NICHD International Activities Catalog

2017

OFFICE OF GLOBAL HEALTH

Eunice Kennedy Shriver National Institute of Child Health and Human Development
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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>
<td>Antenatal Corticosteroids Trial</td>
</tr>
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<td>AFM</td>
<td>Atomic Force Microscopy</td>
</tr>
<tr>
<td>AG</td>
<td>Affinity Group</td>
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<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
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<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>BME</td>
<td>Biomedical Engineering</td>
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<tr>
<td>BMGF</td>
<td>Bill &amp; Melinda Gates Foundation</td>
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<tr>
<td>BPD</td>
<td>Bronchopulmonary Dysplasia</td>
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<td>BRAD</td>
<td>Biomedical/Behavioral Research Administrators Development Award</td>
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<td>BRINDA</td>
<td>Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia</td>
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<td>CATCH</td>
<td>Counseling and Testing for Children at Home</td>
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<td>Centers for Disease Control and Prevention</td>
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<td>CHAP</td>
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<td>ChIP-seq</td>
<td>Chromatin Immunoprecipitation Sequencing</td>
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<td>CIPHER</td>
<td>Collaborative Initiative on Pediatric HIV Research</td>
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<td>CLEER</td>
<td>Collaborative for Enhancing Emergency Care Research in LMICs</td>
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<td>CNRS</td>
<td>French National Center for Scientific Research</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<td>CP</td>
<td>Cerebral Palsy</td>
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<td>CPAP</td>
<td>Continuous Positive Airway Pressure</td>
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<td>CRISPR</td>
<td>Clustered Regularly Interspaced Short Palindromic Repeat</td>
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<td>DER</td>
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<td>DMPA</td>
<td>Depot Medroxyprogesterone Acetate</td>
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<td>dMRI</td>
<td>Diffusion MRI</td>
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<td>DRG</td>
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<td>DSi</td>
<td>Down Syndrome International</td>
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<td>EuPFI</td>
<td>European Pediatric Formulations Initiative</td>
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<td>FAS</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FIC</td>
<td>Fogarty International Center</td>
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<td>FIRS</td>
<td>Fetal Inflammatory Response Syndrome</td>
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<td>GA</td>
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<td>Gestational Diabetes Mellitus</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>GRIP</td>
<td>Global Research in Pediatrics Initiative</td>
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<td>GU</td>
<td>Genitourinary</td>
</tr>
<tr>
<td>HAI</td>
<td>Human-Animal Interaction</td>
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<td>HAPO</td>
<td>Hyperglycemia and Adverse Pregnancy Outcome Study</td>
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<td>HBeAg</td>
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<tr>
<td>HBV</td>
<td>Hepatitis B Virus</td>
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<td>HCMV</td>
<td>Human Cytomegalovirus</td>
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<td>Hib</td>
<td>Haemophilus influenzae type B</td>
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<td>HITSystem©</td>
<td>HIV Infant Tracking System</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HSV-2</td>
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<td>HTEC</td>
<td>HIV Testing and Enhanced Counseling</td>
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<td>IAA</td>
<td>Interagency Agreement</td>
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<td>ICs</td>
<td>NIH Institutes and Centers</td>
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<td>IGMCD</td>
<td>International Guide for Monitoring Children’s Development</td>
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<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>ING</td>
<td>Inhibitor of Growth</td>
</tr>
<tr>
<td>INRIA</td>
<td>French Institute for Research in Computer Science and Automation</td>
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<td>INSPIRE</td>
<td>Inflammation and Nutritional Science for Programs/Policies and Interpretation of Research Evidence</td>
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<td>IOM</td>
<td>Institute of Medicine</td>
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<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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<td>iYCF</td>
<td>Investing in Young Children Forum</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>MCH</td>
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<td>MODS</td>
<td>Multiple Organ Dysfunction Syndrome</td>
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<td>Abbreviation or Acronym</td>
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<td>MEPI</td>
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<td>MICS</td>
<td>Multiple Indicator Cluster Survey</td>
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<td>MINERVa</td>
<td>Multigenerational Familial and Environmental Risk for Autism Network</td>
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<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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<tr>
<td>NACS</td>
<td>Nutritional Assessment, Care, and Support</td>
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<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
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<td>NCMRR</td>
<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>NIAAA</td>
<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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<td>NICHID</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>NIH</td>
<td>National Institutes of Health</td>
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<td>NIMH</td>
<td>National Institute of Mental Health</td>
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<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>Nutrition Guidance Expert Advisory Group</td>
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<td>Office of Dietary Supplements</td>
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<td>Office of the Global AIDS Coordinator</td>
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<td>ORF</td>
<td>Open Reading Frames</td>
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<td>OVC</td>
<td>Orphans and Vulnerable Children</td>
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<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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<td>PEEP</td>
<td>Positive End-Expiratory Pressure</td>
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<tr>
<td>PENTA</td>
<td>Pediatric European Network for Treatment of AIDS</td>
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<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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<td>PMA</td>
<td>Post-Menstrual Age</td>
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<tr>
<td>PMTCT</td>
<td>Prevention of Maternal-Child HIV Transmission</td>
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<tr>
<td>POFO</td>
<td>Positive Outcomes for Orphans</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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<td>RFA</td>
<td>Request for Applications</td>
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<td>RNA-seq</td>
<td>RNA Sequencing</td>
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<td>SAIL Study</td>
<td>Sustained Inflation for Lung Expansion</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>
</tr>
<tr>
<td>SI</td>
<td>Sustained Inflation</td>
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<td>SIDS</td>
<td>Sudden Infant Death Syndrome</td>
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<td>Abbreviation or Acronym</td>
<td>Full Term</td>
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<tr>
<td>SMFM</td>
<td>Society for Maternal-Fetal Medicine</td>
</tr>
<tr>
<td>SMI</td>
<td>Superb Microvascular Imaging</td>
</tr>
<tr>
<td>SSI</td>
<td>Statens Serum Institut</td>
</tr>
<tr>
<td>STAC</td>
<td>Scientific and Technical Advisory Committee</td>
</tr>
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<td>STI</td>
<td>Sexually Transmitted Infection</td>
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<td>SWE</td>
<td>Sheer Wave Elastography</td>
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<td>T1DM</td>
<td>Type 1 Diabetes</td>
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<td>TALEN</td>
<td>Transcriptional Activator Like Effector Nuclease</td>
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<td>Tuberculosis</td>
</tr>
<tr>
<td>TBI</td>
<td>Traumatic Brain Injury</td>
</tr>
<tr>
<td>tDCS</td>
<td>Transcranial Direct Current Stimulation</td>
</tr>
<tr>
<td>TH</td>
<td>Thyroid Hormone</td>
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<tr>
<td>THL</td>
<td>National Institute for Health and Welfare (Finland)</td>
</tr>
<tr>
<td>TR</td>
<td>Thyroid Hormone Receptor</td>
</tr>
<tr>
<td>UNC</td>
<td>University of North Carolina</td>
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<tr>
<td>USAID</td>
<td>U.S. Agency for International Development</td>
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<tr>
<td>USG</td>
<td>U.S. Government</td>
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<td>U.S. PFI</td>
<td>U.S. Pediatric Formulations Initiative</td>
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<tr>
<td>UTI</td>
<td>Urinary Tract Infection</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
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 and U.S. Department of Health and Human Services 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, 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 four-sections representing the: OD, Division of Extramural Research (DER), 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 a description of international trainees and a list of key publications.
Office of the Director

The NICHD Office of the Director (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

WHO Consultation on Operationalizing Nurturing Care (Geneva, Switzerland, August 2017). There is a growing recognition that protecting, promoting and supporting early childhood development is essential for the transformation that the world seeks to achieve in the next 15 years, guided by the United Nations Sustainable Development Goals. In 2016, the Lancet series, “Advancing Early Childhood Development: from Evidence to Scale,” coined the concept of “nurturing care” referring to a cluster of interventions related to health, nutrition, responsive caregiving, safety and security, and early learning. In August 2017, WHO convened a technical meeting to review scientific and programmatic evidence for a core package of early childhood interventions that support responsive caregiving and provision of nurturing care. This WHO consultation was the first step towards development of implementation guidance for policy makers on how to operationalize nurturing care and support cognitive development of children in the critical early years of life. The final document will be part of the documentation that WHO will make available to Members States during the 71th World Health Assembly in May 2018, in support of the annual progress report on the Global Strategy for Women's, Children's and Adolescents’ Health. OGH represented NICHD and NIH at this August 2017 WHO Consultation on Nurturing Care and will participate in working groups in preparation for the 2018 World Health Assembly.

NICHD Global Health Writing Teams for Pediatrics Journal Supplement. OGH staff worked closely with 24 authors and NICHD co-editors to review and finalize 7 manuscripts for a journal supplement in Pediatrics on, “Research Gaps at the Intersection of Child Neurodevelopment, Nutrition, and Inflammation.” This journal supplement is a follow up activity to the NICHD Global Health Consultation Meeting held on February 11-12, 2015 on this topic. This NICHD meeting included over 80 researchers, program implementers, and
policy makers in global health, including representatives from the Bill & Melinda Gates Foundation (BMGF), World Health Organization (WHO), U.S. Agency for International Development (USAID), U.S. Department of Health and Human Services (DHHS), U.S. Centers for Disease Control and Prevention (CDC), Institute of Medicine (IOM), World Bank, Grand Challenges Canada, and the Sackler Institute.

**National Institutes of Health (NIH) – Bill and Melinda Gates Foundation (BMGF) Collaboration.** [http://www.nih.gov/about/director/10082014_statement_gates.htm](http://www.nih.gov/about/director/10082014_statement_gates.htm) 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, TB drug discovery, etc. This has included annual NIH-BMGF Global Health Meetings held on the NIH campus, with NICHD representatives included 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 this past year included secondary referral to BMGF of NICHD SBIR/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.

**U.S. National Academy of Medicine “Investing in Young Children” Forum (iYCG).** In January 2014, the National Academies' Board on Global Health and Board on Children, Youth, and Families launched the “Forum on Investing in Young Children Globally.” The goal of the Forum was to establish a community of international stakeholders to identify innovative international research and to translate this evidence into policies and practices in health, nutrition, education, and social protection for children and their families in resource-limited settings. The OGH Director represented NICHD on the iYCG Executive Committee and the Mental Health and Development Delays and Disabilities (MENDDD) Working Group, and several planning committees for iYCG regional meetings. The MENDDD working group prepared a manuscript to be published in the PLOS One journal titled, “Global services and support for children with developmental delays and disabilities: Bridging research and policy gaps.” A series of regional reports and communications resources have been developed over the past three years, and a summary report describing the achievements of the overall iYCG Forum was published in the spring of 2017 and is posted on the National Academies website.

**NIH IC AIDS Coordinator and Chairperson of the NICHD AIDS Coordinating Committee.** The OGH Director has served in the dual capacity of NIH IC AIDS Coordinator
for trans-NIH HIV/AIDS activities, and as the internal Chairperson for the NICHD AIDS Coordinating Committee. The NICHD AIDS Coordinator serves on the Executive Committee of the Office of AIDS Research (OAR), facilitated NICHD’s response to the revision of the Trans NIH HIV/AIDS Strategic Plan, and was actively involved in the review of the NICHD HIV/AIDS portfolio in response to the NIH Directors Overarching HIV/AIDS Priorities published in August 2015. The Chairperson of the NICHD AIDS Coordinating Committee, also works in close collaboration with the NICHD Director of Extramural Research, NICHD Science Director, Office of Budget, and several NICHD branches on development of extramural HIV-related initiatives. Additional NICHD proposals were prepared in consultation with NICHD program staff for the FY16 Common Pool Funds and FY17 HIV/AIDS Discretionary Funds, as well as approval requests for funding announcements, administrative supplements, funding plans, review of HIV/AIDS prorating criteria, etc. The NIH and NICHD AIDS portfolios include both domestic and global research activities.

**USG “Children in Adversity” Initiative.** NICHD and other NIH representatives serve on the 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. A NICHD staff member served as co-editor of a special supplement in the journal *Child Abuse and Neglect*, and several 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 Workshop on Stigma in Health Research** (NIH Campus in Bethesda, Maryland, June 5-7, 2017). OGH was the NICHD representative on a trans-NIH Planning Group led by the Fogarty International Center for a workshop on stigma in health research. Follow on activities include several scientific teams writing papers that describe recent science advances and research gaps in stigma research. FIC and OAR have also taken the lead in developing a funding announcement that addresses stigma in HIV/AIDS populations, which will include NICHD’s participation.

**Fellowship Meeting of the Vanderbilt, Emory, Cornell, & Duke (VECD) Fogarty Consortium** (Vanderbilt University, Nashville, Tennessee, January 2017). OGH represented NICHD on an NIH Panel at the VECD Fellowship Meeting at Vanderbilt University to discuss research and technology gaps and opportunities at the interface of global infectious and non-communicable diseases in low resource settings. Attendees included U.S. and international researchers, clinicians, policymakers, and funding partners, as well as fellows and alumni from all Global Health Fellows Consortia.
**NIH Workshop on Conducting Health Research in Humanitarian Crises.** 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 will represent NICHD 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. This project seeks to: (1) encourage more, high-priority health research in humanitarian crises; (2) increase collaboration between researchers and humanitarian organizations; and (3) identify strategies to ensure optimal uptake of evidence into policy and practice in humanitarian crisis environments.

**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, and Congressional senior leadership in Uganda, Japan, China, and Vietnam.

- **Coordination of Visits by Foreign Delegations.** Participated in the coordination of meetings and preparation of briefing materials for visits by foreign delegations e.g., Greek Ambassador to the United States, Rwandan Minister of Health, NIH/HHS Representatives in the US Embassy in India, among others.

- **PL109-95 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 PL109-95 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, 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
- NIH-BMGF Child Health and Development Working Group. Representative: Vesna Kutlesic Isaacs
- NICHD OD Co-Funding Working Group. Representative: Vesna Kutlesic
- NICHD Zika Round-up Working Group. Representative: Vesna Kutlesic
- HHS/USAID/OMB Zika Coordination Group. Representative: Vesna Kutlesic
- OAR Executive Committee. Representative: Vesna Kutlesic
- NICHD AIDS Coordinating Committee. Representative: Vesna Kutlesic
- NICHD Reproductive Health Working Group. Representative: Vesna Kutlesic
- Fogarty IC International Representatives Working Group. Representative: Vesna Kutlesic
- Trans-NIH Global Health Research Working Group. Representative: Vesna Kutlesic
- Trans-NIH International Clinical Research Subcommittee. Representative: Vesna Kutlesic
- National Academies Investing in Young Children Forum Executive Committee. Representative: Vesna Kutlesic
- USG Children in Adversity Strategy Working Group. Representative: Vesna Kutlesic
- FIC BRAIN Disorders Initiative Working Group. Representative: Vesna Kutlesic

Point-of-Contact

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Office of Health Equity (OHE)

Mission
The OHE, within the Office of the Director at the NICHD, develops, coordinates, and supports programs and initiatives that strengthen the Institute's commitment to ensuring the health and well-being of all children, adults, families, and communities. OHE's mission is to inform the public about issues related to health disparities; develop scientific leadership and initiatives in colleges and universities worldwide that will encourage, facilitate, and increase participation of diverse populations and developing nations in biomedical and behavioral research endeavors; and disseminate evidence-based research findings that can be used to ultimately eliminate differences in health outcomes. The OHE works closely with other NICHD Branches and Offices as well as other NIH organizations to accomplish its mission.

There are no international activities to report at this time.

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 CDB Branch 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 Fogarty International Center 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 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 Low and Middle-Income Countries (LMICs) will fail to reach their developmental potential as adults, predominantly due to poverty, poor health and nutrition, and inadequate cognitive and psychosocial stimulation. Early childhood development (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.

Neural, Cognitive, and Behavioral Development. The Branch supports a study of the long-term effects of prenatal testosterone exposure on the sexual differentiation of brain structures and behavior in two clinical disorders of sex development syndromes: congenital adrenal hyperplasia and complete androgen insensitivity syndrome. Researchers are located in the United Kingdom (UK) and are using a unique UK-based registry of individuals with these rare conditions from which to recruit participants. Information obtained through this project will enhance understanding of the neural mechanisms involved in sexual differentiation of the human brain and behavior and will also be relevant to many psychological disorders that differ by sex.

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 also supporting a collaboration with Norway to investigate the relationship of maternal and child infection, fever and immune disorders to ADHD risk, and 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 and children during pregnancy and at birth and determine their association with ADHD risk, as well as examine the role of specific infectious agents in 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 UK.

**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 on children's mental and physical health and on socioeconomic indicators. 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. In a randomized, controlled study in Zambia, psychosocial counseling is being compared to trauma focused-cognitive behavioral therapy as a means of reducing HIV risk behaviors, improving emotional and behavioral health, social support, and overall well-being in OVC affected by HIV/AIDS. Results from this study will inform future programs for OVC by addressing psychosocial problems, mental health, and HIV. Another study in Zambia seeks to longitudinally assess the cognitive development and educational outcomes of 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 Contraception Research Branch 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 FY16 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 FY16 which is one of the first studies of the relationship between the use of injectable contraceptives (DMPA and norethisterone enanthat) and the incidence of both HIV and HSV-2. It will also study their effects on other common sexually-transmitted infections and sexual risk behaviors in this vulnerable population, which has unusually high rates of HIV and unwanted pregnancies.

International Guidelines for Family Planning. Through an interagency agreement with the U.S. Agency for International Development (USAID) that began twelve years ago, CRHB continued in FY16 to provide both financial and technical support to the World Health Organization’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 Bill & Melinda Gates Foundation (BMGF). CRB staff continued to work with the BMGF and other organizations in FY16 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

- CRB staff continued a Collaborative Research and Development Agreement with HRA (Paris, France). Products resulting from this collaboration include ella®/ellaOne® for emergency contraception and a novel drug for uterine fibroids that is pending submission to the FDA and is currently sold in Europe as Esmya® and in Canada as Fibristal®.

- CRB continued funding contracts in fy16 supporting a multisite male contraceptive efficacy trial that includes the following foreign sites: Karolinska Institute, Sweden; University of Chile; University of Manchester, United Kingdom (UK); University of Bologna, Italy; University of Edinburgh, UK; and University of Nairobi, Kenya.

International Partnerships

- CRB continued its ongoing collaborations with the World Health Organization (WHO) throughout FY16. Through CRB’s interagency agreement with USAID, the process of collecting and analyzing the world’s literature on contraception continued to provide the background for the continuously revised WHO documents described above.

- 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.
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 between: 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. [See https://www.nichd.nih.gov/about/org/der/branches/dbsvb/Pages/overview.aspx for details.]

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 ~6% 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 aged 1-4 years (#2 cause of death), 5-14 years (#3) and 15-24 years (#6). Birth defects are, therefore, one of the most important childhood healthcare issues. However, little is known about the causes of most birth defects, and there are few truly effective prevention strategies. This collaboration with investigators in China focuses on one of the top five most common birth defects worldwide: neural tube defects (NTDs), with the goal of understanding the underlying causes in humans and developing of 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 integrate 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.

Multi-National 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 and Sweden:** 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 US research groups that have the necessary cohorts required to perform the validation studies. Consequently, the one investigator performing these studies in the US 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.
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.

**Slovenia**

This project is aimed at understanding the mechanisms that control growth and multicellular development in *Dictyostelium*, the cellular slime mold. This model organism was chosen because it is the simplest possible multicellular organism in which to identify and understand the networks of interacting genes involved in the basic processes of growth and development. Over the years, this project has taken a functional genomics approach to high-throughput mutant phenotyping, transcriptional profiling, and computational modeling that allowed functional inferences for hundreds of genes. Currently, their efforts are focused on understanding transcriptional control during development and bacterial recognition, both during the growth of solitary *Dictyostelium* amoebae and in the context of an innate immune response during their development. They are testing which regulators are responsible for the dramatic transcriptional changes that accompany *Dictyostelium* development. Using RNA sequencing (RNA-seq) and Chromatin Immunoprecipitation (ChIP-seq) to identify genes that are directly regulated by these transcription factors, the investigators are developing computational techniques and integrative data mining procedures to infer gene function and to construct consensus gene network models for use as scaffolds upon which we can propose additional experiments and add layers of information from other experiments. This work will help establish this amoeba as a model system for the study of innate immunity, leading to the development of tools and techniques that can be applied to understanding the response of eukaryotic cells to bacteria. The foreign component in the Slovenia provides the computational modeling that allows interpretation of the genetic data generated by the other collaborators. In spite of the fact that this work uses such simple organisms, the computational methods and tools that have been developed over the years by this group of investigators can be applied to other model systems and human, improving our ability to predict gene function in development and in disease.

**United Kingdom**

One of DBSVB's goals is to better understand the biophysics of developmental processes. Another project funded in the United Kingdom looks at the implications of tissue stiffness on axonal guidance during brain development. During development of the nervous system, neurons grow over large distances and need to be precisely guided to their targets. Errors in neuronal growth and guidance may lead to severe defects such as neurodevelopmental disorders and the failing of neuronal regeneration after spinal cord injuries. Numerous studies have been done to elucidate the biochemical mechanisms of axon guidance. However, little is known about the mechanical and biophysical interactions of neurons with their environment. This project will elucidate, for the first time, how the mechanical properties of the brain contribute to proper axon guidance. Using Atomic Force Microscopy (AFM), this project will generate real-time brain stiffness maps in the Xenopus embryo.
while simultaneously measuring retinal ganglion cell axon growth to study the effect of tissue stiffness on axon pathfinding over different developmental stages. Included are studies that will use physical, genetic, and chemical approaches to study how changes in tissue stiffness affect axonal pathfinding. This research may show definitively that stiffness is an important guidance cue for the developing nervous system, thus justifying its strong potential impact.

**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.

There are no international activities to report at this time.

**Point-of-Contact**

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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. Obstetric fistula (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 Mutilation. Female genital mutilation or cutting (FGC) 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 and can result in death from unclean practices, obstructed labor, and chronic vulvar/vestibular pain, urination problems, and sexual dysfunction. The World Health Organization estimates that over 125 million girls and women alive today have undergone this procedure. As there are still immigrant communities in the United States carrying out this procedure, 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.
Recent Achievements in International Health
There have not been any specific achievement in this area over the past year due to the relatively recent initiation of the current projects.

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 IDD Branch sponsors research and research training aimed at preventing and ameliorating intellectual and related developmental disabilities. The IDD Branch has a longstanding history of providing support for a diverse portfolio of research projects, training programs, and research centers dedicated to promoting the well-being of individuals with intellectual and developmental disabilities (IDD). When the Institute was created 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 intellectual and developmental disabilities.

The mission of the IDD Branch 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 Intellectual and Developmental Disabilities (IDD); (2) Understand the Complexity of Comorbid Symptoms; (3) Improve Screening and Early Diagnosis and Develop Early Interventions and Treatments; (4) Natural
History and Neurobiological and Behavioral Transitions; (5) Develop Appropriate, Valid Biomarkers and Preclinical and Clinical Outcome Measures; and (6) Translational and Implementation Research.

Intellectual and developmental disabilities 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 IDD Branch supports a portfolio of research and conference grants that serve to identify the prevalence of IDD in low- and middle-income (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 IDD Branch is currently coordinating NICHD activities on cookstove-related household air pollution.

**Major International Initiatives over the Past Year**

N/A

**Recent Achievements in International Health**

- The IDD Branch participates in the Fogarty International Center-led, “Brain Disorders in the Developing World: Research across the Lifespan Initiative.” 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. CNS malaria survivors receiving training showed significant improvements and the CCRT program was 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.

- 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 US and Brazil will undertake a comprehensive longitudinal study of infants with congenital Zika syndrome and their families to investigate the early childhood development, potential treatment and family
adaptation. This project has the potential to fill the knowledge gap about the developmental course of congenital Zika syndrome, the treatment needs of children and support for family caregivers.

- Another international study has developed and is validating a reliable and valid tool to assess and monitor children's development in lower- and middle income countries. The International Guide for Monitoring Children's Development (IGMCD) has been developed in four LMIC countries—Argentina, India, South Africa, and Turkey—making it applicable for international use. In addition to monitoring children's development, the IGMCD includes an assessment of biologic and psychosocial risk factors that affect children's development.

- While mortality from premature births in Sri Lanka has decreased by 50%, 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 proof of concept study by adapting mobile health technologies to transfer ambulatory EEG and evoked potential recording performed remotely and transferring the data to a central hub for analysis. This will expand care for children with neurological disorders related to premature birth.

- The IDD Branch participates in the Office of Rare Diseases Research-led Rare Diseases Clinical Research Network, which promotes natural history studies, clinical trials, and treatment development 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.

- NICHD 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 study is to identify biomarkers to better understand the pathophysiology of FSHD muscle weakness and to develop animal models and therapeutic technologies for the treatment of this condition.

- DS-Connect® (http://DSConnect.nih.gov) 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 3500 registrants in the United States and abroad and has supported recruitment for over a dozen research projects through its membership. International partners include Down Syndrome International (DSi), 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 rolling out a responsive web design to facilitate access on a wide variety of mobile platforms.

- 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 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**

- An Independent Scientist Award (K02) awardee has established birth cohorts in China to determine whether exposure to high levels of ambient air pollutants during pregnancy is associated with reduced fetal growth, and whether the impact of exposure on fetal growth varies by windows of exposure during pregnancy (Branch: PDB).

- In a study of 37,870 pregnant women in six of the Global Network sites, women who lived in households using polluting fuels were 15% more likely to have a low birth weight (LBW) baby than those living in households using clean fuels. This risk was over and above other risk factors for having a LBW 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% more likely to have a stillborn baby or baby who died in the first seven 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).

- NICHD is partnering with NHLBI, NCI, NIEHS, the NIH Common Fund and the Bill and Melinda Gates Foundation to support a randomized controlled trial (RCT) of introducing liquefied petroleum gas (LPG) cookstoves in 4 countries: India, Guatemala, Peru and Rwanda. Primary outcomes will 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 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 (Branch: IDDB).

**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 MPID Branch 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.

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. NICHD funds 15 domestic sites including Puerto Rico and 14 international sites in five countries; Argentina, Brazil, Kenya, Tanzania, and Thailand. Through collaborations with the National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Mental Health (NIMH), Centers for Disease Control and Prevention 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 datacenters in Africa, Asia, 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 multi-regional studies to evaluate the effect of HIV and its treatment on children in resource-limited countries. Furthermore, these data
continue to inform the World Health Organization (WHO) estimates of the global pediatric HIV epidemic.

**NICHD HIV Prevention Trials Network (HPTN) 040 Clinical Trial:** The overall mission of the [HIV Prevention Trials Network](https://www.hptn.org) (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 (MTC) HIV transmission, 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 yet diagnosed until delivery and did not receive anti-HIV drugs during pregnancy. While the trial is now completed, additional secondary analyses of the data and stored samples are ongoing. These resources are available through NICHD DASH ([https://dash.nichd.nih.gov/](https://dash.nichd.nih.gov/)).

**The NICHD Latin American/Caribbean International Site Development Initiative (NISDI):** The NICHD International Site Development Initiative (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 drug 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 six to twelve months postpartum. The NISDI pediatric protocol described the demographic, clinical, immunologic, and virologic characteristics of children and adolescents with HIV. There have been multiple 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 had the majority of participants. Analyses of the databases and stored samples remain ongoing, and data and specimens are now available via the NICHD Data and Specimen Hub ([https://dash.nichd.nih.gov/](https://dash.nichd.nih.gov/)).

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 in international studies 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:
• MPID/NICHD in collaboration with Fogarty International, other NIH institutes, and Office of the Global AIDS coordinator released an RFA entitled “Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA)” in FY 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 FY 2012 and FY 2014 that are currently funding active projects:
  
  o **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.

  o **Disclosure of HIV-Status to Children in Low- and Middle-Income Country 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.

  o **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.

  o **NIH/PEPFAR Collaboration for Advancing Implementation Science in Prevention of Maternal-Child HIV Transmission (RFA HD-12-210).** MPID/NICHD, together with the Office of the Global AIDS Coordinator
(OGAC), developed this RFA for implementation science projects that will inform the President’s Emergency Plan for AIDS Relief (PEPFAR) as they develop more efficient and cost-effective methods to deliver proven interventions for prevention of maternal-child HIV transmission (PMTCT). This NICHD-led initiative represents a multi-agency (OGAC, Centers for Disease Control and Prevention and U.S. Agency for International Development PEPFAR partners) and multi-institute (NICHD, Fogarty International Center, 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 PMTCT 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 Mother-to-Child HIV Transmission (RFA HD-14-027).** This RFA solicited R01 grant applications to evaluate the safety and overall population-based effectiveness of implementation of triple ARV drug strategies for PMTCT 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 PMTCT 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) new scientific research priority in 2015 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 (antiretroviral therapy (ART) initiated at < 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 life) 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.

- MPIDB/NICHD in collaboration with NIAID, the National Institute on Drug Abuse, and NIMH issued an internationally-focused request for applications (RFA) in FY 2015: Increasing Access and Uptake of HIV Testing and Counseling and Appropriate HIV-Related Services for Adolescents in Low- and Middle-Income Countries (RFA HD-15-17). This RFA solicited 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.

- MPIDB/NICHD issued the following FY16 RFA that is currently funding active projects: HIV-Infected Adolescents: Transitioning from Pediatric to the Adult Care Settings (RFA-HD-033/034). The five awarded grants offer a range of approaches and geographical locations (Kenya, Nigeria, 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.

- MPID/NICHD issued the following RFA for FY 2017, in collaboration with NIMH: Understanding and addressing the multi-level influences on uptake and adherence to HIV prevention strategies among adolescent girls and young women in sub-Saharan Africa (RFA-MH-17-550/555).


**TB in children and pregnant women**

The MPID Branch 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 RFA’s include:

- RFA-HD-006 Diagnostic and Pharmacokinetic Research in Pediatric HIV/TB Co-Infection and RFA-HD-09-015 (R01) and 016 (R21), Pharmacokinetic Research in Pediatric HIV/TB Co-Infection. Three international grants 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. Several grants funded through these RFAs as well as investigator initiated grants are evaluating novel assays to diagnose TB in children and the use of dried blood spots for measurement of TB drug levels in low resource settings, including Ghana, Kenya, South Africa, and Uganda.

- A clinical trial to assess optimal treatment of TB meningitis will start soon in Malawi and India. This is the first for TB meningitis since 1986.
- NIH/PEPFAR Collaboration on Implementation Science for HIV: Towards an AIDS free generation RFA-AI-15-020 (R01) NIH, in collaboration with the Office of Global AIDS Coordinator (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. MPID/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 in Nigeria.

**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, a clinical trial evaluated ways to improve prevention of mother-to-child hepatitis B virus (HBV) transmission in pregnant women with hepatitis B infection who are hepatitis B e antigen positive (HBeAg) with normal liver function tests and who are not HIV infected. The study assessed the efficacy and safety of giving the anti-HBV drug tenofovir versus placebo, in addition to standard infant HBV vaccine and immune globulin, to prevent transmission to their infants.
**Zika**

- Rapid Assessment of Zika Virus (ZIKV) 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, MPID/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.

**HIV Prevention and Treatment in Children**

- 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 six or twelve 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 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 two 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 PMTCT program that includes risk reduction and medication adherence by HIV-positive pregnant women in Phase I. The male partners will be added to 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 15-24 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.

• 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.

**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 mother to child transmission (PMTCT) 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 PMTCT 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.

Recent Achievements in International Health

• A clinical trial in Uganda demonstrated that dihydroartemisinin-piperaquine was superior to sulfadoxine-pyrimethamine for preventing malaria in pregnant women. (N Engl J Med 2016; 374:928-39)

• Researchers found a strong relationship between the number of malaria bouts and children’s mental and motor development scores at ages 2 and 3 years. Children who had been exposed to HIV at birth were also more likely to have lower mental development scores at age 3. The findings indicate that early bouts of malaria reduce mental development in young children, and anemia strengthens the relationship. (Malaria Journal 2016;15:210)

• Improved bone health found in children with HIV in South Africa receiving efavirenz. (AIDS 2016;30:2459-67)

International Partnerships

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

- WHO Paediatric Antiretroviral Drug Optimization Working Group. Member: Dr. Rohan Hazra
- WHO Infant Diagnosis Technical Working Group. Member: Dr. George Siberry
- WHO Working group to develop PrEP implementation module for adolescents. Member: Dr. Bill Kapogiannis
- UNICEF/UNITAID Adolescent PrEP Program Technical Advisory Group. Member; Dr. Bill Kapogiannis
- PEPFAR Pediatric/Prevention of Mother-to-Child HIV Transmission Technical Working Group. Member: Dr. George Siberry
- Scientific and Technical Advisory Committee (STAC) for the International AIDS Society Collaborative Initiative on Pediatric HIV Research (CIPHER). Member: Dr. Rohan Hazra

Point-of-Contact

Dr. Rohan Hazra  
haazrar@mail.nih.gov  
301-435-6868

Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB)

Mission

The overarching goal of the OPPTB is to centralize 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 used with children and adolescents. The PTN has developed international collaborations with clinical sites in Canada, Israel, Singapore, and the United Kingdom to conduct clinical studies as part of the
BPCA Program. Currently, the international sites are participating in a clinical study (i.e., opportunistic study) that evaluates pharmacology data on children receiving standard of care treatments for various diseases.

**Development of Global Pediatric Clinical Trials Network.** Several meetings have been held to discuss the formation of a global pediatric clinical trials network. This would be a network formed with pharma, academia, U.S. federal government agencies (including the NIH and the Food and Drug Administration), and the European Medicines Agency.

**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.

- Global Research in Pediatrics (GRiP) Initiative. Dr. Anne Zajicek is regularly updated on the U.S.-European Union activities of GRiP Initiative. Steering Committee of the International Neonatal Consortia. Member: PENDING

- Therapies Scientific Committee, International Rare Diseases Research Consortium (IRDiRC). Member: Dr. Katerina Tsilou
Pediatric Growth and Nutrition Branch (PGNB)

Mission

As the focal point within NICHD for nutrition science and pediatric endocrine research and training, the PGNB 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, neurodevelopment (cognition, 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 breast milk and their roles in infant health, with an emphasis on the immunologic properties of breast milk, the intestinal microbiome, and the role of breast 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 osteoporosis 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 including:

**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 becomes six years old and then again at age ten.

**The 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 pre-eclampsia quintuples, from 3% to 15% over the range of fasting plasma glucose noted above. The rates of operative delivery doubled from 13% to 26% over the same range of glycemia, despite the blinding. NICHD and the National Institute of Diabetes and Digestive and Kidney Diseases are collaborating on a follow-up study of the offspring of the women in this study to ascertain rates of obesity, beta cell failure, type 2 diabetes, and metabolic syndrome.

**The PGNB portfolio 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.

**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 6-21 years of age and are being examined again at 12-27 years of age. The large sample size and twin study design will yield significant information on the epidemiology of the metabolic syndrome

**International Partnerships**

PGNB has established a close working relationship with 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, U.S. Food and Drug Administration, USAID, U.S. Department of Defense, WHO, UNICEF, World Food Programme, BMGF, and numerous other organizations and members of the private sector engaged in global efforts to address the role and impact of food and nutrition on global health.

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

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

**Point-of-Contact**

Dr. Daniel Raiten
raitend@mail.nih.gov
301-435-7568

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**Pediatric Trauma and Critical Illness Branch (PTCIB)**

**Mission**

The PTCIB is a new branch at NICHD that 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
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

St. George Hospital University Medical Center, Beirut, Lebanon

This newly funded study 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)**

Fogarty's Center for Global Health Studies (CGHS) is leading a project to address barriers and solutions to conducting research in emergency or acute care settings in low-and middle-income countries (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 will 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

- U.S. Agency for International Development Children in Adversity –PL109 95 Working Group. Representative: Dr. Valerie Maholmes
- Collaborative for Enhancing Emergency Care Research in LMICs (CLEER) Working Group. Representative: Dr. Valerie Maholmes

Point-of-Contact

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maholmev@mail.nih.gov
301-496-1514

Population Dynamics Branch

Mission

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

Data Archiving

The Population Dynamics Branch uses the standard R01 Research Project Grant mechanism to support documenting, archiving, and dissemination of many international datasets, making these resources available to the research community. Projects that curate multiple data sets also harmonize data across multiple countries and/or time periods and provide documentation in English, thereby substantially increasing the usability of these data sets. The multi-country and multi-time period data sets 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>Multi-generational demographic data</td>
<td>China</td>
<td>R01HD070985</td>
<td>Campbell, Cameron UCLA</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>
</tr>
<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>North Atlantic censuses, micro- and meta data</td>
<td>Albania, Britain, Canada, Denmark, Egypt, Germany, Iceland, Ireland, Mexico, Norway, Sweden, United Kingdom, United States</td>
<td>R01HD052110</td>
<td>Ruggles, Steve University of Minnesota</td>
</tr>
</tbody>
</table>
The Population Dynamics Branch sponsored a new 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 Data Sets (R03)* PAR-16-149.) Many of the PDB grants funded through this program will make available data from international health and development research projects.

<table>
<thead>
<tr>
<th>Dataset/Description</th>
<th>Country(ies)</th>
<th>Grant</th>
<th>PI/Institution</th>
</tr>
</thead>
<tbody>
<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>
<tr>
<td>Chitwan Valley Family Study</td>
<td>Nepal</td>
<td>R03HD092516</td>
<td>Axinn, William University of Michigan</td>
</tr>
<tr>
<td>Cross-National Equivalent Files: Health and demographic measures</td>
<td>United States, Germany, Canada, United Kingdom, Australia, Switzerland, Korea, Russia</td>
<td>R03HD091871</td>
<td>Lillard, Dean Ohio State University</td>
</tr>
<tr>
<td>Indian Human Development Surveys</td>
<td>India</td>
<td>R03HD091315</td>
<td>Vanneman, Reeve University of Maryland</td>
</tr>
<tr>
<td>Fertility and reproductive health</td>
<td>United States, Uganda, Bangladesh</td>
<td>R03HD091468</td>
<td>Finer, Lawrence Guttmacher Institute</td>
</tr>
</tbody>
</table>
Developing Methodology to Improve Global Health

The Population Dynamics Branch 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 middle- and low-income countries that lack adequate vital registration systems and health information systems.

### Purpose of Methodology

<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 prevalence and the size of at-risk groups in sexually transmitted infection epidemics</td>
<td>All countries</td>
<td>R01HD054511</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 and South Asia/Elsewhere</td>
<td>R21HD087811</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>
</tbody>
</table>

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

### Global Partnerships

The Population Dynamics Branch supports three grants under the Global Partnerships for Social Science AIDS Research (R24), [https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-13-012.html](https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-13-012.html). The program supports collaborative grants between institutions in the United States, or other developed countries, and research institutions in developing countries affected by the HIV/AIDS epidemic, with the goal of strengthening the research infrastructure of local institutions in developing countries and supporting small portfolios of research on HIV/AIDS. The three partnerships supported are in Vietnam, South Africa, and Haiti; all three involve a U.S. partner.
<table>
<thead>
<tr>
<th>Country/Major Foreign Institution</th>
<th>Grant</th>
<th>PI/U.S. Institution</th>
</tr>
</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>
<tr>
<td>Haiti/State University of Haiti</td>
<td>R24HD077946</td>
<td>Lescano, Celia/University of South Florida</td>
</tr>
</tbody>
</table>

**Supporting Offices of Research and Sponsored Programs**

The Population Dynamics Branch 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 low- and middle-income countries in the Caribbean and South America are eligible to apply. The Branch currently supports programs in Zimbabwe, Peru, and Zimbabwe.

<table>
<thead>
<tr>
<th>Country</th>
<th>PI/Institution</th>
<th>Grant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda</td>
<td>Kiweewa, Francis/Makerere University</td>
<td>G11HD085538</td>
</tr>
<tr>
<td>Peru</td>
<td>Chan, Michelle/Universidad Peruana Cayetano Heredia</td>
<td>G11HD088113</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>Kangwende, Rugare/Africa University</td>
<td>G11HD088121</td>
</tr>
</tbody>
</table>

**Scientific Pipeline**

The Branch supports 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>
<tr>
<td>Effects of a national vaccination campaign on reducing disparities in urban-rural child mortality</td>
<td>Turkey</td>
<td>K01HD084709</td>
<td>Alsan, Marcella Stanford University</td>
</tr>
<tr>
<td>Effects of introduction of antibiotics to reducing SES disparities infectious-disease mortality</td>
<td>Italy</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Effect of economic and environmental factors on households' adoption of hygienic practices</td>
<td>India</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Topic</td>
<td>Country studied/Applicable to</td>
<td>Grant</td>
<td>PI/Institution</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
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<td>-----------------------------------------------------</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Measuring and 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 University of California Los Angeles*</td>
</tr>
<tr>
<td>Adolescent fertility and social networks</td>
<td>Honduras</td>
<td>K01HD087551</td>
<td>Shakya, Holly University of California San Diego</td>
</tr>
<tr>
<td>Intervention research addressing reproductive coercion among medically underserved female adolescents</td>
<td>Mexico</td>
<td>K23HD084756</td>
<td>Servin, Argentina University of California San Diego</td>
</tr>
<tr>
<td>Role of gender inequality and food insecurity on maternal and child health</td>
<td>Nepal</td>
<td>K01HD086281</td>
<td>Diamond-Smith, Nadia University of California, San Francisco</td>
</tr>
<tr>
<td>Influence of service delivery factors on contraceptive use</td>
<td>Kenya</td>
<td>K99HD086270</td>
<td>Tumlinson, Katherine University of North Carolina Chapel Hill</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>
</tbody>
</table>

*See also Developing Methodology section; LMIC=Low- and middle-income countries

**International Partnerships**

N/A

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

N/A

**Point-of-Contact**

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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
The Global Network for Women's and Children's Health Research (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.

Current studies in the Global Network include:

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 lower-middle income countries, including the Democratic Republic of the Congo, Guatemala, India, Kenya, Pakistan, and Zambia. All pregnant women in participating sites are registered and their outcomes tracked for six 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 as the basis of 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 poor 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. Enrollment began in August 2013, and an initial set of analyses have been completed. Infants were followed through age 2 years to assess growth and neurodevelopmental outcomes.

Ultrasound Study. This multi-country 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 RCT anywhere in the world to test the value of routine antenatal ultrasound screening to improve pregnancy outcomes.

Aspirin Supplementation for Pregnancy Indicated Risk Reduction in Nulliparas (ASPIRIN). This multi-country 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 (ASA), initiated between 6 0/7 weeks and 13 6/7 weeks gestational age (GA) and continued to 36 0/7 weeks GA compared to an identical-appearing placebo. The primary objective is to determine whether daily LDA initiated between 6 0/7 -13 6/7 weeks GA and continued to 36 0/7 weeks GA reduces the risk of preterm birth. Secondary outcomes of interest are the rate of preeclampsia/eclampsia, small for gestational age (SGA), perinatal mortality and the impact of malaria on pregnancy. Enrollment was initiated in February 2016 and is anticipated to be completed in 24 months. A total of 11,920 women will be enrolled (5,960 in each arm).

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 inter-related. 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 being developed.

**Cytomegalovirus Vaccines: Reinfecion and Antigenic Variation, Brazil.** The goal of this study is to define the natural history and the characteristics of human cytomegalovirus (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% of live births in the United States and exceeds 1% 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 (UNC) 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 UNC at Chapel Hill. This program will provide two 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's of Science in Clinical Research, providing the necessary theoretical framework for later practical training;
- Leverage the vast global health expertise at the UNC School of Medicine and Gillings School of Global Public Health to expand the scope and depth of academic mentorship; and
- Introduce the UNC 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 three-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 (PTD) in Relation to Partner Abuse, Mood, and Anxiety (Peru). There is increasing evidence that PTD is a complex cluster of problems with a set of overlapping factors and influences. As recently summarized by the Institute of Medicine (IOM), the causes of PTD 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 PTD 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 PTD risk with mood disorder and anxiety disorder early in pregnancy and the extent to which risk of PTD is influenced by alternations in multiple biological markers of maternal neuroendocrine, vascular, and immune status.

Triggers of Abruptio Placentae: A Case-Crossover Study of an Ischemic Placental Disease (Peru). Abruptio placenta (AP) is a life threatening obstetric condition that complicates roughly 1-2% of all pregnancies. Results from previous studies suggest a significant genetic component in the pathogenesis of AP. The investigators are conducting a large multi-center 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 low- and middle-income countries (LMICs). Preterm birth and infections account for the majority, or 60%, of the estimated four million annual global neonatal deaths. About 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.

**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. The findings from this study will help doctors around the world in treating infants with low blood sugar and could help reduce brain injury. Several recent papers from this study have begun to provide better definitions for neonatal hypoglycemia.

**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. The study is expected to be completed by 2016.

**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 a FDA-registered probiotic 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% 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 accepted for publication 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, “SUPPORT Trial,” 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.

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% 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% 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.

**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 23-26 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 (PMA). These trials have often changed clinical practice.

**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.

**Human Placental Project Grants:** The following newly awarded grants to US 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, UK**
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.

**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 1st and early 2nd 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.

**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.

**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.

**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.

**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 MR methodologies to assess placental structure, microstructure and function across gestation, to integrate these into one comprehensive MR 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.

**Recent Achievements in International Health**

- **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 six months from birth to three years of age. Mothers were tested for malaria, filariasis, and schistosomiasis. It was found that 64% of the pregnant women were infected with parasites: 46% 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 (ACS). 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 ACS 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 ACS in community settings.

**Zika Virus (ZIKV)**

- **Rapid Assessment of Zika Virus (ZIKV) 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, MPID/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.**

**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 and Activities

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

N/A

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 and Risk of All-Cause Mortality, Functional, and Financial Burden: A Decade-Long Population Based Cohort Study**

Comorbidity is prevalent after traumatic brain injury (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**

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 spinal cord injury (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 Injured Knee**

The continuation of this prospective international cohort study of patients after acute unilateral anterior cruciate ligament (ACL) injury will help influence the care of the 200,000 or more Americans who rupture their ACL’s 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**

The purpose of this project is to improve physical activity (PA) measures in children with cerebral palsy (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 PA type, walking speed, and energy expenditure in ambulant children and adolescents with CP; 2) compare the accuracy of PA 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 PA levels of their patients to improve health and function. Improved
objective measures of PA will also enable health researchers to better understand the short- and long-term health benefits of regular PA and impact of PA on adverse health conditions associated with CP.

**Multi-Center Trial of Augmented Sensory Feedback in Children with Dyskinetic Cerebral Palsy**

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 cerebral palsy (CP), stroke, and traumatic brain Injury (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 multi-center 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 multidisciplinary 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 multi-disciplinary 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 Cerebral Palsy**

Unilateral cerebral palsy 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, SOCS3, 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**

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 Phantom Limb Pain (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 Traumatic Brain Injury and Post Traumatic Stress Disorder**

While mild Traumatic Brain Injury (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.

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

**Point-of-Contact**
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Mission and Activities

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 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 Statens Serum Institut (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 Statens Serum Institut (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 the Statens Serum Institut (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 the Statens Serum Institut (SSI), Copenhagen, Denmark, NICHD investigators are working on the Danish National Birth Cohort to investigate genetic and non-genetic determinants for the progression from gestational diabetes to type

- In collaboration with the Statens Serum Institut (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, Drs. C. Zhang, E. Schisterman.

- Global pregnancy collaborative consortium on major pregnancy outcomes (CoLab) Drs. C. Zhang and 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).

- World Health Organization advisory committee for developing a practice guide to implementation research on non-communicable disease prevention and control, Committee member: Dr. C. Zhang.

- In collaboration with investigators at the Statens Serum Institut (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.

Investigators Involved in International Activities

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

N/A

**Point-of-Contact**

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Division of Intramural Research (DIR)

The Division of Intramural Research 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 ensure that women and men have good reproductive health, that children are born healthy, and that people develop to live healthy and productive lives.

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, and approximately 300 postbaccalaureate, clinical, and postdoctoral fellows and graduate students.

Scientists and physicians in the NICHD Division of Intramural Research (DIR) are organized into 13 affinity groups (AGs). Each AG 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
DIR research addresses several fundamental questions:

1. 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?

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

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

4. When these processes go awry and disease ensues, how may we intervene in this pathologic sequence and treat the disease?

Child and Family Research Section

Investigator: Marc H. Bornstein, Ph.D.

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

Mission

Child and Family Research in the DIR was established with the broad aim of investigating human development and the ways in which human development is affected by variations in the conditions under which human beings are reared. Researchers investigate dispositional, experiential, and environmental factors that contribute to physical, mental, emotional, and social development in human beings across the first three decades of life. The research goals are to describe, analyze, and assess (i) the capabilities and proclivities of developing children and youth, including their physiological functioning, perceptual and cognitive abilities, emotional and social growth, and interactional styles; (ii) the nature and consequences of interactions within the family and the social world for offspring and parents; (iii) the effects on development of exposure to areas of childhood vulnerability (to
illness, to accidents, in risk taking); and (iv) influences on development of children's exposure to and interactions with the natural and designed environments.

**Major International Initiatives**

In addition to the United States, CFR international study sites include Argentina, Belgium, Brazil, Cameroon, France, Israel, Italy, Japan, Kenya, and the Republic of Korea. In all places, researchers pursue intra-cultural as well as cross-cultural comparisons.

In addition, CFR collaborates internationally with several groups over several topics:

- Canada: Maternal sensitivity
- Chile: Mother-infant interaction in low-socioeconomic status communities
- China and Japan: Neuroscience of parenting
- Italy: Childhood cancer survival, neuroscience of parenting, developmental disabilities (autism, Down syndrome), language development
- Peru: Prenatal and infant nutrition and child development
- UNICEF: Multiple Indicator Cluster Survey: Data from ~50 low- and middle-income countries
- United Kingdom and Germany: Preterm birth and developmental sequelae

**Publications with International Collaborators**

From 2016 to present, 46 reports dealing with international or cross-cultural samples and collaborations were published.


Recent Achievements in International Health


- Present-day knowledge about young girls’ and boys’ development is sparse in non-U.S. and non-European countries. Little to nothing is still known scientifically about how a child’s gender affects his or her development in low- and middle-income countries (LMIC) where a majority of the world’s child population resides.
- To examine protective and risk factors related to child gender, we used the Multiple Indicator Cluster Survey (MICS), a nationally representative and internationally comparable household survey. Data from more than 2 million individuals in 400,000 families in 41 LMIC were collected. Gender differences in growth and mortality, caregiving, discipline and violence, and child labor were explored.
- In terms of growth (height and weight) and mortality, boys were at a disadvantage relative to girls and the gender difference was larger in countries with the most socioeconomic risk.
- In terms of caregiving, few gender differences emerged in overall exposure to caregiving, but parents were more likely to engage with their same-gendered child. For example, mothers engaged in slightly more cognitive caregiving with girls than boys, and fathers engaged in slightly more cognitive caregiving with boys than girls.
- In terms of discipline and violence, boys received slightly harsher treatment than girls.
- In terms of child labor, a slightly higher percentage of boys than girls were involved in child labor, but gender differences varied by type of labor and country.
• Overall, we found that most gender effects (when there were any) were small. Most gender-related patterns also varied considerably by country. These findings inform policy interventions by identifying children who are at greater risk in different domains (e.g., boys in growth and mortality and discipline, and girls in some forms of caregiving and labor) and countries.

International Trainees
• Hirokazu Doi, Ph.D., School of Medicine, Nagasaki University, Nagasaki, Japan
• Paola Rigo, Ph.D., Visiting Fellow from the Department of Psychology and Cognitive Science, University of Trento, Italy
• Rebecca Pearson, Ph.D., University of Bristol, Bristol, UK
• Iryna Culpin, University of Bristol, Bristol, UK
• Maida Mustafić, Ph.D., University of Luxembourg, Luxembourg

International Partnerships
See above.

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

Point-of-Contact
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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

**WHO Classification of Tumours**

**WHO Classification of Tumours**

**WHO Classification of Tumours**

**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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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 (Past 5 years)


**Recent Achievements in International Health**

Work on the genetics of protein kinase A, phosphodiesterases, GPCRs 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, MD, 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 MSc., 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, etc.

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

N/A

**Point-of-Contact**

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Section on Environmental Gene Regulation (SEGR)

Investigator: Dr. Gisela Storz

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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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

- Identification of antigenic spectra of individual HIV-1 virions: A collaborative project with the Imperial College London, UK (PI: Dr. Robin Shattock)
- Development of ex vivo models of atherosclerotic plaques A collaborative project with Moscow University of Medicine and Dentistry, Moscow, Russia (PIs: Dr. Elena Vasilieva and Alexander Shpektor)
- Morphological analysis of extracellular vesicles generated by CMV-infected cells and their role in HIV infection: A collaborative project with Cochin Institute, Paris, France (PIs: Dr. Morgan Bomsel)
- Investigation of the role of Lactobacillus-generated extracellular vesicles in protection against vaginal HIV transmission: A collaborative project with the University of Bologna, Bologna, Italy (PIs: Dr. Beatrice Vitali)
- 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. Rogesrs Palomina is an International trainee from the University of Bologna, Italy.
- Dr. Sonia Zicari is an International trainee from the University of Brescia, Italy.
- Ms. Daria Vorobyeva was trained as a Ph.D. Student from Moscow Medical University.
- Mr. Ezequiel Dantas from Argentina is trained as a recipient of the Fulbright Award

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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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


8. Sun, G., Roediger, J., and Shi, Y.-B. (2016) Thyroid hormone regulation of adult intestinal stem cells: Implications on intestinal development and homeostasis. Reviews in Endocrine and Metabolic Disorders in press


**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
**Section on Molecular Neurobiology (SMN)**

**Investigator:** Dr. Andres Buonanno

**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**

- Tanveer Ahmed, Ph.D.: Assistant Professor, Dept of Biochemistry, University Grants Commission, New Delhi, India
- Sharmila Basu, Ph.D.: President and Chief Scientific Officer, MindSpec, McLean, VA
- Soledad Calvo, M.D.,Ph.D.: Assistant Professor, Facultad de Medicina at Alicante University, Spain
- Claudia Colina-Prisco, Ph.D.: Postdoctoral Fellow, NIAAA, NIH, MD
- Rolando Garcia, Ph.D.: Senior Scientist, Wellstat Therapeutics, Gaithersburg, MD
- Carmen M Gonzalez, Ph.D.: Dept. of Pathology and Exp Therapy University of Barcelona, Spain
- Ryoichi Kimura, Ph.D. Assist Professor, Dept. Physiology, Hyogo College of Med 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 (IDEA), Caracas, Venezuela
- Elias Leiva-Salcedo, Assist Professor, Facultad de Química y Biología, Universidad de Santiago, Chile
- Joerg Neddens, Ph.D.: Senior Scientist, Dept. of Histology, JSW Life Sciences, Austria
- Daniel Paredes, Ph.D.: Investigator, Lieber Institute for Brain Development, Baltimore, USA
- 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, MD

**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 memorandum of understanding (MOU) for graduate student stipend for Ms. Larissa Erben to work in lab.

Oslo University, Norway. Had a 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 Neuronal Connectivity (SNC)

Investigator: Chi-Hon Lee, M.D. Ph.D.
Affinity Group: Cell Regulation and Development

Mission

The Section on Neuronal Connectivity investigates the development and function of color-vision circuits in *Drosophila*. This section uncovered that afferent-derived growth factors, such as insulin and TGF-beta, regulate dendritic development of second-order neurons and synaptic formation. The section is also developing novel genetic tools to dissect the structure and functions of synaptic circuits. By targeted inactivation of selected neurons, this group recently delineated the visual pathways that mediate spectral preference and color vision.

Major International Initiatives

This section has a long-term collaboration with Dalhousie University, Canada to investigate the connectivity of visual synaptic circuits. This section also collaborates with researchers from the Tokyo University, Japan to identify second-order neurons in the gustatory circuits. Collaboration with researchers from the Tata Institute of Fundamental Research in India and the University of Vienna in Austria led to novel insight in axonal guidance neural circuit assembly.
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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leechih@mail.nih.gov
301-435-1940
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.

Publications with International Collaborators


Recent Achievements in International Health
N/A

International Trainees
N/A

International Partnerships
N/A
Section on Protein Biosynthesis (SPB)

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

Mission
The Section on Protein Biosynthesis 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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