  South Korea
• Marines Longart, Ph.D.
  Principal Investigator
  Center for Biosciences, Institute for Advanced Studies
  Caracas, Venezuela
• Elias Leiva-Salcedo
  Assistant Professor
  Facultad de Química y Biología, Universidad de Santiago
  Chile
• Joerg Neddens, Ph.D.
  Senior Scientist,
  Department of Histology
  JSW Life Sciences, Austria
• Daniel Paredes, Ph.D.
  Investigator, Lieber Institute for Brain Development
  Baltimore, Maryland
• Zaheer Rana, Ph.D.: Staff Scientist, Dept of Mol Biosciences, University of Oslo,
  Norway
• Alon Shamir, Ph.D.
  Head of Research Laboratory
  Mazra Mental Health Center, Israel
• Miguel Skirzewski, Ph.D.
  Postdoctoral Fellow
  NICHD, NIH

• Raluca Yonescu, Ph.D.
  Sr. Research Specialist
  John Hopkins Cytogenetics, Maryland

International Partnerships

• Universidad de los Andes, Merida, Venezuela. Had memorandum of understanding (MOU) and joint graduate student stipend for Dr. Miguel Skirzewski to work in lab.

• University of Bonn. Presently have MOU for graduate student stipend for Ms. Larissa Erben to work in lab.

• Oslo University, Norway. Had an MOU for Dr. Zaheer Rana to perform his dissertation in lab.

Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

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Section on Nutrient Control of Gene Expression (SNCGE)

Investigator: Alan Hinnebusch, Ph.D.
Affinity Group: Cell Regulation and Development

Mission

Work from this Section on the mechanism of protein synthesis initiation in budding yeast provided the foundation for a collaboration with researchers at the MRC Laboratory of Molecular Biology in Cambridge, England, on high-resolution cryo-electron microscopy of reconstituted preinitiation complexes, which reveal conformational changes that occur on the transition from the scanning phase of initiation to that of start codon recognition. Collaborative work with researchers at Shimane University School of Medicine, Shimane, Japan, provided structural analysis of interactions among translation initiation factors using nuclear magnetic resonance spectroscopy.

Major International Initiatives

N/A

Publications with International Collaborators


Recent Achievements in International Health

N/A

International Trainees

N/A

International Partnerships

N/A
Staff Membership on Global Health Committees/Working Groups

N/A

Point-of-Contact

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301-496-4480
Section on Protein Biosynthesis (SPB)

Name of Investigator: Thomas Dever, Ph.D.
Affinity Group: Cell Regulation and Development

Mission

The SPB is studying cellular protein synthesis. Their efforts include characterizing the structure and function of translation factors, the molecular principles of kinase-substrate recognition by the stress-responsive eIF2a kinases, and the role of the factor eIF5A in promoting the reactivity of poor substrates in protein synthesis. The group recently reported that the translation factor eIF5A functions generally in translation elongation and is especially required for the synthesis of peptides containing polyproline sequences. The group has also revealed a role for the novel diphthamide modification of the translation elongation factor eEF2 in promoting high fidelity during protein synthesis, and they have characterized mutations in the translation factor eIF2 that cause MEHMO syndrome, an X-linked intellectual disability syndrome.

Major International Initiatives

Molecular genetic and biochemical studies on the mechanism and regulation of protein synthesis from this Section established the groundwork for collaborations with human molecular geneticists, with chemists, and with structural biologists. Together with x-ray crystallographers at the IGBMC in Strasbourg, France, the structure of the translation factor eIF5A and its polyproline substrate on the ribosome provided insights into how eIF5A promotes translation of proteins containing runs of proline residues. Work with chemists in Japan revealed the chemical properties of proline that impose the requirement for eIF5A in protein synthesis. Studies in collaboration with geneticists in Germany and Slovakia identified mutations in the translation factor eIF2gamma as the cause of MEHMO syndrome and revealed how these mutations cause dysregulation of protein synthesis and induce a cellular stress response.

Publications with International Collaborators


**Recent Achievements in International Health**
N/A

**International Trainees**
N/A

**International Partnerships**
N/A

**Staff Membership on Global Health Committees/Working Groups**
N/A

**Point-of-Contact**
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