

# NICHD International Activities Catalog



**2016**

**OFFICE OF GLOBAL HEALTH**



*Eunice Kennedy Shriver* National Institute  
of Child Health and Human Development

# Table of Contents

<b>List of Acronyms</b> .....	<b>5</b>
<b>Overview</b> .....	<b>8</b>
<b>Office of the Director</b> .....	<b>9</b>
<b>Office of Global Health (OGH)</b> .....	<b>10</b>
Mission.....	10
Major International Initiatives over the Past Year.....	10
Recent Achievements in International Health.....	12
International Partnerships .....	13
Examples of Staff Membership on Global Health Committees/Working Groups .....	13
Website .....	14
Point-of-Contact.....	14
<b>Office of Health Equity (OHE)</b> .....	<b>15</b>
Mission.....	15
Website .....	15
Point-of-Contact.....	15
<b>Division of Extramural Research (DER)</b> .....	<b>16</b>
<b>Child Development and Behavior Branch (CDBB)</b> .....	<b>17</b>
Mission of Branch .....	17
Major International Activities over the Past Year.....	17
Website .....	18
Point-of-Contact.....	18
<b>Contraception Research Branch (CRB)</b> .....	<b>19</b>
Mission of Branch .....	19
Major International Initiatives over the Past Year.....	19
Recent Achievements in International Health.....	20
International Partnerships .....	20
Website .....	20
Point-of-Contact.....	20
<b>Developmental Biology and Structural Variation Branch (DBSVB)</b> .....	<b>21</b>
Mission of Branch .....	21
International Activities Involving Human Subjects .....	21
International Activities Involving Animal Models .....	22
Website .....	24
Point-of-Contact.....	24
<b>Fertility and Infertility Branch (FIB)</b> .....	<b>25</b>
Mission of Branch .....	25
Website .....	25
Point-of-Contact.....	25
<b>Gynecologic Health and Disease Branch (GHDB)</b> .....	<b>26</b>
Mission of Branch .....	26
Major International Initiatives over the Past Year.....	26
Recent Achievements in International Health.....	26
Website .....	26
Point-of-Contact.....	26

<b>Intellectual and Developmental Disabilities Branch (IDDB)</b> .....	<b>27</b>
Mission of Branch .....	27
Recent Achievements in International Health .....	27
Cookstove-Related Achievements: .....	29
Website .....	29
Point-of-Contact.....	29
<b>Maternal and Pediatric Infectious Disease Branch (MPIDB)</b> .....	<b>30</b>
Mission of Branch .....	30
Major International Initiatives .....	30
Recent Achievements in International Health .....	36
Staff Membership on Global Health Committees/Working Groups.....	36
Website .....	36
Point-of-Contact.....	36
<b>Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB)</b> .....	<b>37</b>
Mission of Branch .....	37
Major International Initiatives over the Past Year.....	37
Staff Membership on Global Health Committees/Working Groups.....	37
Website .....	38
Point-of-Contact.....	38
<b>Pediatric Growth and Nutrition Branch (PGNB)</b> .....	<b>39</b>
Mission of Branch .....	39
Major International Initiatives over the Past Year.....	39
International Partnerships .....	43
Website .....	44
Point-of-Contact.....	44
<b>Pediatric Trauma and Critical Illness Branch (PTCIB)</b> .....	<b>45</b>
Overview .....	45
Major International Initiatives over the Past Year.....	45
Recent Achievements in International Health.....	45
Staff Membership on Global Health Committees/Working Groups.....	46
Website .....	46
Point-of-Contact.....	46
<b>Population Dynamics Branch (PDB)</b> .....	<b>47</b>
Mission of Branch .....	47
Major International Initiatives over the Past Year.....	47
Prevention and Treatment of HIV/AIDS—Collaboration between the United States and Russia..	48
Brief Overview of the Research Topics, by Country, Supported by PDB. ....	48
International Partnerships .....	49
Website .....	49
Point-of-Contact.....	49
<b>Pregnancy and Perinatology Branch (PPB)</b> .....	<b>50</b>
Mission of Branch .....	50
Major International Initiatives over the Past Year.....	50
Current Studies in the Global Network.....	50
Recent Achievements in International Health .....	57
Website .....	58
Points-of-Contact .....	58

<b>National Center for Medical Rehabilitation Research (NCMRR)</b> .....	<b>60</b>
Mission of Center .....	60
International Partnerships .....	60
Website .....	63
Point-of-Contact.....	63
<b>Division of Intramural Population Health Research (DIPHR)</b> .....	<b>64</b>
Mission of Division .....	64
Major International Initiatives over the Past Year.....	64
International Partnerships .....	65
Epidemiology Branch Investigators Involved in International Activities .....	65
Website .....	66
Point-of-Contact.....	66
<b>Division of Intramural Research (DIR)</b> .....	<b>67</b>
DIR research addresses several fundamental questions: .....	68
<b>Child and Family Research Section (CFRS)</b> .....	<b>69</b>
Mission of Section .....	69
Major International Initiatives .....	69
Publications with International Collaborators.....	69
Recent Achievements in International Health.....	73
Description of International Trainees .....	74
International Partnerships .....	74
Website .....	74
Point-of-contact: .....	74
<b>Section on Environmental Gene Regulation (SEGR)</b> .....	<b>75</b>
Mission of Section .....	75
Publications with International Collaborators.....	75
Recent Achievements in International Health.....	75
Description of International Trainees .....	75
Website .....	75
Point-of-Contact.....	75
<b>Section on Genetics and Endocrinology (SGE)</b> .....	<b>76</b>
Mission of Section .....	76
Major International Initiatives.....	76
Selected Publications with International Collaborators .....	76
Recent Achievements in International Health.....	78
Description of International Trainees .....	79
International Partnerships .....	79
Website .....	80
Point-of-Contact.....	80
<b>Section on Intercellular Interactions (SII)</b> .....	<b>81</b>
Mission of Section .....	81
Major International Initiatives .....	81
Publications with International Collaborators.....	81
Description of International Trainees .....	82
International Partnerships .....	82
Website .....	82
Point-of-contact: .....	82

<b>Section on Molecular Morphogenesis (SMM)</b> .....	<b>83</b>
Mission of Section .....	83
Major International Initiatives .....	83
Publications with International Collaborators .....	84
Website .....	85
Point-of-Contact.....	85
<b>Section on Molecular Neurobiology (SMN)</b> .....	<b>86</b>
Mission of Section .....	86
Major International Initiatives .....	86
Publications with International Collaborators .....	86
Recent Achievements in International Health .....	87
Description of International Trainees .....	87
International Partnerships .....	88
Website .....	88
Point-of-Contact.....	88
<b>Section on Neuronal Connectivity (SNC)</b> .....	<b>89</b>
Mission of Section .....	89
Major International Initiatives .....	89
Relevant Publications:.....	89
Website .....	90
Point-of-Contact.....	90
<b>Section on Nutrient Control of Gene Expression (SNCGE)</b> .....	<b>91</b>
Mission of Section .....	91
Publications with International Collaborators .....	91
Website .....	91
Point-of-Contact.....	91
<b>Section on Protein Biosynthesis (SPB)</b> .....	<b>92</b>
Mission of Section .....	92
Major International Initiatives .....	92
Relevant Publications:.....	92
Website .....	92
Point-of-Contact.....	92

## List of Acronyms

ABI	Acquired Brain Injury
ACL	Anterior Cruciate Ligament
ACS	Antenatal Corticosteroids
ACT	Antenatal Corticosteroids Trial
AFM	Atomic Force Microscopy
AG	Affinity Group
AIDS	Acquired Immune Deficiency Syndrome
AP	Abruptio Placenta
ART	Antiretroviral Therapy
ARV	Antiretroviral
ASA	Acetylsalicylic Acid
ASPIRIN	Aspirin Supplementation for Pregnancy Indicated Risk Reduction in Nulliparas
BPCA	Best Pharmaceuticals for Children Act
BME	Biomedical Engineering
BMGF	Bill & Melinda Gates Foundation
BPD	Bronchopulmonary Dysplasia
BRAD	Biomedical/Behavioral Research Administrators Development Award
BRINDA	Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia
CATCH	Counseling and Testing for Children at Home
CCRT	Computerized Cognitive Rehabilitation Therapy
CDC	Centers for Disease Control and Prevention
CHAP	Community Health Advocacy Program
ChIP-seq	Chromatin Immunoprecipitation Sequencing
CIPHER	Collaborative Initiative on Pediatric HIV Research
CNRS	French National Center for Scientific Research
CNS	Central Nervous System
CP	Cerebral Palsy
CPAP	Continuous Positive Airway Pressure
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeat
DER	Division of Extramural Research
DHHS	U.S. Department of Health and Human Services
DIPHR	Division of Intramural Population Health Research
DIR	Division of Intramural Research
DMPA	Depot Medroxyprogesterone Acetate
dMRI	Diffusion MRI
DRG	Dorsal Root Ganglion
DSi	Down Syndrome International
EU PFI	European Pediatric Formulations Initiative
FAS	Fetal Alcohol Syndrome
FDA	Food and Drug Administration
FIC	Fogarty International Center
FIRS	Fetal Inflammatory Response Syndrome
FSHD	Facioscapulohumeral Muscular Dystrophy
GA	Gestational Age
Global Network	Global Network for Women's and Children's Health Research
GRiP	Global Research in Pediatrics Initiative

GU	Genitourinary
HAI	Human-Animal Interaction
HAPO	Hyperglycemia and Adverse Pregnancy Outcome Study
HBeAg	Hepatitis B e Antigen Positive
HBV	Hepatitis B Virus
HCMV	Human Cytomegalovirus
Hib	Haemophilus influenzae type B
HITSsystem©	HIV Infant Tracking System
HIV	Human Immunodeficiency Virus
HSV-2	Herpes Simplex Virus 2
HTEC	HIV Testing and Enhanced Counseling
IAA	Interagency Agreement
ICs	NIH Institutes and Centers
IGMCD	International Guide for Monitoring Children’s Development
IeDEA	Pediatric International Epidemiologic Databases to Evaluate AIDS
IMPAACT	International Maternal Pediatric Adolescent AIDS Trials Network
ING	Inhibitor of Growth
INRIA	French Institute for Research in Computer Science and Automation
INSPIRE	Inflammation and Nutritional Science for Programs/Policies and Interpretation of Research Evidence
IOM	Institute of Medicine
IRDiRC	International Rare Diseases Research Consortium
IUD	Intrauterine Device
IUGR	Intrauterine Growth Retardation
iYCG	Investing in Young Children Forum
LBW	Low Birth Weight
LDA	Low Dose Aspirin
LMICs	Low- and Middle-Income Countries
MCH	Maternal and Child Health
MODS	Multiple Organ Dysfunction Syndrome
MEPI	Medical Education Partnership Initiative
MICS	Multiple Indicator Cluster Survey
MINERVa	The Multigenerational Familial and Environmental Risk for Autism Network
MOU	Memorandum of Understanding
mTBI	Mild Traumatic Brain Injury
NACS	Nutritional Assessment, Care, and Support
NCI	National Cancer Institute
NCMRR	National Center for Medical Rehabilitation Research
NeOProm	Neonatal Oxygenation Prospective Meta-analysis Collaboration
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	<i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NISDI	NICHD Latin American/Caribbean International Site Development Initiative
NTDs	Neural Tube Defects

NUGAG	Nutrition Guidance Expert Advisory Group
ODS	Office of Dietary Supplements
OGAC	Office of the Global AIDS Coordinator
ORF	Open Reading Frames
OVC	Orphans and Vulnerable Children
PA	Physical Activity
PASS Network	Prenatal Alcohol in SIDS and Stillbirth Network
PEARL Study	Pregnancy and Early Life-Style Improvement Study
PEEP	Positive End-Expiratory Pressure
PENTA	Pediatric European Network for Treatment of AIDS
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PLP	Phantom Limb Pain
PMA	Post-Menstrual Age
PMTCT	Prevention of Maternal-Child HIV Transmission
POFO	Positive Outcomes for Orphans
PTD	Preterm Delivery
PTN	Pediatric Trials Network
RFA	Request for Applications
RNA-seq	RNA Sequencing
SAIL Study	Sustained Inflation for Lung Expansion
SCI	Spinal Cord Injury
SGA	Small for Gestational Age
SI	Sustained Inflation
SIDS	Sudden Infant Death Syndrome
SMFM	Society for Maternal-Fetal Medicine
SSI	Statens Serum Institut
STAC	Scientific and Technical Advisory Committee
STI	Sexually Transmitted Infection
T1DM	Type 1 Diabetes
TALEN	Transcriptional Activator Like Effector Nuclease
TB	Tuberculosis
TBI	Traumatic Brain Injury
tDCS	Transcranial Direct Current Stimulation
TH	Thyroid Hormone
THL	National Institute for Health and Welfare
TR	Thyroid Hormone Receptor
UNC	University of North Carolina
USAID	U.S. Agency for International Development
USG	U.S. Government
U.S. PFI	U.S. Pediatric Formulations Initiative
UTI	Urinary Tract Infection
WHO	World Health Organization

## Overview

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

OGH works in close collaboration with NICHD Divisions and Offices, as well as other National Institutes of Health (NIH) and U.S. Department of Health and Human Services (DHHS) entities, to improve the overall health of populations worldwide by providing leadership, coordination, and support for NICHD's global health mission and activities. Key activities include:

- Coordinating, advocating, identifying, and mobilizing policies, programs, resources, and opportunities in global health research and training;
- Building and maintaining global health partnerships and collaborations;
- Providing leadership in the development of cross-cutting policies, plans, and programs related to NICHD's global health research; and
- Assisting the Institute's components in enhancing their international research portfolios and other global health activities.

In implementing these activities, OGH works in partnership with multiple national and global health organizations, including the DHHS Office of Global Affairs (OGA); the U.S. Centers for Disease Control and Prevention (CDC); other NIH Institutes and Centers, such as the Fogarty International Center (FIC); the U.S. Agency for International Development (USAID); U.S. Department of State; the World Health Organization; 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 five-sections representing the: OD, Division of Extramural Research (DER), National Center for Medical Rehabilitation and Research (NCMRR), Division of Intramural Population Health Research (DIPHR), and 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, website where additional information can be found, 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.

Website: <https://www.nichd.nih.gov/about/org/od/pages/index.aspx>

## 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

#### **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). Following visits by Mr. Bill Gates, BMGF, to the NIH campus in January 2014 and April 2016, a new phase of cooperation has been initiated between the two organizations 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 five of the eight working groups (i.e., Maternal and Newborn Health, Child Health and Development, Pediatric Pneumonia and Indoor Air Pollution, Contraceptive Research, and HIV/AIDS Working Groups). OGH co-chairs the Child Health and Development Working Group which includes representation from NICHD, BMGF, the National Institute of Mental Health (NIMH), and the National Institute of Drug Abuse (NIDA). This working group aims to identify new research collaborations in the areas of child neurodevelopment, nutrition and growth, and neurocognitive assessment, among other areas. Joint activities this past year include the planning of a BMGF Sleep and Neurodevelopment Convening on July 14, 2016 in Seattle, Washington and an NIH Baby Toolbox Meeting in fall 2016; secondary referral to BMGF of NICHD SBIR/STTR grants on neurodevelopmental assessment; NIH-BMGF data sharing; a planned NIH Common Fund proposal on neurodevelopment; and possible collaborations with the NIMH Collaborative Hubs and/or on maternal depression research and the NIDA Adolescent Brain Cognitive Development (ABCD) longitudinal study. NIH representatives have also been invited to participate in the BMGF Grand Challenges Meetings in Beijing, China and London, England.

**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.

**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 is to establish a community of international stakeholders that will identify innovative international research and translate this evidence into policies and practices in health, nutrition, education, and social protection for children and their families in resource-limited settings. NICHD serves 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 including an Americas Meeting on implementation science and

indigenous populations, and a West African Meeting on research innovation and capacity building. The MENDDDD working group is also preparing two manuscripts for submission to the PLOS One journal on research priorities for developmental disabilities in low resource settings. A series of regional reports have been published as well as several communications resources have been developed over the past three years, and a summary report describing the achievements of the overall iYCG Forum will be published in fall 2016.

**NICHD Meeting on “Bridging Knowledge Gaps to Understand How Zika Virus Exposure and Infection Affect Child Development.”** OGH Staff served on the planning group for this NICHD Meeting to be held on September 22-23, 2016 in Bethesda, MD. The purpose of this meeting is to identify optimal approaches for treating and caring for the generation of children exposed to Zika virus (ZIKV) in the womb. This workshop aims to: 1) develop a clinical and research strategy on how to appropriately assess, evaluate, and monitor the neonate/infant/child affected by ZIKV in utero; 2) describe the available complications of in utero ZIKV exposure and infection (e.g., microcephaly); 3) use available information from other vertically transmitted pathogens to provide recommendations for assessment, evaluation, and management; 4) outline the research needs for treatment and rehabilitation approaches that optimize cognitive and physical function for Zika-affected children; and 5) evaluate and expand on treatment options currently offered, such as intensive physical therapy and immersion therapies, role of parents and caregivers in treatment, including the evidence base for these therapies and current research gaps.

**U.S. Government (USG) Meeting on USG Ebola Research Activities.** OGH staff served on the Ebola Research Agenda Steering Committee that organized this USG meeting held February 10, 2015 on the NIH Bethesda campus. The goals of this forum included: 1) sharing and discussing a landscape analyses of USG-supported Ebola research, as well as an identification of gaps and potential opportunities for collaboration, and 2) holding technical-level conversations around lessons learned from the USG research response to inform preparedness across the USG to launch and execute research in response to another infectious disease outbreak. NICHD OGH staff served on a panel and gave a presentation on, “Ebola Virus Disease: The Maternal and Child Health Perspective,” highlighting the unique needs of pregnant women, infants and children during the Ebola epidemic.

**NIH IC AIDS Coordinator and Chairperson of the NICHD AIDS Coordinating Committee.** The OGH Director serves 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 OGH also supported the Office of the NICHD Director by leading the implementation of the DIR/DIPHR FY16 HIV/AIDS Research Award, a competitive funding opportunity intended to support NICHD intramural studies with the potential to advance the goals of the FY16 Trans-NIH Plan for HIV-Related Research. 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.

**2016 Trans-NIH Global Health Symposium to honor Dr. Francis Collins.** OGH staff serves on the planning committee for this NIH-wide meeting honoring global health achievements during the tenure of NIH Director Dr. Francis Collins. The NICHD guest speaker at this meeting will be a long-standing researcher with the NICHD Global Network for Women’s and Children’s Research.

**“Forum on the Well-Being of the World’s Children.”** The Canadian Institutes for Advanced Research (CIFAR) are launching this initiative with an inaugural meeting in London, England in November 2016. The purpose of this Forum is to convene researchers, practitioners, and public officials from universities, NGOs, international organizations, and from the public and private sectors to explore a broad set of topics related to child well-being. The goals of the Forum include: 1) To generate insights and ideas on critical questions and priority challenges that could be addressed through an interdisciplinary global research network; 2) To build a coalition of partners that will help design a Global Call for proposals and who may support a future research network on child well-being with funding; and 3) To share information and ideas emerging at the forum with international partners and stakeholders publicly.

## **Recent Achievements in International Health**

- **Planning of International Site Visits by Senior NICHD, NIH, DHHS, and Congressional Leadership.** In collaboration with NICHD program staff, prepared briefing materials and helped plan site visits for NICHD, NIH, and DHHS senior leadership in Rwanda, Thailand, 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 including e.g., Cuban Minister of Public Health, South African Medical Research Council, Ethiopian Minister of Health, NIH Representative in US Embassy in India, American University of Beirut (Lebanon), the HHS Health Attaché Meeting, 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.** 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. Completed HHS Office of Global Affairs (OGA) information request on NIH-supported MCH research for Brazil, Chile, Colombia, Cuba, Guatemala, Haiti, Mexico and Peru. Scientific input also provided on interagency documents from several organizations including the HHS Disorders of Sexual Development Briefing, Action Plan on Children in Adversity Interagency Working Group Annual Report, WHO Non-communicable Disease (NCD) Global Coordination Mechanism discussion paper on Essential Medicines and Basic Health Technologies for NCDs, World Health Assembly USG Position Papers, WHO Zika Strategic Response Plan, USG comments on UN Sustainable Development Goal 3 related to Global Health, and WHO Zika draft research protocols.

## 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.** Representatives: Dr. Vesna Kutlesic and Dr. Maggie Brewinski Isaacs
- **NIH-BMGF Child Health and Development Working Group.** Representatives: Dr. Vesna Kutlesic and Dr. Maggie Brewinski Isaacs
- **NICHD R56 Program Internal Review Committee.** Representative: Dr. Maggie Brewinski Isaacs
- **NICHD OD Co-Funding Working Group.** Representative: Dr. Vesna Kutlesic
- **NICHD Zika Round-up Working Group.** Representatives: Dr. Vesna Kutlesic and Dr. Maggie Brewinski Isaacs
- **HHS/USAID/OMB Zika Coordination Group.** Representatives: Dr. Vesna Kutlesic and Dr. Maggie Brewinski Isaacs
- **Americas Region Interagency Coordination Group on Zika Virus.** Representatives: Dr. Vesna Kutlesic and Dr. Maggie Brewinski Isaacs
- **OAR Executive Committee.** Representative: Dr. Vesna Kutlesic
- **NICHD AIDS Coordinating Committee.** Representatives: Dr. Vesna Kutlesic and Dr. Maggie Brewinski Isaacs
- **NICHD Clinical Trial Stewardship Working Group.** Representative: Dr. Maggie Brewinski Isaacs
- **NICHD Reproductive Health Working Group.** Representative: Dr. Maggie Brewinski Isaacs
- **Fogarty IC International Representatives Working Group.** Representative: Dr. Vesna Kutlesic
- **Trans-NIH Global Health Research Working Group.** Representative: Dr. Vesna Kutlesic

- Trans-NIH International Clinical Research Subcommittee. Representative: Dr. Vesna Kutlesic
- National Academies Investing in Young Children Forum Executive Committee. Representative: Dr. Vesna Kutlesic
- National Academies Investing in Young Children Forum Mental Health and Developmental Disabilities Working Group. Representative: Dr. Vesna Kutlesic
- USG Children in Adversity Strategy Working Group. Representative: Dr. Vesna Kutlesic
- FIC BRAIN Disorders Initiative Working Group. Representative: Dr. Vesna Kutlesic

### **Website**

<https://www.nichd.nih.gov/about/org/od/ogh/Pages/index.aspx>

### **Point-of-Contact**

Dr. Vesna Kutlesic

[vesna.kutlesic@nih.gov](mailto:vesna.kutlesic@nih.gov)

301-435-7566

## **Office of Health Equity (OHE)**

### **Mission**

The OHE, within the NICHD Office of the Director, 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.

### **Website**

<https://www.nichd.nih.gov/about/org/od/ohe/Pages/overview.aspx>

### **Point-of-Contact**

Dr. Catherine Spong  
[catherine.spong@nih.gov](mailto:catherine.spong@nih.gov)  
(301) 496-1848

## 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.

DER Scientific Branches have recently updated their Research Priorities. For each Branch entry, a website is included which provides additional information, including key research gaps and priorities.

**Website:** <https://www.nichd.nih.gov/about/org/der/Pages/index.aspx>

## Child Development and Behavior Branch (CDBB)

### Mission of Branch

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 that addresses how parents' discipline strategies affect children's development. Researchers collect data from eight countries, including China, India, Italy, Kenya, the Philippines, Sweden, Thailand, and the United States, to examine the impact of disciplinary approaches on children's psychosocial adjustment and whether adjustment is moderated by cultural norms and expectations. 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 or not improved parenting mediates child outcomes.

**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. The Branch supports another UK study that is examining risks associated with epigenetic X environment interactions in an existing database that includes a large sample of children followed from birth through nine years of age. The study examines the risks, beginning in gestation through late childhood, that may correlate with changes in DNA methylation (from birth through nine years of age), and then relates the trajectory of methylation changes to environmental stressors and early onset of behavior conduct problems. 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.

**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, include Canada, China, France, Israel, 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. 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.

### **Website**

<https://www.nichd.nih.gov/about/org/der/branches/cdbb/Pages/overview.aspx>

### **Point-of-Contact**

Dr. Lisa Freund

[Lisa.freund@nih.gov](mailto:Lisa.freund@nih.gov)

301-435-6879

## Contraception Research Branch (CRB)

### Mission of Branch

The mission of the CRB, formerly the Contraception Development and Discovery Branch (CDDB), includes supporting research and research training programs in contraceptive discovery and development. Major research areas include studies of new contraceptive methods; mechanisms of action and effects of contraceptive and reproductive hormones, drugs, devices, and procedures; and optimal formulations and dosages of contraceptive agents, including spermicidal microbicides.

### 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 oenanthate) 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.

**U54 Contraceptive Development Program.** Through the U54 cooperative agreement with the Population Council, the Branch has supported research on a contraceptive vaginal ring in the Dominican Republic and France.

### **Recent Achievements in International Health**

- CRB staff continues a Collaborative Research and Development Agreement with HRA (Paris, France). Products resulting from this collaboration include ella<sup>®</sup>/ellaOne<sup>®</sup> 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<sup>®</sup> and in Canada as Fibrystal<sup>®</sup>.
- 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 (CDC).

### **Website**

<https://www.nichd.nih.gov/about/org/der/branches/crb/Pages/overview.aspx>

### **Point-of-Contact**

Daniel S. Johnston, Ph.D.  
[daniel.johnston@nih.gov](mailto:daniel.johnston@nih.gov)  
301-827-4663

# Developmental Biology and Structural Variation Branch (DBSVB)

## Mission of Branch

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 [Gabiella Miller Kids First Pediatric Research Program](#).

## 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 China focuses on one of the top five most common birth defects worldwide: neural tube defects (NTDs), with the goal of understanding the underlying causes in humans and developing new strategies for prevention.

NICHD-supported investigators have established collaborations with several sites in China including investigators at Peking University, The Shanghai Institute of Medical Genetics, Fudan University in

Shanghai, and The Capital Institute of Pediatric Research in Beijing. These collaborations with groups in China enable investigators on domestic NICHD-supported grants to leverage well-established clinical and research infrastructures in China and provide a unique opportunity to obtain biological specimens and information on environmental and genetic contributions to the etiology of NTDs. The scope of these collaborative studies broadly 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 will integrate 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.

## 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.

**Netherlands:**

One of the long-term goals of DBSVB is to understand how genes are turned on and off during embryonic development. Gene activity during development of the frog species, *Xenopus tropicalis*, is being studied in this NICHD-supported project because, unlike mammalian embryos, *Xenopus* embryos can be easily experimentally manipulated. Investigators will use a combination of powerful new technologies allowing them to identify which genes are turned on and off by chemical modifications of DNA and chromosomal structure as the embryo matures and also to identify which parts of the genome are acting as switches to control the activity of other genes. Because of the conservation of genes and genetic pathways across the animal kingdom, it is likely that much of what is learned will also apply to the development of human embryos and provide clues to the formation of structural birth defects.

**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 study 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 humans, improving our ability to predict gene function in development and in disease.

### **United Kingdom:**

Most of the projects that DBSVB supports involve the use of model systems such as the frog, *Xenopus*. One example of an important resource is a consortium of investigators, including a collaborator in the United Kingdom, whose goal is to assemble a complete collection of DNA sequences coding for all proteins in the genome of *Xenopus*. These DNA sequences, called Open Reading Frames (ORFs), will be cloned into bacterial plasmids that will allow the sequences and their protein products to be easily manipulated for a variety of research uses. The ORF-containing plasmids will then be made available to the research community. This collection, the *Xenopus* ORFeome, will greatly facilitate the work of scientists who use *Xenopus* as a model system for basic biological studies. The assembly and availability of the *Xenopus* ORFeome will provide an essential resource to the biomedical research community that will facilitate studies into the molecular basis of development, health, and disease.

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.

### **Website**

<https://www.nichd.nih.gov/about/org/der/branches/dbsvb/Pages/overview.aspx>

### **Point-of-Contact**

Dr. Tyl Hewitt

[hewittt@mail.nih.gov](mailto:hewittt@mail.nih.gov)

301-496-5543

## **Fertility and Infertility Branch (FIB)**

### **Mission of Branch**

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.

### **Website**

<https://www.nichd.nih.gov/about/org/der/branches/fi/Pages/overview.aspx>

### **Point-of-Contact**

Dr. Louis De Paolo

[depaolol@mail.nih.gov](mailto:depaolol@mail.nih.gov)

301-435-6970

# Gynecologic Health and Disease Branch (GHDB)

## Mission of Branch

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 of the menstrual cycle, uterine fibroids, endometriosis, polycystic ovary syndrome, pelvic floor disorders, and menopause transition/perimenopause, as well as studies of the mechanisms underlying chronic pelvic pain, vulvodynia, and dysmenorrhea. International activities include support of research on obstetric fistula and female genital mutilation.

## Major International Initiatives over the Past Year

**Obstetric Fistula.** Obstetric fistula is a debilitating birth injury resulting from obstructed labor which results in constant leaking of urine and/or feces. Obstetric fistula is estimated to affect 50,000 to 100,000 women each year with as many as two million women with untreated obstetric fistula in Asia and Sub-Saharan Africa. Women with obstetric fistula often can be successfully treated with surgery, but even then, are often not reintegrated into the community. In the past year, the GHDB has funded a recently completed study in Uganda with the goals of better understanding reintegration into family and community post fistula surgery; development of a measurement tool to assess long-term reintegration success; and evaluation of the feasibility of long-term follow-up among this group utilizing mobile phone technology. A newly funded study, also in Uganda, focuses on patient expectations following obstetric fistula treatment.

**Female Genital Mutilation.** Female genital mutilation or cutting 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. Applications have been received in this area but have not yet been funded.

## Recent Achievements in International Health

The publication of a study protocol for the evaluation of family and community reintegration after obstetric fistula surgery (Byamugisha J et. al., *Reprod Health*, 2015).

## Website

<https://www.nichd.nih.gov/about/org/der/branches/ghdb/Pages/overview.aspx>

## Point-of-Contact

Dr. Lisa Halvorson

[lisa.halvorson@nih.gov](mailto:lisa.halvorson@nih.gov)

301-480-1646

# Intellectual and Developmental Disabilities Branch (IDDB)

## Mission of Branch

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.

## 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.

- 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.
- Neonatal jaundice, if untreated, can lead to acute bilirubin encephalopathy, which has been linked to cerebral palsy, deafness, language difficulty and, in some cases, death. A major problem in many LMIC countries is that this condition is unrecognized and untreated, as most infants are born in settings where diagnosis and treatment of jaundice are often unavailable. By the time this condition is recognized, these infants have experienced irreversible brain damage. The Branch is supporting development of a community-based instrument that can be used in field settings to identify infants at risk for acute bilirubin-induced encephalopathy in Nigeria. This instrument will have application across many countries.
- 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).

### **Website**

<https://www.nichd.nih.gov/about/org/der/branches/iddb/Pages/overview.aspx>

### **Point-of-Contact**

Dr. Danuta Krotoski

[Krotoskd@mail.nih.gov](mailto:Krotoskd@mail.nih.gov)

301-496-5576

## Maternal and Pediatric Infectious Disease Branch (MPIDB)

### Mission of Branch

The MPID Branch supports and conducts both domestic and international research on the epidemiology, natural history, 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 as a whole.

### Major International Initiatives

**The NICHD International and Domestic Pediatric and Maternal HIV Clinical Trials Network.** The network conducts clinical trials on treatment, prevention, and persistence of HIV in infants, children, adolescents, and women. NICHD funds 15 sites in Puerto Rico and mainland United States and 14 international sites in five countries, including Argentina, Brazil, Kenya, Tanzania, and Thailand. The NICHD Network conducts clinical trials in collaboration with the International Maternal Pediatric Adolescent AIDS Trials (IMPAACT) Network funded by the National Institute of Allergy and Infectious Diseases (NIAID), NICHD, and National Institute of Mental Health (NIMH), the Adult Clinical Trials Group funded by NIAID, the Pediatric European Network for Treatment of AIDS (PENTA), the Tuberculosis Trials Consortium funded by the Centers for Disease Control and Prevention and other international partners.

**NICHD HIV Prevention Trials Network (HPTN) 040 Clinical Trial.** This was a clinical trial conducted in 17 sites in Argentina, Brazil, South Africa, and the United States to identify the optimal anti-HIV drug regimen to prevent mother-to-child HIV transmission from pregnant women in whom HIV infection was not identified until delivery and hence who 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.

**The NICHD Latin American/Caribbean International Site Development Initiative (NISDI).** The NICHD International Site Development Initiative (NISDI) was designed to provide capacity building and training for international sites/investigators through the conduct of two observational studies in HIV-infected pregnant women and children. The observational studies also provided important data about the demographic, clinical, immunologic, and virologic characteristics of HIV-infected pregnant women and children in Latin America. NISDI began in 1999; most of the NISDI sites and investigators subsequently graduated to the NICHD Network and are participating in clinical drug trials. Enrollment has completed and study patient follow-up ended in 2012.

The NISDI perinatal protocol was a prospective study of HIV-infected pregnant women 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 HIV-infected children and adolescents. There have been multiple publications from the NISDI investigators, providing critical information on the long-term safety of exposure to antiretroviral (ARV) drugs in uninfected infants as well as issues on 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 patients. Analyses of the databases and stored samples remain ongoing. Data are now available via the NICHD Data and Specimen Hub (<https://dash.nichd.nih.gov/>).

**Pediatric International Epidemiologic Databases to Evaluate AIDS (IeDEA):** IeDEA is a NIAID project that funds regional datacenters in Africa, Asia, North and South America to collect data on HIV-infected individuals receiving clinical care. NICHD is funding a pediatric component to this study in four regions in Africa, as well as the Asia-Pacific and South America/Caribbean regions. Data on over 140,000 HIV-

infected children receiving therapy are currently included in this database. These data enable large multi-regional studies to evaluate the effect of HIV and its treatment on infected children in resource-limited countries and help to inform World Health Organization (WHO) estimates of the global pediatric HIV epidemic.

**Other research grants:** A number of grants are supporting research on the effects of HIV, its treatment, potential functional cure 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:

- 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 had several **internationally-focused RFAs** in FY 2012 and FY 2014 that are currently funding active projects:
  - **U.S.- South Africa Program for Collaborative Biomedical Research (RFA AI-14-009, 14-010, and 14-018).** This series of RFAs solicited R01, R21, and U01 grants to establish this binational program for collaborative research in the areas of HIV/AIDS, TB, and cancer. Funding was also provided by the South African Medical Research Council. NICHD grants were awarded in maternal and pediatric HIV and in TB.
  - **Disclosure of HIV-Status to Children in 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.
  - **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 already surviving into adolescence, young adulthood, and beyond, and will face the potential consequences of prolonged HIV infection and long-term antiretroviral therapy (ART), which may be

exacerbated by endemic diseases and co-morbidities not seen in resource-rich countries such as the United States. Five R01 grants were awarded for studies in Thailand and South Africa.

- **NIH/PEPFAR Collaboration for Advancing Implementation Science in Prevention of Maternal-Child HIV Transmission (RFA HD-12-210).** 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 from 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).** 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. The trial will assess whether this early treatment initiation affects remission of HIV, thus allowing for discontinuation of ART at 18 months of age without viral rebound. The trial will include careful and sophisticated evaluations of immunological responses.
- MPIDB/NICHD issued the following **RFA** for FY 2016:

- **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 in this area as well as funding 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 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 study of 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. MPIDB/NICHD funded investigators in the Democratic Republic of Congo are evaluating strategies to improve long-term therapy in maternal and child health clinics, while investigators in Nigeria are evaluating HIV testing approaches and breastfeeding practices.

## **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 the 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 will identify viral co-infecting pathogens, determine if the presence of a viral co-infecting pathogen changes rates of morbidity or mortality, and investigate whether children with viral co-infection can be identified using routine laboratory or clinical parameters.

### Hepatitis B

- In Thailand, a clinical trial is evaluating 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 is assessing 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. The drugs are given from 28 weeks gestation until two months postpartum, and both infant infection status and maternal health are evaluated. The results of this study should be available soon and have the potential to define appropriate policy for management of HBV-infected HBeAg positive pregnant women globally.

### Zika

- **Rapid Assessment of Zika Virus (ZIKV) Complications (R21) PAR-16-106.** The purpose of the RFA was to provide expedited funding mechanism for research on Zika virus and its complications. Several NIH institutes joined the RFA. MPID/NICHD funded grants on the natural history and pathogenesis of Zika in reproductive age women.
- **MPIDB led efforts to develop the ZIP Study (Zika in Infants and Pregnancy),** which will enroll 10,000 pregnant women in the first trimester in multiple sites throughout Latin America and the Caribbean.

### 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 being breastfed 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, to 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.

### **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 HTEC with couples can further enhance this effect. Enhanced counseling will emphasize the concept of a HIV-free and healthy baby and in family-based on primary prevention, adequate infant feeding, and family planning.
- In Lilongwe and Malawi, MPIDB supports a study that aims to 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 HIV and the impact on infant outcomes.

### **Recent Achievements in International Health**

- In South Africa, a clinical trial found that HIV-infected children exposed in the womb to nevirapine, a drug used to prevent mother-to-child HIV transmission, can safely and effectively transition to efavirenz. (*JAMA* 2015; 314:1808-17)
- A study in Nigeria found that a church-based HIV screening program was effective in increasing HIV testing and treatment rates. (*Lancet Glob Health* 2015;3:e692-700)
- 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)

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

- WHO Consolidated Antiretroviral Guideline Development Group: Maternal and Child Health Guideline Development Group. Member: Dr. George Siberry
- WHO Paediatric Antiretroviral Drug Optimization Working Group. Member: Dr. Rohan Hazra
- WHO Infant Diagnosis Technical Working Group. Member: Dr. George Siberry
- 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
- 21st International AIDS Conference (AIDS 2016) Clinical Research Track Organizing Committee. Member: Dr. Rohan Hazra

### **Website**

<https://www.nichd.nih.gov/about/org/der/branches/mpidb/Pages/overview.aspx>

### **Point-of-Contact**

Dr. Rohan Hazra

[hazrar@mail.nih.gov](mailto:hazrar@mail.nih.gov)

301-435-6868

# Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB)

## Mission of Branch

The overarching goal of the Branch 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. Currently the PTN is developing international collaborations with clinical sites in Canada, Israel, Singapore, and the United Kingdom to conduct clinical studies as part of the BPCA Program.

**Development of Global Pediatric Clinical Trials Network.** Three meetings were held last year 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. Discussions are ongoing.

**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 as well as many others.

**Collaboration with 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.

## Staff Membership on Global Health Committees/Working Groups

- **European Medicines Agency.** OPPTB developed collaborations with the European Medicines Agency to develop a safety database for excipients used in pediatric formulations. Representative: Dr. George Giacoia.
- **Global Research in Pediatrics (GRiP) Initiative.** OPPTB is regularly updated on the U.S.-European Union activities of GRiP Initiative. **Steering Committee of the International Neonatal Consortia.** Representative: Dr. Anne Zajicek

- Therapies Scientific Committee, International Rare Diseases Research Consortium (IRDIRC).  
Representative: Dr. Anne Zajicek

**Website**

<https://www.nichd.nih.gov/about/org/der/branches/opptb/Pages/overview.aspx>

**Point-of-Contact**

Dr. Anne Zajicek

[zajiceka@mail.nih.gov](mailto:zajiceka@mail.nih.gov)

301-435-6865/301-905-7276

## Pediatric Growth and Nutrition Branch (PGNB)

### Mission of Branch

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, cognition, and behavioral development
- Elucidating the interactive roles played by nutrients and hormones in growth and development of the central nervous system and its interactions with the gastrointestinal tract
- Determining the roles played by lactation and breastfeeding in infant nutrition, including studies of the non-nutrient/bioactive components of 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 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 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:

**Nutrition and HIV Activities.** Beginning in 2002, PGNB staff has collaborated with the World Health Organization (WHO) on the development of a series of efforts designed to establish evidence-informed recommendations and guidance for the nutritional care of HIV-infected people. With the initial publication of nutritional recommendations for people living with HIV/AIDS in 2003, this collaboration has included: 1) reviews of extant data on macronutrients, micronutrients, nutrition in pregnancy and lactation, nutrition and growth of infants and children, and the interrelationships between nutrition and antiretroviral therapies, 2) dissemination of specific recommendations, 3) the conduct of three regional consultations to address the impact of these documents in high-prevalence countries in Sub-Saharan Africa, Southeast Asia, and West Africa, 4) the passage of the World Health Assembly resolution to integrate food and nutrition into global programs addressing HIV, 5) the inclusion of a food and nutrition strategy into the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). Developed by the Office of

the U.S. Global AIDS Coordinator (OGAC) PEPFAR Food and Nutrition Technical Working Group (F & N TWG), which includes PGNB staff as a member, this policy has evolved into a new program called Nutritional Assessment, Care and Support (NACS) that is now being implemented in all PEPFAR country plans and rolled out as part of the Medical Education Partnerships Initiative (MEPI), 6) development of new WHO guidelines for nutrition care of HIV-infected infants and children (<14 years of age) published in 2010 with support from NICHD and NIH's Office of AIDS Research. The collaboration between WHO, PGNB, and PEPFAR is in the process of implementing the pediatric guidelines and developing new guidance and a manual for nutritional care that extends beyond age 14 years to include adolescents and adults, including pregnant and lactating women.

With regard to the new guideline development process at WHO, PGNB staff continues its collaboration to focus on the evidence to support: 1) changes in current recommendations for nutritional care of HIV-infected people and 2) the development of new guidelines for the nutritional care of HIV-infected adolescents and adults, including pregnant and lactating women. This guideline development process relies on a well-developed systematic review process that began with a state of the science conference in Washington, D.C. The goal of these activities is to fully integrate food and nutrition into all aspects of prevention, care, and treatment of HIV with particular reference to resource-limited settings.

PGNB staff are currently working with OGAC, the PEPFAR F&N TWG and the U.S. Agency for International Development to fully deploy and utilize NACS to more fully to define how best to integrate, monitor, and assess food and nutrition interventions and programs within PEPFAR settings.

PGNB staff continues to work with PEPFAR, the Academy of Nutrition and Dietetics, and other partners to develop a nutrition and dietetics curriculum that will be integrated into medical/nursing training programs supported via PEPFAR (MEPI/Nursing Education Partnership Initiative).

**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.

**Interventions to Improve Nutrition including Micronutrient Nutrition.** According to the recent Global Burden of Disease analyses, the global health context has become even more complex given the dual burden of over- and under-nutrition, superimposed on colliding epidemics of infectious and non-communicable diseases. A significant portion of this burden falls on women, infants, and children. The ability to address this complex health scenario is challenged by a limited understanding of the exact nature of the role of nutrition in these processes and the tools to most effectively explore these relationships as well as to assess the impact of current and new therapies/approaches to care and treatment. These limitations have necessitated application of new strategies to address current approaches, as well as the application of new technologies (e.g., “-omics”) to better evaluate the role of nutrients within relevant biological systems. NICHD/PGNB has initiated a number of activities designed to address various aspects of these challenges:

- 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.
- In addition to funding of investigator-initiated grants, PGNB staff serves as a technical resource to the global health community through such activities as membership in the WHO Nutrition Guidance Expert Advisory Group (NUGAG) sub-committee on single and multiple micronutrient interventions and membership in steering committees for several domestic and global health focused organizations representing the food and nutrition enterprise.

**Iron and Malaria Project.** In partnership with the Bill & Melinda Gates Foundation (BMGF), and with support from various NIH Institutes and Centers (ICs) (most prominently the Office of Dietary Supplements (ODS)), PGNB is conducting a project intended to address issues that impact the safe and effective use of available and emerging new interventions to prevent and treat iron deficiency. This project has a particular emphasis on resource-constrained settings with a high burden of malaria and other infectious diseases. The project has included a translational tract that involved the development of an evidence-informed review to address 1) potential mechanisms to explain adverse effects of iron interventions in the context of infection, 2) evaluation of available and potential new biomarkers to assess nutritional iron status, and 3) a review of the data regarding the safety of iron interventions. This review was completed in 2009 and is currently being revised. The 2009 report was used by WHO in its efforts to revise global guidelines for iron interventions.

In addition, this project supports ten cooperative agreement (U01) grants addressing key aspects of the iron/malaria question. With additional resources that have been made available via co-funding from

NIH's ODS and NICHD, the Iron and Malaria Project also conducted two independent projects: 1) a collaboration with the Centers for Disease Control and Prevention (CDC) to develop standards to be applied to the harmonization of soluble transferrin receptor (sTfr) assay which has emerged as a high priority biomarker for iron assessment globally, and 2) a collaboration with CDC and the Global Alliance for Improved Nutrition to utilize 17 country national nutrition datasets to look at the impact of inflammation on biomarkers of iron and other nutrients and to identify other determinants (aside from iron) of anemia. The project is called Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA). The outputs from the BRINDA project have already been incorporated into a WHO Working Group for the use of ferritin as a biomarker of iron for populations.

Two Additional Projects Resulting from the Iron and Malaria Umbrella:

- **Inflammation and Nutritional Science for Programs/Policies and Interpretation of Research Evidence (INSPIRE).** The INSPIRE project evolved out of the emerging appreciation of the importance and bi-directional relationship between nutrition and the inflammatory process. The project was designed to pull together the extant evidence with regard to both the impact of nutrition on inflammation and vice versa as well as identify strategies to address the impact of the inflammatory process on selection, use and most importantly interpretation of biomarkers of nutrient status. The summary of the INSPIRE project was published in 2015 in the *Journal of Nutrition*.
- **International Union of Nutrition Sciences (IUNS) Task Force on Irons** the IUNS Task Force will for the first time conduct a series of risk: benefit analyses to address the safe and effective use of interventions to prevent and treat iron deficiency.

**Biomarkers of Nutrition for Development (BOND).** This project is also supported by a core grant from the BMGF along with several NIH ICs (ODS and the Division of Nutrition Research Coordination). It includes a steering committee composed of a consortium of public and private partners that represents the breadth of the U.S. government (USG) and global food and nutrition enterprise. The BOND project has developed a process for the harmonization of decisions about the best biomarkers for specific uses under specific conditions. The goal is also to identify a research agenda that will advance the discovery, development and implementation of new biomarkers and technologies for both point-of-care and population-based assessments of nutritional status including nutrient exposure, status, and health impact. BOND produced an interactive web-based resource that is available to the global health community to provide links to relevant programs and agencies and provide evidence-based advice on what biomarkers might be most useful to a given user irrespective of their level of expertise or need. The first phase of the BOND project included information about six nutrients (iron, zinc, iodine, folate, vitamin A and vitamin B12) selected by the BOND Steering Committee based on their global significance.

Phase II of the BOND project will focus on specific biological systems and relevant nutrient clusters within those systems. Two initial focal points will be:

- **Biomarkers in Growth (BIG):** Focused on both body composition and linear growth and relevant nutrient clusters
- **Micronutrients in Neuro-development (MIND):** Focused on the role of nutrition in the developing nervous systems
- **Complementary Bio-Indicators for Nutritional Evaluation (COMBINE):** Because of the focus on the role of nutrition in the function of biological systems, a need exists for complementary

measures of function that while not providing the sensitivity or specificity of biomarkers, nevertheless provide valuable information about the function of the systems of interest. Bio-indicators serve as sentinels of change within the relevant systems and will provide important tools in the evaluation not only of the role of nutrition in those systems but also how those systems respond to nutritional interventions.

**Multigenerational Studies on the Impact of Malnutrition and Food Supplementation.** This is a landmark longitudinal cohort study to understand the importance of nutrition in long-term cognitive and neurological development and health that has been conducted in Guatemala. This multigenerational study has been able to examine the effects of nutritional interventions in malnourished mothers. The two studies were carried out over two decades: the Institute of Nutrition of Central America and Panama (INCAP) Longitudinal Study (1966-1977) and its follow-up (1988-1989). The study included a nutrition intervention that improved the energy and nutrient intakes of women and preschool children. Its effects included improved birth weights, reduced infant mortality rates, and improved growth rates in children less than three years of age. The follow-up study, conducted when the subjects were 11-27 years old, found long-term effects including greater stature and fat-free mass, particularly in females; improved work capacity in males; and enhanced intellectual performance in both genders. These studies have confirmed the importance of good nutrition not only for the short-term outcomes of pregnancy, but also long-term impacts on the quality of life and economic development.

**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.

**Global Multilevel Research on the Etiology of Childhood Obesity:** In light of the global obesity epidemic, PGNB, in conjunction with the NICHD Behavioral and Social Sciences Consortium, is developing a new initiative to study the multiple levels of factors contributing to childhood obesity. The goal is to generate observational studies that encompass at least three levels of etiologic factors (e.g., individual nutrition and biology, family processes, and social policies) that are potentially modifiable in future interventions. Attempts will be made to standardize measures of the same etiologic level across studies. Ultimately, these data can be fed into systems models to help us better understand the causes and predict the outcomes of childhood obesity.

### **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.
- In addition, PGNB staff serves on numerous interagency committees involved in current and emerging efforts to address the role of nutrition in global health. This includes membership on various WHO/NUGAG sub-committees. In addition to the ones mentioned above, this includes PEPFAR/Global Health Initiative working groups, the interagency research Steering Committee for Feed the Future, the interagency committee to explore potential partnerships between NIH,

USDA, and the National Science Foundation, and membership in the newly established Sackler Institute for Nutrition Science, among others.

**Website**

<https://www.nichd.nih.gov/about/org/der/branches/pgnb/Pages/overview.aspx>

**Point-of-Contact**

Dr. Daniel Raiten

[raitend@mail.nih.gov](mailto:raitend@mail.nih.gov)

301-435-7568

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

### **Overview**

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
- Ethical Issues Related to the Care of Critically Ill Children and Their Families
- Interplay of Physical and Psychological Trauma in Children
- Multiple Organ Dysfunction Syndrome (MODS) in Critically Ill Children
- Prevention and Treatment of Life Threatening Traumatic Injuries in Children

### **Major International Initiatives over the Past Year**

#### **Biological Pathways of Risk and Resilience in Syrian Refugee Children**

Principal Investigators: Dr. Michael Pluess: Queen Mary University of London; Dr. Elie Georges Karam 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 8-16 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.

### **Recent Achievements in International Health**

A staff member from PTCIB will attend the **Safety 2016 Worlds Conference- 12th World Conference on Injury Prevention & Safety Promotion** in Tampere, Finland from 9/17/2016 - 9/21/2016. They will be presenting on PTCIB program priorities in injury research and training.

The World Conference on Injury Prevention and Safety Promotion is the 12th biennial, international conference on injury prevention and safety promotion. The conference will bring together the world's leading researchers, practitioners, policy-makers and advocates in the field of injury prevention and safety to debate, discuss and share information and experiences. Safety 2016 is proudly hosted by the National Institute for Health and Welfare (THL) and several partners and colleagues from Finland, Europe and the international community. The conference is co-sponsored by the World Health Organization (WHO). Injuries - violence and unintentional - are a major burden on public health worldwide. While experts in injury prevention and safety promotion recognize the need for action, the state-of-the-art knowledge and practice from these fields are not consistently applied to policies and

programs in the field. The main theme for the Safety 2016, “From research to implementation”, seeks to provoke new ideas and experiences to address this gap.

### **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

### **Website**

<https://www.nichd.nih.gov/about/org/der/branches/ptcib/Pages/overview.aspx>

### **Point-of-Contact**

Dr. Valerie Maholmes

[maholmev@mail.nih.gov](mailto:maholmev@mail.nih.gov)

301-496-1514

## Population Dynamics Branch (PDB)

### Mission of Branch

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.

### Major International Initiatives over the Past Year

The NICHD Population Dynamics Branch supports extensive research on the health and development of populations in many foreign countries. In 2016, there were 119 publications on research outside the United States supported by PDB. A brief overview of the research topics, by country, is provided in the table below. The PDB international research portfolio is supported through a number of requests for applications (RFA), most calling for research on HIV/AIDS. Most PDB international research, however, is investigator initiated, supported by regular research grants (R01s), program projects (P01s), or small grants (R03s and R21s). A number are supported by training and career development grants (F31s, F32s, T32s, and K awards) and by the Population Dynamics Centers Program. While a large share of the PDB-supported international research involves primary data collection, a sizable share involves secondary analysis of existing data, such as censuses, vital statistics, health records, administrative records, and large data collection efforts such as the Demographic and Health Surveys.

**Establishing and enhancing Offices of Research and Sponsored Programs in low and middle income countries.** Through the *Biomedical/Biobehavioral Research Administration Development (BRAD) Award (G11) program (PAR-14-333)*, 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. Institutions in sub-Saharan Africa, India, and low and middle income countries in the Caribbean and South America are eligible to apply. In FY 2016, PDB supported G11 programs at Africa University in Zimbabwe; Universidad Peruana Cayetano Heredia in Peru; and the College of Health Sciences at the University of Zimbabwe, Zimbabwe.

**Global Partnerships for AIDS Social Science Research.** *The Global Partnerships for Social Science AIDS Research (RFA-HD-13-012)* supports partnerships 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 research infrastructure of local institutions in developing countries and providing support for a small portfolio of high impact social and/or behavioral science research on HIV/AIDS. The NICHD Population Dynamics Branch currently supports research partnerships between Columbia University Mailman School of Public Health and Hanoi Medical University in Vietnam; Brown University School of Public Health and the University of Cape Town School of Public Health and Family Medicine in South Africa; and the University of South Florida and the State University of Haiti.

## Prevention and Treatment of HIV/AIDS—Collaboration between the United States and Russia.

Along with NIDA, NCI, NIAAA, NIAID, and NIMH, NICHD participates in the *U.S.-Russia Bilateral Collaborative Research Partnerships (CRP) on the Prevention and Treatment of HIV/AIDS and Co-morbidities (R21) RFA-DA-14-001*. The NICHD Population Dynamics Branch supports one project through this initiative, a study of behavioral and institutional barriers to HIV prevention among migrant women in two Russian cities—Kazan and Nizhny Novgorod.

**Preventing HIV/AIDS by Improving Knowledge of Reproductive Health.** The NICHD Population Dynamics Branch supports three grants through the *Prevention of HIV Transmission/Acquisition through a Better Understanding of Reproductive Health (R01) HD12-198*, an examination of use of safe contraception strategies among HIV clients in Uganda; a couples-based project aimed at reducing sexual and perinatal HIV transmission in Rwanda; and a project on fertility desires, behaviors, and outcomes of men, women, and couples in HIV seroconcordant and discordant couples in Rakai, Uganda.

### Brief Overview of the Research Topics, by Country, Supported by PDB.

Research Topic	Countries
HIV/AIDS and other sexually transmitted infections (e.g. care and treatment; epidemiology; medical male circumcision; partner notification; prevention, including mother to child transmission; stigma; testing and counseling)	Botswana, China, Democratic Republic of the Congo, Dominican Republic, Malawi, Mexico, Mozambique, Peru, South Africa, Uganda, Venezuela , Zambia and multi-country studies
Environmental health	Ecuador, Romania and multi-country studies
Family dynamics and parenting	Guatemala, India, Malawi, Mexico, South Africa
Health communication	Senegal
Indoor air pollution	Malawi
Maternal and child health interventions and outcomes (e.g. breastfeeding, immunizations, postpartum hemorrhage, pregnancy and birth outcomes)	Australia, Bangladesh, China, Denmark, Ghana, India, Japan, Malawi, Mozambique, Nigeria, Romania, Rwanda, Senegal, United Kingdom and multi-country studies
Mental health	Ghana, Sweden, United Kingdom
Migration	Burkina Faso, Canada, Kenya, Mexico, Nigeria, Senegal, Uganda and multi-country studies
Non-communicable diseases	Brazil, China, India, Mexico, Russia, South Africa, United Kingdom
Orphans and vulnerable children	Guatemala, Zimbabwe
Sexual and reproductive health	Brazil, Canada, China, Denmark, India, Kenya, Nepal, Philippines, South Africa, United Kingdom and multi-country studies
Substance abuse	China, Kenya
Violence	Bangladesh, India, Kenya, Mexico, South Africa

## **International Partnerships**

- Joint Working Group on AIDS and Research in Russia

## **Website**

<https://www.nichd.nih.gov/about/org/der/branches/pdb/Pages/overview.aspx>

## **Point-of-Contact**

Dr. Rebecca L. Clark

[rclark@mail.nih.gov](mailto:rclark@mail.nih.gov)

(301) 496-1175

## **Pregnancy and Perinatology Branch (PPB)**

### **Mission of Branch**

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 care systems and health 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**

**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 400,000 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 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. The infants will be followed through 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 utilization 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, and 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. An abstract was accepted for inclusion in the Society for Maternal-Fetal Medicine (SMFM) meeting; with primary analyses are underway. It is also supported by the Bill & Melinda Gates Foundation, GE Healthcare, and the University of Washington.

**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.

**Malaria in Pregnancy: Nutrition and Immunologic Effects.** Malaria in pregnancy is a major public health problem for many countries in Sub-Saharan Africa. Malaria is associated with tremendous morbidity in the mother including severe anemia, as well as in the fetus, in the form of low birth weight (LBW) and fetal loss. Vitamin A and zinc deficiencies are specific factors which can modulate the clinical course of malaria and exacerbate associated complications. Published literature suggests that these two micronutrients favor a reduction in the risk of placental malaria and related clinical outcomes, including malaria and anemia, among women, and LBW. A NICHD funded study is being conducted by the Harvard T.H. Chan School of Public Health in collaboration with Muhimbili University of Health and Allied Sciences in Dar es Salaam, Tanzania. The investigators will study the efficacy of zinc alone, vitamin A alone, both zinc and vitamin A, or placebo in reducing the risk of placental malaria and other maternal/fetal outcomes. The Principal Investigator will recruit 9,000 women of reproductive age and follow them on a monthly basis for pregnancy status, and identify and randomize a target sample of 2,500 pregnant women at or before 13 weeks of gestation. Women, and after-delivery babies, will be followed up until six weeks post-delivery.

**Cytomegalovirus Vaccines: Reinfection 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. Although maternal infection during pregnancy (primary maternal infection) represents a significant risk for virus transmission to the fetus and disease, infection and transmission to the fetus in women with existing immunity to this virus (non-primary maternal infection) is frequent. Disease in babies infected following non-primary maternal infection is well-documented. Worldwide, including most U.S. populations, the disease burden in infected infants born to women with non-primary infections exceeds that of offspring of women with primary maternal infection.

This study will explore mechanisms of non-primary maternal infections, reinfection with new strain of viruses and recurrence/reactivation of a persistent infection. This study will define virological characteristics of non-primary infections and parameters of HCMV specific immunity in a highly seroimmune population in which non-primary maternal infections account for the vast majority of infected babies. These studies 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 obstetricians/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.

**Optimizing Maternal and Child Health in Kenya.** NICHD is funding a multi-disciplinary team of clinician-researchers from Eldoret, Kenya, for two conferences to learn about recent advances on ways to improve the iron, zinc, folate, and vitamin-B12 status of women and children. Undernourishment with

key mineral and micronutrient deficiencies of iron, zinc, folate, and vitamin-B12 among women during pregnancy predisposes to serious complications, especially during labor and delivery. In addition, children of such mothers can develop midline birth defects, altered brain development, and a predisposition to infections. Using a focused approach investigators will identify gaps in the literature that pertain to research-poor settings, and then develop short-term research plans to test clinical interventions to prevent and treat these deficiencies as a prelude to larger community-based interventions in Kenya. These conferences will provide the forum where a local multi-disciplinary faculty group of expert clinician-researchers will meet and develop short-term research projects that can then lay the foundation for a larger preventive strategy to optimize maternal and child nutrition in Kenya.

#### **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. Members of the IOM expert panel also noted that persistent methodological limitations in previous studies, including treating PTD as a single entity and failure to recognize important common pathophysiological pathways that may lead to PTD (e.g., systematic inflammation, endothelial dysfunction, oxidative stress, and placental ischemia) have hindered discovery of potential treatment and prevention strategies.

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. Pathophysiologic mechanisms involved in AP include uteroplacental ischemia, underperfusion, chronic hypoxia, and infarctions. Evidence suggests that transient activation of the sympathetic nervous system might trigger AP. Results from previous studies suggest a significant genetic component in the pathogenesis of AP.

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 abruptio 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. Secondary aims include evaluation of the program impact on the: a) proportion of pregnancies with outcomes occurring prior to 37 weeks (late miscarriage, preterm still birth, and live birth) and b) proportion of newborns with early onset sepsis (Aim 2); determination of the prevalence of abnormal vaginal flora and UTI, including asymptomatic bacteriuria, among pregnant rural Bangladeshi women (Aim 3); and evaluation of the accuracy of simple, low-cost, point-of-care diagnostic tests by community health workers (Aim 4).

The researchers will conduct a cluster randomized, controlled trial enrolling 8,134 pregnant mothers from rural Sylhet, Bangladesh. The intervention group will be screened for GU infections between 12 to 16 weeks; those with abnormal vaginal flora and/or UTI will be treated. The control group will receive usual care. 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.

**Better Methods to Test the Severity of Neonatal Jaundice: Clinical Studies on Jaundice in Newborn Infants.** The existing methods of assessing the extent of newborn infants’ severity of jaundice, or blood concentrations of bilirubin, have major limitations in helping to decide “safe” and “unsafe” degrees of jaundice. Using the current method we measure “indirect” bilirubin, which is bound to albumin in the blood. Instead, if one could use “free” bilirubin that is not bound to albumin, the latter could be a better predictor of long-term outcome.

NICHD has funded two studies awarded to two U.S. institutions, to conduct pilot studies to estimate the value of measuring free indirect bilirubin in predicting outcome of infants with jaundice in countries where jaundice-related brain injury is very high. One study was conducted in India and led by a team of scientists from University of Rochester; the other is located in Egypt and is led by scientists from University of Washington and Stanford University. Their findings provide strong evidence for the first time that indirect bilirubin measurement using U.S.-developed technologies can be used to better predict and treat infants with jaundice globally. Efforts are being made to translate the findings into practice in India.

**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:

1. 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. Additional analyses from this study are pending.
2. A study by scientists at Johns Hopkins University in Baltimore is testing the effects of surface application of sunflower oil as a skin massage to newborns, in lieu of the traditional castor oil massage, on infant mortality in Nepal. A total of 3,707 subjects have been recruited in 430 rural communities; data is currently being analyzed. The findings of this study, if they prove the hypothesis, can significantly impact neonatal and infant mortality rates in the low resource settings.

**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 so the results could be combined with an individual participant data meta-analysis.

**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.

Based on the unique facilities at Monash University, this group of investigators can use large and small animal models to study the most critical issues experienced by preterm infants during their transition to newborn life at birth. They will: 1) identify the most effective ways of initiating ventilation in the delivery room. They will specifically focus on procedures that optimize lung recruitment, facilitate the increase in pulmonary hemodynamics and protect the brain from hemodynamic instability; 2) determine how a sustained inflation, given as the first breath after birth in severely asphyxiated preterm lambs, rapidly restores cardiac function and whether this rapid response increases the risk of brain injury; 3) determine the physiological basis underlying respiratory, cardiovascular, and cerebral vascular improvements observed in response to delayed umbilical cord clamping, and determine the factors that alter these physiological responses.

**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 to Test Maternal Affect on Pregnancy Outcome, University of Colorado, Boulder, with subcontract to King's College, London.** Despite improvements in prenatal care, the rate of poor pregnancy outcomes, such as preterm birth (i.e., < 37 weeks gestation) and LBW, remains high in the United States. This project will provide important evidence concerning the relationships between antenatal maternal mood disorders, pregnancy-specific stress, and poor pregnancy outcomes, as well as what these relationships mean for infant immunologic and neurobehavioral development. The proposed research will test the hypothesis that prenatal maternal mood disorders (anxiety and/or depression) and symptoms increase the risk of poor pregnancy outcomes and compromise infant behavioral and immunological development in the first year of life, and that activation of the hypothalamic-pituitary-adrenal axis and increased inflammatory activity in the perinatal period plays a significant role in these effects.

**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.

**Maternal I-Carbon Metabolism in Low Birth Weight Infants: R01 Award to Cleveland Clinic, Cleveland, OH, with a subcontract to KEM Hospital Research Center, Pune, India.** Researchers will investigate how maternal nutrient metabolism contributes to LBW (<2500 grams birth weight) in a cohort of Indian pregnant women. LBW in infants, due to intrauterine growth retardation (IUGR), remains a critical problem in the developing countries and is a major contributor to the morbidity and mortality. It is estimated that almost 30% of all live births in developing countries are LBW. Studies with humans and experimental animals have shown that perturbation in the methionine and one carbon metabolism in the mother and possibly in the fetus, impacts fetal growth and "programming" of the metabolism of the infant and ultimately causes the observed phenotype. The study's specific aims are to longitudinally document maternal methionine, homocysteine metabolism, relate it to nutrient (protein) intake, folate, B12, pyridoxine status, and measures of insulin resistance. These studies will identify the mechanism of IUGR and lead to the development of strategic recommendations at the identified critical periods in

pregnancy using various methyl donors with the goal of preventing both immediate neonatal and long-term "programming" consequences in the baby. There are major public health and economic implications for this study.

**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 H<sub>2</sub>O 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.

## Recent Achievements in International Health

- **Pregnant Women with Parasitic Infestation and their Offspring's Responses to Childhood Vaccinations: a Secondary Study** funded by NICHD and conducted by researchers from Case Western University in Cleveland has discovered some intriguing findings. It is known that maternal parasitic infections during pregnancy prime the fetal immune responses and induce an immunomodulatory phenotype at birth that may affect subsequent immune responses to commonly administered childhood vaccines. 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) disseminating 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.

## Website

<https://www.nichd.nih.gov/about/org/der/branches/ppb/Pages/overview.aspx>

## Points-of-Contact

### NICHD Global Network for Women's and Children's Health Research

Dr. Marion Koso-Thomas

[kosomari@mail.nih.gov](mailto:kosomari@mail.nih.gov)

301-435-6896

Dr. Menachem Miodovnik

[Menachem.Miodovnik@nih.gov](mailto:Menachem.Miodovnik@nih.gov)

301-451-5031

### NICHD Maternal Fetal Medicine Units Research Network

Dr. Uma Reddy

[reddyu@mail.nih.gov](mailto:reddyu@mail.nih.gov)

301-496-1074

**NICHHD Prenatal Alcohol, Stillbirth and Sudden Infant Death Syndrome Network**

Dr. Marian Willinger

[Marian.Willinger@nih.gov](mailto:Marian.Willinger@nih.gov)

301-435-6896

**For General Global Health Research support from PPB**

Dr. Tonse N. K. Raju

Chief, Pregnancy and Perinatology Branch

[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

301-402-1872

# National Center for Medical Rehabilitation Research (NCMRR)

## Mission of Center

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 in order to capitalize upon the myriad advances occurring in the biological, behavioral, and engineering sciences. These advances are emphasized through four areas:

- Biological Sciences and Career Development
- Behavioral Sciences and Rehabilitation Engineering Technology
- Traumatic Brain Injury and Stroke Rehabilitation
- Spinal Cord and Musculoskeletal Disorders and Assistive Devices

## International Partnerships

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.

### **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 multi-disciplinary efforts at the student, mentor and university level, and promotes outreach to the disabled community. These goals will be met through the following specific objectives: 1) require 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.

### **Website**

<https://www.nichd.nih.gov/about/org/ncmrr/Pages/overview.aspx>

### **Point-of-Contact**

Dr. Ralph Nitkin

[R21e@nih.gov](mailto:R21e@nih.gov)

301-402-4206

## Division of Intramural Population Health Research (DIPHR)

### Mission of Division

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.

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 2 diabetes. Principal Investigator: Dr. C. Zhang; Co-investigators: E. Schisterman, G. Buck Louis, J. Mills, E. Yeung, A. Liu.
- International consortium project on angiogenesis factors and preeclampsia, Drs. C. Zhang, E. Schisterman, E. Yeung.
- 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. Laughon 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.

### **Epidemiology Branch Investigators Involved in International Activities**

Enrique F. Schisterman, Ph.D., M.A.  
I/C: NICHD, DIPHR, Epidemiology Branch  
Role: Chief and Senior Investigator  
schistee@mail.nih.gov

Aiyi Liu, Ph.D.  
I/C: NICHD, DIPHR, Biostatistics and Bioinformatics Branch  
Role: Senior Investigator  
liua@mail.nih.gov

James L. Mills, M.D., M.S.

I/C: NICHD, DIPHR, Epidemiology Branch  
Role: Senior Investigator  
[millsj@exchange.nih.gov](mailto:millsj@exchange.nih.gov)

Cuilin Zhang, M.D., Ph.D., M.P.H.  
I/C: NICHD, DIPHR, Epidemiology Branch  
Role: Senior Investigator  
[zhangcu@mail.nih.gov](mailto:zhangcu@mail.nih.gov)

Katherine Laughon Grantz, M.D.  
I/C: NICHD, DIPHR, Epidemiology Branch  
Role: Investigator  
[laughonsk@mail.nih.gov](mailto:laughonsk@mail.nih.gov)

Edwina Yeung, Ph.D.  
I/C: NICHD, DIPHR, Epidemiology Branch  
Role: Investigator  
[yeungedw@mail.nih.gov](mailto:yeungedw@mail.nih.gov)

### **Website**

<https://www.nichd.nih.gov/about/org/diphr/Pages/default.aspx>

### **Point-of-Contact**

Enrique F. Schisterman, Ph.D., M.A.  
[schistee@mail.nih.gov](mailto:schistee@mail.nih.gov)  
301-435-6893

## 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. DIR aims 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.

Scientists and physicians in the NICHD Division of Intramural Research (DIR) are organized into 14 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
- Behavioral Determinants and Developmental Imaging
- 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
- Integrative Membrane, Cell, and Tissue Pathophysiology
- Metals Biology and Molecular Medicine
- Neurosciences
- Pediatric Endocrinology, Metabolism, and Molecular Genetics
- Perinatal and Obstetrical Research
- Reproductive Endocrine and Gynecology

**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?

**Website:** <https://www.nichd.nih.gov/about/org/dir/Pages/index.aspx>

## **Child and Family Research Section (CFRS)**

**Name of Investigator:** Marc H. Bornstein, Ph.D.

**Name of Lab:** Child and Family Research Section, NICHD

**Affinity Group:** Behavioral Determinants and Developmental Imaging

### **Mission of Section**

The CFRS 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, CFRS 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, the CFRS collaborates internationally with several groups over several topics:

- Caribbean (Jamaica, Haiti) and Belgium and Turkey: Adolescent and parent acculturation
- 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
- Parenting across Cultures: Parent-adolescent development in nine countries (China, Columbia, Italy, Jordan, Kenya, The Philippines, Sweden, Thailand, and the United States)
- 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 2015 to present, 42 reports dealing with international or cross-cultural samples and collaborations were published.

1. Bornstein, M.H., & Esposito, G. (2015). Beyond cry and laugh: Toward a multi-level model of language production. *Behavioral and Brain Sciences*, 37, 548-549.
2. Bornstein, M. H., Putnick, D. L., Lansford, J. E., Deater-Deckard, K., & Bradley, R. H. (2015). A developmental analysis of caregiving modalities across infancy in 38 low- and middle-income countries. *Child Development*, 86, 1571-1587.
3. Bornstein, M. H., Bradley, R., Britto, P. R., Deater-Deckard, K., Lansford, J. E., & Putnick, D. L. (2016). Desarrollo infantil temprano en países en vías de desarrollo [Early child development in developing nations]. En M. Cordero Vega, H. Molina Milman, & R. Mercer (Eds.), *De las moléculas al capital humano [From molecules to human capital]* (pp. 37-45). Washington, DC: Banco Interamericano de Desarrollo.
4. Bornstein, M. H., & Putnick, D. L. (2016). IV. Mothering and fathering daughters and sons in low- and middle-income countries. In M. H. Bornstein, D. L. Putnick, J. E. Lansford, K. Deater-Deckard, & R. H. Bradley, *Gender in low- and middle-income countries. Monograph of the Society for Research in Child Development*, 81, 60-77.
5. Bornstein, M. H., Putnick, D. L., Bradley, R. H., Deater-Deckard, K., & Lansford, J. E. (2016). Gender in low- and middle-income countries: Introduction. *Monographs of the Society for Research in Child Development*, 81, 7-23.
6. Bornstein, M. H., Putnick, D. L., Bradley, R. H., Deater-Deckard, K., & Lansford, J. E. (2016). VII. Gender in low- and middle-income countries: Reflections, limitations, directions, and implications. In M. H. Bornstein, D. L. Putnick, J. E. Lansford, K. Deater-Deckard, & R. H. Bradley, *Gender in low- and middle-income countries. Monograph of the Society for Research in Child Development*, 81, 123-144.
7. Bornstein, M. H., Putnick, D. L., Bradley, R. H., Deater-Deckard, K., Lansford, J. E., & Ota, Y. (2016). Gender in low- and middle-income countries: General methods. *Monographs of the Society for Research in Child Development*, 81, 24-32.
8. Bornstein, M. H. (in press). Parenting and language in ethnic minority and immigrant families in North America and the European Union: Toward an emphasis on positive development. In N. Cabrera & B. Leyendecker (Eds.), *Handbook of Positive Development of Minority Children* (pp. xx-xx). The Netherlands: Springer.
9. Bornstein, M. H., & Lansford, J. E. (in press). Culture and family functioning. In E. Jouriles (Ed.), *Applications of Contemporary Family Psychology. Volume 2 of the APA Handbook of Contemporary Family Psychology* (pp. xx-xx). Editor-in-Chief: B. Fiese. Washington, DC: APA.
10. Bornstein, M. H., Putnick, D. L., Oburu, P., Lansford, J. E., Deater-Deckard, K., Bradley, R. M., Moriguchi, R., & Britto, P. B. (in press). Parenting, environment, and early child development in Sub-Saharan Africa. In A. Abubakar & F. van de Vijver (Eds.), *Handbook of Applied Developmental Science in Sub-Saharan Africa* (pp. xx-xx). New York; Springer.
11. Cote, L. R., Kwak, K., Putnick, D. L., Chung, H.J., & Bornstein, M. H. (2015). The acculturation of parenting cognitions: A comparison of South Korean, Korean Immigrant, and European American mothers. *Journal of Cross-Cultural Psychology*, 46, 1115-1130.

12. De Houwer, A., & Bornstein, M. H. (2015). Balance patterns in early bilingual acquisition: A longitudinal study of word comprehension and production. In J.C. Treffers-Daller & C. Silva-Corvalan (Eds.), *Language Dominance* (pp. 134-155). Cambridge: Cambridge University Press.
13. De Houwer, A., & Bornstein, M. H. (2016). Bilingual mothers' language choice in child-directed speech: Continuity and change. *Journal of Multilingual and Multicultural Development*, 2016, 1-13.
14. De Houwer, A., & Bornstein, M. H. (in press). The frequency of maternal input to bilingual and monolingual children. In T. Grüter & J. Paradis (Eds.), *Input and Experience in Bilingual Development* (pp. xx-xx). Amsterdam/Philadelphia: John Benjamins.
15. Dodge, K. A., Malone, P. S., Lansford, J. E., Sorbring, E., Skinner, A. T., Tapanya, S., Uribe Tirado, L. M., Zelli, A., Alampay, L. P., Al-Hassan, S. M., Bacchini, D., Bombi, A. S., Bornstein, M. H., Chang, L., Deater-Deckard, K., Di Giunta, L., Oburu, P., & Pastorelli, C. (2015). Hostile attributional bias and aggressive behavior in global context. *Proceedings of the National Academy of Science*, 112, 9310-9315.
16. Dudek, J., Faress, A., Bornstein, M. H., & Haley, D. W. Infant cries rattle adult cognition. (2016). *PLoS ONE*, 11(5): e0154283.
17. Esposito, G., Nakazawa, J., Venuti, P., & Bornstein, M. H. (2015). Judgment of infant cry: The roles of acoustic characteristics and sociodemographic characteristics. *Japanese Psychological Research*, 57, 126-134.
18. Esposito, G., Setoh, P. & Bornstein, M. H. (2015). Beyond practices and values: Toward a physio-bioecological analysis of sleeping arrangements in early infancy. *Frontiers in Psychology (Cultural Psychology)*, 6, 264-266.
19. Esposito, G., Valenzi, S., Islam, T., & Bornstein, M. H. (2015). Three physiological responses in fathers and non-fathers' to vocalizations of typically developing infants and infants with Autism Spectrum Disorder. *Research in Developmental Disabilities*, 43-44, 43-50.
20. Esposito, G., Valenzi, S., Islam, T., Mash, C., & Bornstein, M. H. (2015). Immediate and selective maternal brain responses to own infant faces. *Behavioural Brain Research*, 278, 40-43.
21. Esposito, G., Setoh, P., Shinohara, K., & Bornstein, M. H. (Eds.). (in press). Special Issue of *Behavioural Brain Research*. (in press). *The Development of Attachment: Integrating Genes, Brain, Behavior, and Environment*.
22. Esposito, G., Truzzi, A., Setoh, P., Putnick, D. P., Shinohara, K., & Bornstein, M. H. (in press). Genetic predispositions and parental attachment interact to shape adults' physiological responses to social distress. *Behavioural Brain Research*.
23. Ferguson, G. M., & Bornstein, M. H. (2015). Remote acculturation of early adolescents in Jamaica towards European American culture: A replication and extension. *International Journal of Intercultural Relations*, 45, 24-35.
24. Ferguson, G. M., & Bornstein, M. H. (in press). Tridimensional acculturation: Culture and adaptation of Black Caribbean immigrants in the USA. In R. Dimitrova, M. Bender, & F. van de

Vijver (Eds.), *Global perspectives on well-being in immigrant families* (pp. xx-xx). Dordrecht: Springer Science+Business Media.

25. Gartstein, M., Putnick, D. L., Kwak, K., Hahn, C.-S., & Bornstein, M. H. (2015). Stability of temperament in South Korean infants from 6 to 12 to 18 months: Moderation by age, gender, and birth order. *Infant Behavior and Development*, 40, 103-107.
26. Greiff, S., Wüstenberg, S., Götz, T., Vainikainen, M.-P., Hautamäki, J., & Bornstein, M. H. (2015). A longitudinal study of higher-order thinking skills: Working memory and fluid reasoning in childhood enhance complex problem solving in adolescence. *Frontiers in Psychology (Developmental Psychology)*, 6, Article 1060.
27. Karasik, L. B., Tamis-LeMonda, C. S., Adolph, K. E., & Bornstein, M. H. (2015). Places and postures: A cross-cultural comparison of sitting in 5-month-olds. *Journal of Cross-Cultural Psychology*, 2015, 46, 1023-1038.
28. Kringelbach, M. L., Stark, E. A., Alexander, C., Bornstein, M. H., & Stein A. (2016). On cuteness: Unlocking the parental brain and beyond. *Trends in Cognitive Sciences*, 20, 545-558.
29. Lansford, J. E., Godwin, J., Uribe Tirado, L. M., Zelli, A., Al-Hassan, S. M., Bacchini, D., Bombi, A. S., Bornstein, M. H., Chang, L., Deater-Deckard, K., Di Giunta, L., Dodge, K. A., Malone, P. S., Oburu, P., Pastorelli, C., Skinner, A. T., Sorbring, E., Tapanya, S., & Alampay, L. P. (2015). Individual, family, and culture level contributions to child physical abuse and neglect: A longitudinal study in nine countries. *Development and Psychopathology*, 27, 1417-1428.
30. Lansford, J. E., Al-Hassan, S. M., Bacchini, D., Bombi, A. S., Bornstein, M. H., Chang, L., Chen, B.-B., Deater-Deckard, K., Di Giunta, L., Dodge, K. A., Malone, P. S., Oburu, P., Skinner, A. T., Pastorelli, C., Sorbring, E., Steinberg, L., Tapanya, S., Alampay, L. P., Uribe Tirado, M., & Zelli, A. (in press). Parenting and positive adjustment for adolescents in nine countries. In R. Dimitrova (Ed.), *Well-being of youth and emerging adults across cultures* (pp. xx-xx). New York: Springer.
31. Lansford, J. E., Bornstein, M. H., Deater-Deckard, K., Dodge, K. A., Al-Hassan, S. M., Bacchini, D., Bombi, A. S., Chang, L., Chen, B.-B., Di Giunta, L., Malone, P. S., Oburu, P., Pastorelli, C., Skinner, A. T., Sorbring, E., Steinberg, S., Tapanya, S., Alampay, L. P., Uribe Tirado, L. M., & Zelli, A. (in press). How international research on parenting advances understanding of child Development. *Child Development Perspectives*.
32. Lansford, J. E., Godwin, J., Alampay, L. P., Uribe Tirado, L. M., Zelli, A., Al-Hassan, S. M., Bacchini, D., Bombi, A. S., Bornstein, M. H., Chang, L., Deater-Deckard, K., Di Giunta, L., Dodge, K. A., Malone, P. S., Oburu, P., Pastorelli, C., Skinner, A. T., Sorbring, E., & Tapanya, S. (in press). Mothers', fathers' and children's perceptions of parents' expectations about children's family obligations in nine countries. *International Journal of Psychology*.
33. Longobardi, E., Spataro, P., Putnick, D. L., & Bornstein, M. H. (2016). Noun and verb production in maternal and child language: Continuity, stability, and prediction across the second year of life. *Language Learning and Development*, 12, 183-198.
34. Longobardi, E., Spataro, P., Putnick, D. L., & Bornstein, M. H. (in press). Do early noun and verb production predict later verb and noun production? Theoretical implications. *Journal of Child Language*.

35. Messina, I., Cattaneo, L., Venuti, P., De Pisapia, N., Serra, M., Esposito, G., Rigo, P., Farneti, A., & Bornstein, M. H. (2016). Sex-specific automatic responses to infant cries: TMS reveals greater excitability in females than males in motor evoked potentials. *Frontiers in Psychology (Psychology for Clinical Settings)*, 6, Article 1909.
36. Pastorelli, C., Lansford, J. E., Luengo Kanacri, B. P., Malone, P. S., Di Giunta, L., Bacchini, D., Bombi A.S., Zelli, A., Miranda, M. C., Bornstein, M. H., Tapanya, S., Uribe Tirado, L. M., Alampay, L. P., Al-Hassan, S. M., Chang, L., Deater-Deckard, K., Dodge, K. A., Oburu, P., Skinner, A.T., & Sorbring, E. (2016). Positive parenting and children's prosocial behavior in eight countries. *Journal of Child Psychology and Psychiatry*, 2016, 57, 824-834.
37. Pearson, R. M., Bornstein, M. H., Cordero, M., Scerif, G., Mahedy, L., Evans, J., Abioye, A., & Stein, A. (2016). Maternal perinatal mental health and offspring academic achievement at age 16: The mediating role of childhood executive function. *Journal of Child Psychology and Psychiatry*, 57, 491-501.
38. Putnick, D. L., & Bornstein, M. H. (2015). Is child labor a barrier to school enrollment in low- and middle-income countries? *International Journal of Educational Development*, 41, 112–120.
39. Putnick, D. L., & Bornstein, M. H. (2016). VI. Girls' and boys' labor and household chores in low- and middle-income countries. In M. H. Bornstein, D. L. Putnick, J. E. Lansford, K. Deater-Deckard, & R. H. Bradley, *Gender in low- and middle-income countries. Monograph of the Society for Research in Child Development*, 81, 104-122.
40. Rigo, P., De Pisapia, N., Bornstein, M. H., Putnick, D., Serra, M., Esposito, G., & Venuti, P. (in press). Brain processes in women and men in response to emotive sounds. *Social Neuroscience*.
41. Senese, V. P., Venuti, P., Giordano, F., Napolitano, M., Esposito, G., & Bornstein, M. H. (in press). Adults' implicit associations to infant positive and negative acoustic cues: Moderation by empathy and gender. *Quarterly Journal of Experimental Psychology*.
42. Serra, M., De Pisapia, N., Rigo, P., Papinutto, N., Jager, J., Bornstein, M. H., & Venuti, P. (2015). Secure attachment status is associated with white matter integrity in healthy young adults. *NeuroReport*, 26, 1106-1111.

### **Recent Achievements in International Health**

Bornstein, M. H., Putnick, D. L., Lansford, J. E., Deater-Deckard, K., & Bradley, R. H. (2016). Gender in low- and middle-income countries. *Monographs of the Society for Research in Child Development*, 81, 1-199.

- 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.

### **Description of International Trainees**

- Hirokazu Doi, 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, University of Bristol, Bristol, UK

### **International Partnerships**

See above.

### **Website**

<https://science.nichd.nih.gov/confluence/display/cfr/Home>

### **Point-of-contact:**

Dr. Marc H. Bornstein

[Marc\\_H\\_bornstein@nih.gov](mailto:Marc_H_bornstein@nih.gov)

301-496-6832

## Section on Environmental Gene Regulation (SEGR)

Name of Investigator: Gisela Storz

**Name of Lab:** Section on Environmental Gene Regulation, NICHD

**Affinity Group:** Cell and Structural Biology

### Mission of Section

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.

### Publications with International Collaborators

1. Thomason, M. K., Bischler, T., Eisenbart, S. K., Förstner, K. U., Zhang, A., Herbig, A., Nieselt, K., Sharma, C. M. and Storz, G. (2015) Global transcriptional start site mapping using dRNA-seq reveals novel antisense RNAs in Escherichia coli. *J. Bacteriol.* 197, 18-28.

### Recent Achievements in International Health

- The paper listed above was the result of a collaboration with scientists at the University of Tübingen and the University of Würzburg in Germany and reported the transcription start sites of RNAs synthesized genome-wide in Escherichia coli. While the experiments were carried out in non-pathogenic K-12, the results are applicable to pathogenic strains of E. coli.

### Description of International Trainees

- Mr. Hanbo Wang, a graduate student in the lab, is in The Chinese University of Hong Kong-NICHD graduate partnership program.

### Website

<https://science.nichd.nih.gov/confluence/display/segr/Home>

### Point-of-Contact

Dr. Gisela Storz

[storz@helix.nih.gov](mailto:storz@helix.nih.gov)

301-402-0968

## Section on Genetics and Endocrinology (SGE)

**Name of Investigator:** Constantine A. Stratakis, M.D., M. (Med) Sci. – Scientific Director

**Name of Lab:** Section on Genetics and Endocrinology, NICHD

**Affinity Group:** Developmental Endocrine Oncology and Genetics

### Mission of Section

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; and others in 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

1. Iacovazzo D, Caswell R, Bunce B, Jose S, Yuan B, Hernández-Ramírez LC, Kapur S, Caimari F, Evanson J, Ferràù F, Dang MN, Gabrovská P, Larkin SJ, Ansorge O, Rodd C, Vance ML, Ramírez-Rentería C, Mercado M, Goldstone AP, Buchfelder M, Burren CP, Gurlek A, Dutta P, Choong CS, Cheetham T, Trivellin G, Stratakis CA, Lopes MB, Grossman AB, Trouillas J, Lupski JR, Ellard S, Sampson JR, Roncaroli F, Korbonits M. Germline or somatic GPR101 duplication leads to X-linked acro-gigantism: a clinico-pathological and genetic study. *Acta Neuropathol Commun.* 2016 Jun 1;4(1):56.

2. Daly AF, Lysy PA, Desfilles C, Rostomyan L, Mohamed A, Caberg JH, Raverot V, Castermans E, Marbaix E, Maiter D, Brunelle C, Trivellin G, Stratakis CA, Bours V, Raftopoulos C, Beauloye V, Barlier A, Beckers A. GHRH excess and blockade in X-LAG syndrome. *Endocr Relat Cancer*. 2016 Mar;23(3):161-70.
3. Naves LA, Daly AF, Dias LA, Yuan B, Zakir JC, Barra GB, Palmeira L, Villa C, Trivellin G, Júnior AJ, Neto FF, Liu P, Pellegata NS, Stratakis CA, Lupski JR, Beckers A. Aggressive tumor growth and clinical evolution in a patient with X-linked acro-gigantism syndrome. *Endocrine*. 2016 Feb;51(2):236-44.
4. Rostomyan L, Daly AF, Petrossians P, Nachev E, Lila AR, Lecoq AL, Lecumberri B, Trivellin G, Salvatori R, Moraitis AG, Holdaway I, Kranenburg-van Klaveren DJ, Chiara Zatelli M, Palacios N, Nozieres C, Zacharin M, Ebeling T, Ojaniemi M, Rozhinskaya L, Verrua E, Jaffrain-Rea ML, Filipponi S, Gusakova D, Pronin V, Bertherat J, Belaya Z, Ilovayskaya I, Sahnoun-Fathallah M, Sievers C, Stalla GK, Castermans E, Caberg JH, Sorkina E, Auriemma RS, Mittal S, Kareva M, Lysy PA, Emy P, De Menis E, Choong CS, Mantovani G, Bours V, De Herder W, Brue T, Barlier A, Neggers SJ, Zacharieva S, Chanson P, Shah NS, Stratakis CA, Naves LA, Beckers A. Clinical and genetic characterization of pituitary gigantism: an international collaborative study in 208 patients. *Endocr Relat Cancer*. 2015 Oct;22(5):745-57.
5. Perez-Rivas LG, Theodoropoulou M, Ferraù F, Nusser C, Kawaguchi K, Stratakis CA, Faucz FR, Wildemberg LE, Assié G, Beschorner R, Dimopoulou C, Buchfelder M, Popovic V, Berr CM, Tóth M, Ardisasmita AI, Honegger J, Bertherat J, Gadelha MR, Beuschlein F, Stalla G, Komada M, Korbonits M, Reincke M. The Gene of the Ubiquitin-Specific Protease 8 Is Frequently Mutated in Adenomas Causing Cushing's Disease. *J Clin Endocrinol Metab*. 2015 Jul;100(7):E997-E1004.
6. Zilbermint M, Xekouki P, Faucz FR, Berthon A, Gkourogiani A, Scherthaner-Reiter MH, Batsis M, Sinaii N, Quezado MM, Merino M, Hodes A, Abraham SB, Libé R, Assié G, Espiard S, Drougat L, Ragazzon B, Davis A, Gebreab SY, Neff R, Kebebew E, Bertherat J, Lodish MB, Stratakis CA. Primary Aldosteronism and ARMC5 Variants. *J Clin Endocrinol Metab*. 2015 Jun;100(6):E900-9.
7. Espiard S, Drougat L, Libé R, Assié G, Perlemoine K, Guignat L, Barrande G, Brucker-Davis F, Doullay F, Lopez S, Sonnet E, Torremocha F, Pinsard D, Chabbert-Buffet N, Raffin-Sanson ML, Groussin L, Borson-Chazot F, Coste J, Bertagna X, Stratakis CA, Beuschlein F, Ragazzon B, Bertherat J. ARMC5 Mutations in a Large Cohort of Primary Macronodular Adrenal Hyperplasia: Clinical and Functional Consequences. *J Clin Endocrinol Metab*. 2015 Jun;100(6):E926-35.
8. Trivellin G, Daly AF, Faucz FR, Yuan B, Rostomyan L, Larco DO, Scherthaner-Reiter MH, Szarek E, Leal LF, Caberg JH, Castermans E, Villa C, Dimopoulos A, Chittiboina P, Xekouki P, Shah N, Metzger D, Lysy PA, Ferrante E, Strebkova N, Mazerkina N, Zatelli MC, Lodish M, Horvath A, de Alexandre RB, Manning AD, Levy I, Keil MF, Sierra Mde L, Palmeira L, Coppieters W, Georges M, Naves LA, Jamar M, Bours V, Wu TJ, Choong CS, Bertherat J, Chanson P, Kamenický P, Farrell WE, Barlier A, Quezado M, Bjelobaba I, Stojilkovic SS, Wess J, Costanzi S, Liu P, Lupski JR, Beckers A, Stratakis CA. Gigantism and acromegaly due to Xq26 microduplications and *GPR101* mutation. *N Engl J Med*. 2014 Dec 18;371(25):2363-74.
9. Haller F, Moskalev EA, Faucz FR, Barthelmeß S, Wiemann S, Bieg M, Assie G, Bertherat J, Schaefer IM, Otto C, Rattenberry E, Maher ER, Ströbel P, Werner M, Carney JA, Hartmann A, Stratakis CA, Agaimy A. Aberrant DNA hypermethylation of SDHC: a novel mechanism of tumor development in Carney triad. *Endocr Relat Cancer*. 2014 Aug;21(4):567-77.

10. Faucz FR, Zilbermint M, Lodish MB, Szarek E, Trivellin G, Sinaii N, Berthon A, Libé R, Assié G, Espiard S, Drougat L, Ragazzon B, Bertherat J, Stratakis CA. Macronodular adrenal hyperplasia due to mutations in an armadillo repeat containing 5 (*ARMC5*) gene: a clinical and genetic investigation. *J Clin Endocrinol Metab.* 2014 Jun;99(6):E1113-9.
11. Beuschlein F, Fassnacht M, Assié G, Calebiro D, Stratakis CA, Osswald A, Ronchi CL, Wieland T, Sbiera S, Faucz FR, Schaak K, Schmittfull A, Schwarzmayr T, Barreau O, Vezzosi D, Rizk-Rabin M, Zabel U, Szarek E, Salpea P, Forlino A, Vetro A, Zuffardi O, Kisker C, Diener S, Meitinger T, Lohse MJ, Reincke M, Bertherat J, Strom TM, Allolio B. Constitutive activation of PKA catalytic subunit in adrenal Cushing's syndrome. *N Engl J Med.* 2014 Mar 13;370(11):1019-28
12. Forlino A, Vetro A, Garavelli L, Ciccone R, London E, Stratakis CA, Zuffardi O. *PRKACB* and Carney complex. *N Engl J Med.* 2014 Mar 13;370(11):1065-7.
13. Assié G, Libé R, Espiard S, Rizk-Rabin M, Guimier A, Luscap W, Barreau O, Lefèvre L, Sibony M, Guignat L, Rodriguez S, Perlemoine K, René-Corail F, Letourneur F, Trabulsi B, Poussier A, Chabbert-Buffet N, Borson-Chazot F, Groussin L, Bertagna X, Stratakis CA, Ragazzon B, Bertherat J. *ARMC5* mutations in macronodular adrenal hyperplasia with Cushing's syndrome. *N Engl J Med.* 2013 Nov 28;369(22):2105-14.
14. Rothenbuhler A, Horvath A, Libé R, Faucz FR, Fratticci A, Sanson ML, Vezzosi D, Azevedo M, Levi I, Almeida MQ, Lodish M, Nesterova M, Bertherat J, & CA Stratakis. Identification of novel genetic variants in phosphodiesterase 8B (*PDE8B*), a cAMP specific phosphodiesterase highly expressed in the adrenal cortex, in a cohort of patients with adrenal tumors. *Clin Endocrinol (Oxf)* 77(2):195-9, 2012]
15. Vezzosi D, Libé R, Baudry C, Rizk-Rabin M, Horvath A, Levy I, René-Corail F, Ragazzon B, Stratakis CA, Vandecasteele G, Bertherat J. Phosphodiesterase 11A (*PDE11A*) gene defects in patients with ACTH-independent macronodular adrenal hyperplasia (AIMAH): functional variants may contribute to genetic susceptibility of bilateral adrenal tumors. *J Clin Endocrinol Metab.* 97(11):E2063-2069, 2012
16. Faucz FR, Horvath A, Rothenbuhler A, Almeida MQ, Libé R, Raffin-Sanson ML, Bertherat J, Carraro DM, Soares FA, de Campos Molina G, Campos AH, Alexandre RB, Bendhack ML, Nesterova M, & CA Stratakis. Phosphodiesterase 11A (*PDE11A*) genetic variants may increase susceptibility to prostatic cancer. *J Clin Endocrinol Metab.* 96(1):E135-40, 2011.
17. Libé R, Horvath A, Vezzosi D, Fratticci A, Coste J, Perlemoine K, Ragazzon B, Guillaud-Bataille M, Groussin L, Clauser E, Raffin-Sanson ML, Siegel J, Moran J, Drori-Herishanu L, Faucz FR, Lodish M, Nesterova M, Bertagna X, Bertherat J, & CA Stratakis. Frequent phosphodiesterase 11A gene (*PDE11A*) defects in patients with Carney complex (CNC) caused by *PRKAR1A* mutations: *PDE11A* may contribute to adrenal and testicular tumors in CNC as a modifier of the phenotype. *J Clin Endocrinol Metab.* 96(1):E208-14, 2011.

## 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.

## **Description of 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
- Nuria Valdes Gallego, MD, Ph.D., Endocrinologist volunteer visiting fellow  
Department of Endocrinology and Nutrition  
Hospital Central de Asturias, Oviedo.  
Asturias, Spain.
- 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

## **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.

**Website**

<https://science.nichd.nih.gov/confluence/display/segem/Home>

**Point-of-Contact**

Dr. Fabio Rueda Faucz

[fabio.faucz@nih.gov](mailto:fabio.faucz@nih.gov)

301-451-7177

## **Section on Intercellular Interactions (SII)**

**Name of Investigator:** Leonid Margolis, Ph.D.

**Name of Lab:** Section on Intercellular Interactions, NICHD

**Affinity Group:** Behavioral Determinants and Developmental Imaging

### **Mission of Section**

To identify basic mechanisms of cell interactions in norm and pathologies

### **Major International Initiatives**

1. Identification of antigenic spectra of individual HIV-1 virions : A collaborative project with the Imperial College London, UK (PI: Dr. Robin Shattock)
2. The role of extracellular vesicles in viral infection: A collaborative project with the University of Utrecht, Netherlands (PI: Esther Nolte-'t Hoen)
3. Analysis of extracellular vesicles and herpesviruses in patients with acute coronary syndrome A collaborative project with Moscow University of Medicine and Dentistry, Moscow, Russia (PIs: Dr. Elena Vasilieva and Alexander Shpektor)
4. Morphological analysis of extracellular vesicles: A collaborative project with Cochin Institute, Paris, France (PIs: Dr. Morgan Bomsel)
5. Investigation of the protective role of Lactobacillus in vaginal HIV transmission: A collaborative project with the University of Bologna, Bologna, Italy (PIs: Dr. Beatrice Vitali)
6. New multi-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**

1. Vagida M, Arakelyan A, Lebedeva A, Grivel J, Shpektor A, Vasilieva E, Margolis L. Flow analysis of individual blood extracellular vesicles in acute coronary syndrome. *Platelets* 2016;4:382-391.
2. Nikitskaya E, Lebedeva A, Ivanova O, Maryukhnich E, Shpektor A, Grivel JC, Margolis L, Vasilieva E. Cytomegalovirus-Productive Infection Is Associated With Acute Coronary Syndrome. *J. Am. Heart Assoc.* 2016;5:8.
3. Vagida MS, Arakelyan A, Lebedeva AM, Grivel JC, Shpektor AV, Vasilieva EY, Margolis LB. Analysis of Extracellular Vesicles Using Magnetic Nanoparticles in Blood of Patients with Acute Coronary Syndrome. *Biochemistry* 2016;81:382-391.
4. Arakelyan A, Fitzgerald W, Vagida M, Vasilieva E, Margolis L, Grivel J. Addition of thrombin reduces the recovery of extracellular vesicles from blood plasma. *Journal of Circulating Biomarkers* 2016;in press.
5. Nolte-'t Hoen E, Cremer T, Gallo RC, Margolis LB. Extracellular vesicles and viruses: Are they close relatives?. *Proc Natl Acad Sci U S A* 2016;113:9155-9161.

6. Shmagel KV, Saidakova EV, Shmagel NG, Korolevskaya LB, Chereshnev VA, Robinson J, Grivel JC, Douek DC, Margolis L, Anthony DD, Lederman MM. Systemic inflammation and liver damage in HIV/hepatitis C virus coinfection. HIV Med 2016;17:581-589.

### **Description of 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.

### **International Partnerships**

The Section is an International Partner of the OAR Intramural-to-Russia Program

### **Website**

<http://annualreport.nichd.nih.gov/margolis.html>

### **Point-of-contact:**

Dr. Leonid Margolis

Email: [margolil@helix.nih.gov](mailto:margolil@helix.nih.gov)

301- 594-2476

## Section on Molecular Morphogenesis (SMM)

Name of Investigator: Yun-Bo Shi, Ph.D.

**Name of Lab:** Section on Molecular Morphogenesis, NICHD

**Affinity Group:** Cell Regulation and Development

### Mission of Section

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

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.

In studies of thyroid hormone regulation of *Xenopus* metamorphosis, it was discovered in conjunction with researchers at the University of Victoria in Canada, an important role of the Inhibitor of Growth (ING) tumor suppressor proteins in modulating thyroid hormone-dependent gene transcription during metamorphosis. 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

1. Hasebe, T., Kajita, M., Fu, L., **Shi, Y.-B.**, and Ishizuya-Oka, A. (2012) Thyroid hormone-induced Sonic hedgehog signal up-regulates its own pathway in a paracrine manner in the *Xenopus laevis* intestine during metamorphosis. *Dev Dyn.* 241, 403–414.
2. Sun, G., and **Shi, Y.-B.** (2012) Thyroid hormone regulation of adult intestinal stem cell development: Mechanisms and evolutionary conservations. *Int. J. Biol. Sci.* 8, 1217-24.
3. Fu, L., Sun, G., Fiorentino, M., and **Shi, Y.-B.** (2012) Characterization of *Xenopus* Tissue Inhibitor of Metalloproteinases-2: A role in regulating matrix metalloproteinase activity during development. *PLoS One* 7: e36707, 1-8.
4. Miller, T.C., Sun, G., Hasebe, T., Fu, L., Heimeier, R.A., Das, B., Ishizuya-Oka, A., and **Shi, Y.-B.** (2013) Tissue-specific upregulation of MDS/EVI gene transcripts in the intestine by thyroid hormone during *Xenopus* metamorphosis. *PLoS One* 8:e55585, 1-7.
5. Hasebe, T., Fu, L., Miller, T.C., Zhang, Y., Shi, **Y.-B.**, and Ishizuya-Oka, A. (2013) Thyroid hormone-induced cell-cell interactions in the development of adult intestinal stem cells. *Cell & Bioscience* 3:18, 1-10.
6. Sun, G., Heimeier, R.A., Fu, L., Hasebe, T., Das, B., Ishizuya-Oka, A., and **Shi, Y.-B.** (2013) Expression profiling of intestinal tissues implicates novel genes and pathways essential for adult stem cell development. *Endocrinology.* 154(11), 4396–4407.
7. Luu, N., Wen, L., Fu, L., Fujimoto, K., and **Shi, Y.-B.\***, and Sun, G\*. (2013) Differential regulation of two histidine ammonia-lyase genes during *Xenopus* development implicates distinct functions during thyroid hormone-induced formation of adult stem cells. *Cell & Bioscience* 3:43, 1-11. (\*Corresponding Authors)
8. Gimaldi, A., Buisine, N., Miller, T., **Shi, Y.-B.**, and Sachs, M. L. (2013) Mechanisms of thyroid hormone receptor action during development: Insights from amphibian. *Biochimica et Biophysica Acta.* 1830, 3882–3892.
9. Sun, G., Fu, L., and **Shi, Y.-B.** (2014) Epigenetic regulation of thyroid hormone-induced adult intestinal stem cell development during anuran metamorphosis. *Cell & Bioscience* 4:73, 1-8.
10. Sun, G., Fu, L., Wen, L., and **Shi, Y.-B.** (2014) Activation of Sox3 gene by thyroid hormone in the developing adult intestinal stem cell during *Xenopus* metamorphosis. *Endocrinology* 155(12):5024–5032.

11. 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
12. Wen, L., Fu, L., Guo, X., Chen, Y., and **Shi, Y.-B.** (2015) Histone methyltransferase Dot1L plays a role in postembryonic development in *Xenopus tropicalis*. *FASEB J.* 29, 385-393.
13. Wen, L., Hasebe, T., Miller, T.C., Ishizuya-Oka, A., and **Shi, Y.-B.** (2015) A requirement for hedgehog signaling in thyroid hormone-induced postembryonic intestinal remodeling. *Cell & Bioscience* 5:13, 1-12.
14. Wang, F., Shi, Z., Cui, Y., Guo, X., **Shi, Y.-B.**, and Chen, Y. (2015) Targeted gene disruption in *Xenopus laevis* using CRISPR/Cas9. *Cell & Bioscience* 5:15, 1-5.
15. Helbing, C.C., Wagner, M.J., Pettem, K., Johnston, J., Heimeier, R.A., Veldhoen, N., Jirik, F.R., **Shi, Y.-B.**, and Browder, L.W. (2012) Modulation of thyroid hormone-dependent gene expression in *Xenopus laevis* by INhibitor of Growth (ING) proteins. *PLoS One.* 6: e28658, 1-11.
16. Sinclair, L. V., Rolf, J., Emslie, E., **Shi, Y.-B.**, Taylor, P. M., and Cantrell, D. A. (2013) Antigen receptor control of amino acid transport coordinates the metabolic re-programming that is essential for T cell differentiation. *Nature Immunology* 14, 500-8. (Editor's choice, Science, 2013. VOL 340, 10).
17. Poncet, N., Mitchell, F.E., Ibrahim, A.F.M., McGuire, V.A., English, G., Arthur, S.C., and **Shi, Y.-B\***, and Taylor, P.M\*. (2014) The catalytic subunit of the System L1 amino acid transporter (*Slc7a5*) facilitates nutrient signaling in mouse skeletal muscle. *PLoS One* (\*Corresponding Authors) 9(2): e89547,1-14.
18. Xue, L., Cai, J.-Y., Ma, J., Huang, Z., Guo, M.-X., Fu, L., **Shi, Y.-B.\***, and Li, W.-X\*. (2013) Global expression profiling reveals genetic programs underlying the developmental divergence between mouse and human embryogenesis. *BMC Genomics* 14:568, 1-16. (\*Corresponding Authors)
19. Xiong, L.-H., Cui, R., Zhang, Z.-L., Yu, X., Xie, Z.-X., **Shi, Y.-B.**, and Pang, D.-W. (2014) Uniform Fluorescent Nanobioprobes for Pathogen Detection. *ACS Nano* 8 (5), 5116–5124.
20. Liu, S.-L., Zhang, L.-J., Zhang, Z.-L., Wang, Z.-G., Wu, Q.-M., Sun, E.-Z., **Shi, Y.-B.**, and Pang, D.-W. (2014) Globally Visualizing the Microtubule-Dependent Infection Behaviors of Influenza Virus in Live Cells. *Analytical Chemistry* 86 (8), 3902–3908.
21. Xiong, L.-H., Cui, R., Zhang, Z.-L., Tu, J.-W., **Shi, Y.-B.**, and Pang, D.-W. (2015) Harnessing Intracellular Biochemical Pathways for In Vitro Synthesis of Designer Tellurium Nanorods. *Small*, 11 (40): 5416–5422.

## Website

<https://science.nichd.nih.gov/confluence/display/pcrm/Yun-Bo+Shi>

## Point-of-Contact

Dr. Yun-Bo Shi  
[ys1w@nih.gov](mailto:ys1w@nih.gov)  
 301-402-1004

## Section on Molecular Neurobiology (SMN)

Name of Investigator: Dr. Andres Buonanno

**Name of Lab:** Section on Molecular Neurobiology, NICHD

**Affinity Group:** Cell and Structural Biology

### Mission of Section

**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)** There are three major initiatives for this mission:

1. 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.
2. In collaboration with Dr. Huibert Mansvelder's group at the Department of Neuroscience, University of Amsterdam, Netherlands we plan to investigate the effects of the NRG pathway on neuronal excitability using a multi-electrode recording system to analyze neuronal network activity and connectivity.

**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**

1. Golani J, Tadmor H, Buonanno A, Kremer I and Shamir A (2014) Disruption of the ErbB signaling in adolescence increases striatal dopamine levels and affects learning and hedonic-like behavior in the adult mouse. *Eur Neuropsychopharmacology* 24,1808-1818.
2. Kwon OB, Paredes D, Gonzalez CM, Neddens, J., Hernandez L, Vullhorst D, and Buonanno A. (2008) Neuregulin-1 regulates LTP at CA1 hippocampal synapses through activation of dopamine D4 receptors. *Proc Natl Acad Sci USA*. 105:15587-15592.
3. Leqin Yan, Alon Shamir, Elias Leiva-Salcedo, Miguel Skirzewski, Oh-bin Kwon, Irina Karavanova, Daniel Paredes, Oz Malkesman, Kathleen R. Bailey, Detlef Vullhorst, Jacqueline N. Crawley and Andres Buonanno. Neuregulin-2 Ablation Results in Dopamine Dysregulation and Severe Behavioral Phenotypes Associated with Psychiatric Disorders (under review *Mol. Psychiatry*).

### **Project B**

1. Rana Z, Gundersen K, Buonanno A. (2008) Activity-dependent repression of muscle genes by NFAT. *Proc Natl Acad Sci U S A*. 105, 5921-5926.
2. Rana ZA, Gundersen K and Buonanno A (2014) Ets-2 is a fast activity sensor regulating gene transcription in fast-twitch skeletal muscle. (in review).

### **Recent Achievements in International Health**

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

### **Description of International Trainees**

- 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

## **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.
- Oslo University, Norway. Had a MOU for Dr. Zaheer Rana to perform his dissertation in lab.

## **Website**

<http://smn.nichd.nih.gov/>

## **Point-of-Contact**

Andres Buonanno, Ph.D.

[buonanno@mail.nih.gov](mailto:buonanno@mail.nih.gov)

301-496 0170

## Section on Neuronal Connectivity (SNC)

Name of Investigator: Chi-Hon Lee, Ph.D.

**Name of Lab:** Section on Neuronal Connectivity, NICHD

**Affinity Group:** Cell Regulation and Development

### Mission of Section

The Section on Neuronal Connectivity investigates the development and function of color-vision circuits in *Drosophila*. Through work done by the section, it has been found that TGF-beta/Activin signaling plays a key role in coordinating mutual synaptogenesis between R7 photoreceptors and their target neurons Dm8. The section is also developing genetic tools to dissect color-vision circuits. By selectively inactivating or restoring the synaptic activity of various types of neurons, his group recently demonstrated that spectral preference to UV and green light is mediated by two distinct types of second-order interneurons.

### Major International Initiatives

Collaboration with researchers from the University of Sheffield in England and Dalhousie University in Canada on dissecting visual circuits has led to a new understanding of the mechanism of visual motion detection in animals. This section also collaborates with researchers from the University of Tokyo in Japan to carry out anatomical characterization of gustatory circuits. Partnerships with researchers from Tata Institute of Fundamental Research in India and the University of Vienna in Austria have led to new insight in neural circuit assembly and axon and dendrite development.

### Relevant Publications:

1. Kulkarni, A., Ertekin, D., Lee, C.-H., Hummel, T. (2016) Birth Order Dependent Growth Cone Segregation Determines Synaptic Layer Identity in the *Drosophila* Visual System. *eLIFE* 5, e13715.
2. Lin, T.-Y., Luo, J., Shinomiya, K., Ting, C.-Y., Lu, Z., Meinertzhagen, I.A., Lee, C.-H. (2016) Mapping Chromatic Circuit in the *Drosophila* Visual System. *J. Comp. Neurol.* 524, 213-227.
3. Miyazaki, T., Lin, T.-Y., Ito, K., Lee, C.-H., and Stopfer, M. (2015) A gustatory second-order neuron that connects sucrose-sensitive primary neurons and a distinct region of the gnathal ganglion in the *Drosophila* brain. *J. Neurogenetics* 25, 1-26.
4. Shinomiya, K., Karuppudurai, T., Lin, T.-Y., Lu, Z., Lee, C.-H., Meinertzhagen, I.A. (2014) Candidate Neural Substrates for Off-Edge Motion Detection in *Drosophila*. *Current Biology* 10:1062-70.
5. Ting, C.-Y., McQueen, P. G., Pandya, N., Lin, T.-Y., Yang, M., Reddy, O. V., O'Connor, M. B., McAuliffe, M. and Lee, C.-H. (2014) Photoreceptor-Derived Activin Promotes Dendritic Termination and Restricts the Receptive Fields of First-Order Interneurons in *Drosophila*. *Neuron* 81: 830-46.
6. Meinertzhagen, I.A and Lee, C.-H. The Genetic Analysis of Functional Connectomics in *Drosophila*. *Advances in Genetics*, 80, 99-151, 2012.

7. Wardill, T.J., List, O., Li, X., Dongre, S., McCulloch, M., Ting, C.-Y., O’Kane, C. J., Tang, S., Lee, C.-H., Hardie, R. C., Juusola, M. Multiple Spectral Inputs Contribute to Motion Discrimination in the *Drosophila* Visual System. *Science*, 336, 925-931, 2012.
8. Takemura, S., Karuppudurai, T., Ting, C.-Y., Lu, Z., Lee, C.-H., Meinertzhagen, I.A. Cholinergic circuits integrate neighboring visual signals in a *Drosophila* motion detection pathway. *Current Biology*, 21, 2077-2084, 2011.

### **Website**

<https://science.nichd.nih.gov/confluence/display/pcrm/Chi-Hon+Lee>

### **Point-of-Contact**

Dr. Chi-Hon Lee

[leechi@mail.nih.gov](mailto:leechi@mail.nih.gov)

301-435-1940

## Section on Nutrient Control of Gene Expression (SNCGE)

**Name of Investigator:** Alan Hinnebusch, Ph.D.

**Name of Lab:** Section on Nutrient Control of Gene Expression, NICHD

**Affinity Group:** Cell Regulation and Development

### Mission of Section

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 electronmicroscopy 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.

### Publications with International Collaborators

1. Conformational Differences between Open and Closed States of the Eukaryotic Translation Initiation Complex. Llácer JL, Hussain T, Marler L, Aitken CE, Thakur A, Lorsch JR, Hinnebusch AG, Ramakrishnan V. Mol Cell. 2015 Aug 6;59(3):399-412.
2. Structural changes enable start codon recognition by the eukaryotic translation initiation complex. Hussain T, Llácer JL, Fernández IS, Munoz A, Martin-Marcos P, Savva CG, Lorsch JR, Hinnebusch AG, Ramakrishnan V. Cell. 2014 Oct 23;159(3):597-607. doi: 10.1016/j.cell.2014.

### Website

<https://science.nichd.nih.gov/confluence/display/pcrm/Alan+Hinnebusch>

### Point-of-Contact

Alan Hinnebusch, Ph.D.

[alanh@mail.nih.gov](mailto:alanh@mail.nih.gov)

301-496-4480

## Section on Protein Biosynthesis (SPB)

Name of Investigator: Thomas Dever, Ph.D.

**Name of Lab:** Section on Protein Biosynthesis, NICHD

**Affinity Group:** Cell Regulation and Development

### Mission of Section

The Section on Protein Biosynthesis is working to characterize the structure and function of several translation initiation factors and the molecular principles of kinase-substrate recognition by the stress-responsive eIF2a kinases. The group recently reported that rapid evolution of the kinase domain of the eIF2a kinase PKR alters the sensitivity of the kinase to poxvirus inhibitors, identified functionally important contacts between the GTPase translation factor eIF5B and the body of the small (40S) ribosomal subunit, and demonstrated that the hypusine-containing protein eIF5A promotes translation elongation.

### 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 structural biologists. Together with scientists at the MRC Laboratory of Molecular Biology in Cambridge, England, high-resolution cryo-electronmicroscopic images of the ribosome provided insights into a unique mechanism of initiation of viral mRNA translation and revealed a function for a novel diphthamide modification of the translation elongation factor eEF2. Work with x-ray crystallographers at the IGBMC in Strasbourg, France revealed the structure of the translation factor eIF5A and its hypusine modification on the ribosome providing insights into how eIF5A promotes translation of proteins containing runs of proline residues.

### Relevant Publications:

1. Structural characterization of ribosome recruitment and translocation by type IV IRES. Murray J, Savva CG, Shin BS, Dever TE, Ramakrishnan V, Fernández IS. *Elife* 2016 May 9;5. pii: e13567. doi: 10.7554/eLife.13567. PMID:27159451.
2. Crystal Structure of Hypusine-Containing Translation Factor eIF5A Bound to a Rotated Eukaryotic Ribosome. Melnikov S, Mailliot J, Shin BS, Rigger L, Yusupova G, Micura R, Dever TE, Yusupov M. *J Mol Biol*. 2016 May 16. pii: S0022-2836(16)30154-1. doi: 10.1016/j.jmb.2016.05.011. [Epub ahead of print]. PMID:27196944.

### Website

<https://science.nichd.nih.gov/confluence/display/pcrm/Thomas+Dever>

### Point-of-Contact

Dr. Thomas Dever

[Thomas.Dever@nih.gov](mailto:Thomas.Dever@nih.gov)

301-496-4519