NICHD International Activities Catalog

2015

OFFICE OF GLOBAL HEALTH

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

Table of Contents

List of Acronyms

AP	Abruptio Placenta
ART	Antiretroviral Therapy
ARV	Antiretroviral
BPCA	Best Pharmaceuticals for Children Act
BMGF	Bill & Melinda Gates Foundation
BRAD	Biomedical/Behavioral Research Administrators Development Award
BRINDA	Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia
CDC	U.S. Centers for Disease Control and Prevention
CDH	Congenital Diaphragmatic Hernia
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
FAS	Stillbirth and Fetal Alcohol Syndrome
FIC	Fogarty International Center
FIRS	Fetal Inflammatory Response Syndrome
Global Network	Global Network for Women's and Children's Health Research
GU	Genitourinary
HAI	Human-Animal Interaction
HAPO	Hyperglycemia and Adverse Pregnancy Outcome Study
HBeAg	Hepatitis B e Antigen Positive
HBD	Human Beta-Defensins
HBV	Hepatitis B Virus
HCMV	Human Cytomegalovirus
HNP	Human Neutrophil Defensins
HSV-2	Herpes Simplex Virus 2
IAA	Interagency Agreement
ICs	NIH Institutes and Centers
IDMCD	International Guide for Monitoring Children's Development
IFLS	Indonesian Family Life Surveys
INSPIRE	Inflammation and Nutritional Science for Programs/Policies and Interpretation of Research Evidence
IOM	Institute of Medicine
iRIM	Initiative on Research and Innovation Management
IUD	Intrauterine Device
IUGR	Intrauterine Growth Retardation
iYCG	Investing in Young Children Forum
KNIH	Korean National Institute of Health
LBW	Low Birth Weight
LMICs	Low- and Middle-Income Countries
MCH	Maternal and Child Health
MEPI	Medical Education Partnership Initiative
MFLS	Malaysian Family Life Surveys
MOU	Memorandum of Understanding

NACS	Nutritional Assessment, Care, and Support
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NISDI	NICHD International Site Development Initiative
NISDI	NICHD Latin American/Caribbean International Site Development Initiative
NTD	Neural Tube Defects
NUGAG	Nutrition Guidance Expert Advisory Group
ODS	Office of Dietary Supplements
OVC	Orphans and Vulnerable Children
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
POFO	Positive Outcomes for Orphans
PTD	Preterm Delivery
PTN	Pediatric Trials Network
RFA	Request for Applications
SIDS	Sudden Infant Death Syndrome
STI	Sexually Transmitted Infection
T1DM	Type 1 Diabetes
TB	Tuberculosis
UNC	University of North Carolina
USAID	U.S. Agency for International Development
USG	U.S. Government
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 and U.S. Department of Health and Human Services entities, to improve the overall health of populations worldwide by providing leadership, coordination, and support for NICHD's global heath mission and activities. Key activities include:

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

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

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

Office of the Director

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

Office of Global Health (OGH)

Mission

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

Major International Initiatives over the Past Year

NICHD Global Health Consultation Meeting, February 11-12, 2015. OGH organized a scientific meeting focused on identifying research gaps and priorities at the intersection of child neurodevelopment, inflammation, and nutrition from conception through adolescence in culturally-diverse, resource-limited settings. The meeting included over 80 researchers, program implementers, and policymakers 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), CDC, Institute of Medicine (IOM), World Bank, Grand Challenges Canada, and the Sackler Institute. A targeted research agenda initially discussed at this NICHD meeting is being expanded upon by six working groups in papers addressing specific developmental periods and cross-cutting assessment challenges. These six manuscripts will be published as a supplement to the journal *Pediatrics*, with an estimated publication date in early 2016.

National Institutes of Health (NIH) - BMGF Collaboration. Following the visit of Mr. Bill Gates, BMGF, to the NIH campus in January 2014, a new phase of cooperation was 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.: http://www.nih.gov/about/director/10082014_statement_gates.htm. 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, Contraceptive Research, Child Health and Development, Pediatric Pneumonia and Indoor Air Pollution, and HIV/AIDS Working Groups). OGH co-chairs the Child Health and Development Working Group which includes representation from NICHD, BMGF, National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke. The Child Health and Development Working Group aims to identify new research collaborations in the areas of child neurodevelopment, nutrition and growth, and neurocognitive assessment, among other areas.

The "Survive & Thrive" Global Development Alliance. As part of the response to the Child Survival Call to Action initiated by USAID and UNICEF in 2012, NICHD was invited to participate in the Survive & Thrive Global Development Alliance (S&T GDA) led by USAID in partnership with the American Academy of Pediatrics, American College of Nurse-Midwives, American College of Obstetricians and Gynecologists, Johnson & Johnson, Laerdal Global Health, and Save the Children. The overall goal of the S&T GDA is to train health care providers in resource-limited settings in health interventions (e.g., "Helping Babies Breathe" program) that improve the quality of facility-based maternal, newborn, and child care. As part of this effort, NICHD staff has participated in several technical working groups aimed at developing and tracking the progress of country-specific, capacity building projects established to reduce maternal, newborn, and child mortality and morbidity. In June 2015, NICHD also participated in the "Helping Babies Survive Implementation Meeting" and the "Laerdal 75th Anniversary Program" in Stavanger, Norway.

IOM's "Investing in Young Children" Forum (iYCG). In January 2014, the Board on Children, Youth, and Families of IOM and the National Research Council, in collaboration with the IOM Board on Global Health, 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 Working Group, and several planning committees for iYCG regional meetings including those held this past year in the Czech Republic, Ethiopia, and Hong Kong.

NICHD Global Injury Prevention Meeting, July 28-29, 2015. OGH participated on the planning committee of this NICHD Office of the Director meeting on global injury prevention, led by Dr. Bruce Simons Morton, Associate Director for Prevention at NICHD. This meeting was held in recognition of the prevalence and importance of injury as a cause of mortality, non-fatal trauma, health care utilization, and disability, particularly children in low- and middle-income countries (LMICs). Investigators supported by the Fogarty International Center (FIC) Collaborative Trauma and Injury Research Training Program were invited to identify research priority areas within pediatric injury prevention and share their broader research interests in injury research within international contexts.

U.S. Government (USG) "Children in Adversity" Initiative. NICHD representatives serve on the technical working group that developed an interagency strategy that describes 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 Dr. Alan Guttmacher serving as a co-author. A NICHD staff member served as co-editor of a special journal in *Child Abuse and Neglect*, and several NICHD and NIH staff members served as co-authors of several articles that described results of the evidence review teams. NICHD hosted a Pre-Summit for this initiative at NIH in October 2011 and was a partner in the USG Evidence Summit held in December 2011 at USAID, which was supported by senior leadership of seven USG agencies, including NICHD.

NIH IC AIDS Coordinator and Chairperson of the NICHD AIDS Coordinating Committee. The OGH Director serves as the NIH Office of AIDS Research (OAR) IC AIDS Coordinator to facilitate communication and collaboration with OAR; share NICHD activities and priorities with the committee and support NICHD staff in their HIV/AIDS research efforts. The NIH and NICHD AIDS portfolios include both domestic and global research activities. As the Chairperson of the NICHD AIDS Coordinating Committee, work in close collaboration with the NICHD Director of Extramural Research, NICHD Science Director, Office of Budget, and several NICHD branches on development of HIV-related initiatives. Organize and coordinate the annual NICHD HIV/AIDS Operational Planning Meeting and prepare annual HIV/AIDS proposal for clearance by NICHD leadership before submission to OAR for consideration. Communicate important developments in HIV/AIDS research to both internal and external scientific partners. Develop briefings and provide input to intra- and inter-agency documents related to the NICHD HIV/AIDS research and training portfolio. Most recently, consulted with the NICHD AIDS Committee for input and implementation of the New OAR HIV/AIDS priorities published on August 12, 2015.

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 China, Korea, South Africa, and Tanzania.

- **Coordination of Visits by Foreign Delegations.** Participated in the coordination of meetings and preparation of briefing materials for visits by foreign delegations including Health Minister from Rwanda, Chinese National Science Foundation, Indian Department of Biotechnology, and the Japanese Neonatal Network, 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. Recent seminar titles include: "Mapping Maternal Deaths and Other Outcomes;" "Pregnancy & HIV/AIDS in Mali & Atlanta;" "Ebola Response: Perspectives from NICHD Staff Deployments to Liberia and Sierra Leone;" and "An Update on the U.S. Global Development Lab."

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

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: Vesna Kutlesic and Maggie Brewinski Isaacs

- **R56 Review Group**. Representative: Maggie Brewinski Isaacs

- **NICHD AIDS Coordinating Committee**. Representatives: Vesna Kutlesic and Maggie Brewinski Isaacs

- **Fogarty IC International Representatives Working Group**. Representative: Vesna Kutlesic

- **Trans-NIH Global Health Research Working Group**. Representative: Vesna Kutlesic

- **Trans-NIH International Clinical Research Subcommittee**. Representative: Vesna Kutlesic

- **Survive and Thrive Global Development Alliance.** Representatives: Linda Wright and Maggie Brewinski Isaacs

- **IOM iYCG Forum**. Representative: Vesna Kutlesic
- **WHO Every Newborn Action Plan (ENAP) Metrics Task Team**. Representatives: Linda Wright and Maggie Brewinski Isaacs
- **Save the Children Newborn Indicators Working Group**. Representatives: Linda Wright and Maggie Brewinski Isaacs
- **Steering Committee for Maternal Mortality Mapping Technical Consultation**. Representative: Linda Wright
- **UN Commodities Commission Working Group**. Representative: Linda Wright
- **Children in Adversity Strategy Working Group**. Representative: Vesna Kutlesic
- **Partnerships for Enhanced Engagement in Research (PEER) Health Steering Committee**. Representative: Vesna Kutlesic
- **FIC BRAIN Disorders Initiative Working Group**. Representative: Vesna Kutlesic

Point-of-Contact

Dr. Vesna Kutlesic
vesna.kutlesic@nih.gov
301-435-7566

Office of Health Equity (OHE)

Mission

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.

Major International Initiatives over the Past Year

Biomedical/Behavioral Research Administrators Development Award (BRAD). This initiative is focused on building administrative research capacity at institutions in Sub-Saharan Africa, South and Central America, and India. This program is co-sponsored by the Fogarty International Center (FIC) and the National Institute of Allergy and Infectious Diseases (NIAID) and provides an opportunity for institutions abroad to gain skills and knowledge in grants management and reporting requirements of funding agencies. Having the capability to efficiently manage research grants is a vital component to a successful research enterprise, and the BRAD program addresses this need by providing training in:

- Fiscal accountability
- Data management
- Project oversight
- Knowledge of scientific reporting requirements of the NIH and other international research funding agencies.
- Skilled preparation and submission of successful grant applications
- Knowledge of available funding opportunities

This five-year grant provides distance learning opportunities and a three-week on-site residency program at the NIH with faculty representation across the various NIH Institutes and Centers. The BRAD program is currently supporting the following institutions:

Sub-Saharan Africa (alpha order by country)

- Moi University, Kenya• University of Nairobi, Kenya
- University of Ibadan, Nigeria
- Human Science Research Council, Pretoria, South Africa
- University of Cape Town, South Africa
- Muhimbili University of Allied Health Sciences, Tanzania
- Joint Clinical Research Center, Uganda
- Makerere University Walter Reed Project, Uganda
- Mbarara University of Science & Technology, Uganda
- University of Zimbabwe, College of Health Sciences

Recent Achievements in International Health

- One of the most recent achievements of this program is the execution of the Initiative on Research and Innovation Management (iRIM). The iRIM provided support for the development of innovative and novel research administrative training programs across Sub-Saharan Africa. These trainings were held in Kenya, Nigeria, Senegal, South Africa, Tanzania, and Zambia. These six trainings provided outreach to over 200 individuals representing over 30 countries. BRAD Principal Investigators and individuals trained under iRIM continue to provide local and regional trainings in Sub-Saharan Africa.

Creating Research Administration Training Tools

In an effort to strengthen research in Sub-Saharan Africa, NICHD supported the training of researchers and administrators from 32 African countries on aspects of good grantsmanship. Training materials, including tutorials, videos, and slides, are available online at http://www.researchadministrationtools.org/.

International Partnerships

- U.S. President's Emergency Plan for AIDS Relief/iRIM – Regional Research Administrators Training Workshops in Sub-Saharan Africa

- FIC & NIAID/BRAD

Staff Membership on Global Health Committees/Working Groups

- **NIH Human Heredity and Health in Africa (H3Africa) Executive Committee**. Representative: Regina James

- **Trans NIH Grant Writing Working Group**. Representative: Regina James

- **NIH Medical Education Partnership Initiative Workgroup**. Representatives: Regina James and Jean Flagg-Newton

- **NICHD Global Health Interest Group.** Representative: Regina James

Point-of-Contact

Dr. Regina Smith James
rjames@mail.nih.gov
301-435-2692

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.

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 started in August 2013 and will continue until October 2016.

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 study is ongoing and will be completed in June 2016. It is also supported by the Bill & Melinda Gates Foundation, GE Healthcare, and the University of Washington.

Prenatal Alcohol in SIDS and Stillbirth (PASS) Network. The PASS Network, co-funded by NICHD, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute on Deafness and Other Communication Disorders, 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 obstetrician/gynecologists pursuing academic careers in global women's health;

- Allow trainees to complete degree requirements for a Master's of Science in Clinical Research, providing the necessary theoretical framework for later practical training;

- Leverage the vast global health expertise at the UNC School of Medicine and Gillings School of Global Public Health to expand the scope and depth of academic mentorship; and

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

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.

The investigators are conducting a large multi-center epidemiologic study of AP in Lima, Peru. A self-matched case-crossover design will be used to evaluate the acute effects of: 1) maternal smoking and alcohol consumption; 2) physical exertion; 3) sexual activity; 4) abdominal trauma secondary to falls or motor vehicle crashes; and 5) exposure to intimate partner violence as potential "triggers" of AP. They will also study genetic variants that influence the pathogenesis of AP in well-characterized 900 mother-infant abruption case pairs and 900 mother-infant control pairs. Collectively, these new insights may facilitate the development of new approaches for the primary prevention of AP at the public health level and may also facilitate the development of new therapies and methods for diagnosis.

Maternal Genitourinary (GU) Infections and Adverse Perinatal Outcomes, Bangladesh. Maternal GU infections, particularly bacterial vaginosis and urinary tract infections (UTI) are common but inadequately quantified in low- and middle-income countries (LMICs). Preterm birth and infections account for the majority, or 60%, of the estimated four million annual global neonatal deaths. About half of preterm births and the majority of early onset neonatal sepsis are attributed to maternal GU infections.

The primary aim of this study is to determine the impact of community-based screening and treatment of abnormal vaginal flora and UTI in early pregnancy, from 12 to 16 weeks, on preterm live birth in Sylhet District, Bangladesh. 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 bactiuria, 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.

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. 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 developing world.

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 (preterm birth; < 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 H2O in the delivery room, as compared to early lung recruitment using sustained inflation (SI) in the delivery room, will result in a lower rate of the combined endpoint of death or bronchopulmonary dysplasia (BPD) (using a standardized oxygen reduction test) at 36 weeks post-menstrual age (PMA). These trials have often changed clinical practice.

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) diffusing recommendations to healthcare providers for antenatal corticosteroids use, (2) training healthcare providers to identify the signs of preterm labor and eligibility criteria for antenatal corticosteroid use among pregnant women, (3) providing birth attendants with preassembled kits containing supplies necessary for a full course of antenatal steroids and reminders to healthcare providers on the use of the kits, and (4) using a color-coded tape to measure uterine height in order to estimate gestational age in women at risk for preterm delivery with unknown gestational age.

- The study enrolled over 100,000 women and their infants and has been published in the *Lancet*. The primary findings showed that the intervention effectively increased ACS administration in <5th percentile infants (45% vs 10%); however, among all births, the intervention resulted in a 3.5 per 1000 absolute increase in neonatal deaths and a 5.1 per 1000 increase in perinatal deaths. These results have generated extensive interest regarding the current practice and guidelines around the use of ACS in community settings.

Point-of-Contact

Dr. Marion Koso-Thomas
kosomari@mail.nih.gov
301-435-6896

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 research 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 normal 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 specific birth defects in humans.

The study of developmental biology is without a doubt foundational to the study of birth defects because they represent developmental defects or "inborn errors of morphogenesis." Whether these perturbations are due to genetic changes, environmental insults, or a combination of both, understanding the underlying developmental mechanisms only will 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 fostering the formation of the Trans-NIH Structural Birth Defects Working Group.

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 of new strategies for prevention.

NICHD-supported investigators have established collaborations with several sites in China including investigators at Peking University, The Shanghai Institute of Medical Genetics, Fudan University in Shanghai, and The Capital Institute of Pediatric Research in Beijing. These collaborations with groups in China enable investigators on a domestic NICHD-supported P01 [and other projects at NICHD and other Institutes] 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.

Netherlands: Congenital diaphragmatic hernia (CDH) is a common, life-threatening birth defect that affects approximately one in 4,000 births. Our long-term goal is to identify genes that cause CDH and determine the molecular mechanisms by which they interfere with normal diaphragm development. Using a combination of human subjects and animal models, genes suspected of being related to CDH in humans can be tested for function using a mouse model. The collaborator in the Netherlands will provide DNA from children with CDH and their parents which will be screened for mutations that may have caused or contributed to the birth defect.

- **Multi-National Collaborations**: In an effort to obtain enough subjects for studies that will result in statistically significant findings, members of our Branches Structural Birth Defects Working Group often form collaborations with investigators in other countries. We support several Program Projects [P01s] that use this strategy to strengthen their studies. Below are two major initiatives: **Canada, Chile, and Israel**: The overall goal of this P01 is to study the underlying genetics of cardiac birth defects (particularly conal truncal defects) by studying patients with 22q11deletion syndrome (22q11DS). The occurrence of rare and common copy number variations (CNVs) in these patients is being assessed in one of the subprojects of this P01. DNA from patients with 22q11DS as well as DNA from controls with no cardiac defects is being compared. The domestic collaborators have recruited human subjects under this grant to perform these analyses. In addition they have formed collaborations with investigators in Canada, Chile, and Israel thus increasing the power of their Genome Wide Association Study (GWAS) meta-analysis. This research is significant in that it will lead to the identification of genetic factors involved in conal truncal cardiac birth defects.

- **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 system 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 analysis of the data. This provides a resource to the research community, ensuring that important data is available and easily accessible to guide further research projects and to avoid unnecessary duplication of effort. In serving this function it 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 DBSV Branch is systems developmental biology because it offers an opportunity 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 approach replaces the one-gene-at-a-time approach to development with a more holistic approach 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 (ChlP-seq) to identify genes that are directly regulated by these transcription factors, they are developing computational techniques and integrative data mining 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 the 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 project continues a successful collaboration providing the computational modeling that allows interpretation of the genetic data generated by the other investigators. In spite of the fact that this work uses such simple organisms, the computational methods and tools that have been developed over the years by this group of investigators can be applied to other model systems and human, improving our ability to predict gene function in development and in disease.

United Kingdom: 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 that code for all of the proteins that are encoded in the genome of the frog *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 the frog *Xenopus* as a model system for basic biological studies. The use of *Xenopus* by researchers allows experiments to be conducted that would be prohibitively difficult and expensive to conduct in mammals, although much of what is learned also applies to human biology. 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 funding a project 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 neuronal regeneration after spinal cord injuries. Numerous studies have been done to elucidate the biochemical mechanisms of axon guidance. However, very 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.

Point-of-Contact

Dr. Tyl Hewitt
hewittt@mail.nih.gov
301-496-5541

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. 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 IDD Branch, formerly the Mental Retardation and Developmental Disabilities Branch, was formed to address this need.

The mission of the IDD Branch is as follows: (1) to develop and support research and research training programs in IDD, including common and rare neuromuscular and neurodevelopmental disorders, such as Down, Fragile X, and Rett syndromes, inborn errors of metabolism, autism spectrum and other disorders; (2) to promote studies designed to understand the etiology and pathophysiology of abnormal nervous system development; (3) to promote studies to delineate genetic, genomic, and epigenetic bases of IDD; (4) to promote studies designed to examine the screening, diagnosis, treatment, and management of IDD and other conditions identified by newborn screening or other screening methods; (5) to administer a program of support for centers for research in IDD; (6) to promote multidisciplinary and translational research in IDD through programs that integrate basic and applied research, training, and service activities for those with IDD and their families; and (7) to partner with patient advocacy groups, non-governmental organizations, and other federal agencies to advance efforts toward the prevention and diagnosis of IDD as well as early intervention and treatment for these conditions.

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 countries (LMICs) 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. IDD staff 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 investigators funded under this Initiative, Liliana Mayo, from the Centro Anne Sullivan del Peru in Lima has undertaken a cost-effective method of large-scale screening for early signs of behavioral problems in developmental disorders in Peru and has utilized mass media campaigns and

innovative “train-the-trainer” methods that included veteran mothers as interviewers. Not much research is available on mass screening methods for children with disabilities, although this method has been used in hard-to-reach populations in the United States. The mass screening method used in Peru was very effective in identifying infants and toddlers at risk for aggression, self-injury, and stereotyped behavior. These children will be followed for a year, and those that continue to exhibit these behaviors will be enrolled in an early intervention study. These results will provide a new public health strategy for reaching children with developmental disorders and provide opportunities for early, effective intervention.

- 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 very different 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 affects 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 developing countries is that this condition is unrecognized and untreated, as most children are born in settings where diagnosis and treatment of jaundice are often unavailable. By the time this condition is recognized, they 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 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 Consortium, Sterol and Isoprenoid Disorders Consortium, and the North American Mitochondrial Disease Consortia, all of which have international sites in Canada and Europe.

- DS-Connect® is an online, secure registry to promote sharing of health information that will advance research to benefit individuals with Down syndrome and their families. Sponsored by the Down Syndrome Consortium, the registry was created by the NIH under NICHD leadership, to connect families with researchers on projects of shared interest. DS-Connect® has attracted over 3,200 registrants in the United States and abroad. International partners include Down Syndrome International (DSi), Jerome Lejeune Foundation, and International Mosaic Down Syndrome Association (IMDSA), who are active members of the Down Syndrome Consortium and helped us to promote DS-Connect® internationally. A Spanish translation of the entire website is available to increase the registry’s outreach to Spanish speaking families within the United States and in Latin America. The Consortium is actively involved in exploring translation of DS-Connect® into other languages.

- 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 analysis 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, they found that 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).

Point-of-Contact

Dr. Danuta Krotoski
Krotoskd@mail.nih.gov
301-496-5576

Contraception Discovery and Development Branch (CDDB)

Mission of Branch

The CDDB, formerly the Contraception and Reproductive Health Branch (CRHB), develops and supports 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 as well as optimal formulations and dosages of contraceptive agents and spermicidal microbicides.

Major International Initiatives over the Past Year

Hormonal Contraception and HIV/AIDS. CDDB 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 Thailand, Uganda, and Zimbabwe. This project is designed to understand the associations between systemic hormonal 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.

Evaluation of a Progesterone Vaginal Ring as a New Contraceptive Option in India. This investigator-initiated research grant ended in FY15 and found that the new contraceptive ring was not inferior to the standard Copper T intrauterine device regarding efficacy and continuation rate.

Effects of Contraceptive Ring on Vaginal Microbiota, HIV Shedding, and Local Immunity. CDDB continued support in FY15 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. CDDB continued supporting this grant in FY15 which funds one of the first studies of the relationship between use of injectable contraceptives (DMPA and norethisterone oenanthate) and the incidence of both HIV and HSV-2. It will also study these agents' 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.

Relationship between Vaginal Micobiota and T. Vaginalis Acquisition. This Mentored Patient-Oriented Research Career Development Award, which ended in FY15, supported research training for a promising new investigator who collected data in in Kenya that will help inform the development of public health strategies aimed at reducing women's susceptibility to T. vaginalis infection.

International Guidelines for Family Planning. Through an interagency agreement (IAA) with the U.S. Agency for International Development (USAID) that began twelve years ago, CRHB continued in FY15 to provide both financial and technical support to the World Health Organization's (WHO) Department of

Reproductive Health and Research for a series of technical documents on contraception written for family planning program officials and providers worldwide. The documents are among the most highly respected guidelines for family planning personnel around the world, and have had significant impact on enabling family planning programs to provide evidence-based contraceptive services.

Collaboration with the Bill & Melinda Gates Foundation (BMGF). CDDB staff continued to work with the BMGF and other organizations in FY15 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. One of the products developed by CRHB/CDDB, levonorgestrel butanoate, made it to the top of the list of products eligible for BMGF support.

U54 Contraceptive Development Program. Through the U54 cooperative agreement with the Population Council, the Branch has supported research on a contraceptive vaginal ring at sites, including the Dominican Republic and Chile.

Recent Achievements in International Health

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

- Late in FY15, CDDB awarded contracts to conduct a multisite male contraceptive efficacy trial that includes the following foreign sites: Karolinska Institutet, Sweden; University of Chile; University of Manchester, United Kingdom (UK); University of Bologna, Italy; University of Edinburgh, UK; and University of Nairobi, Kenya. The trial is expected to start in late 2016.

International Partnerships

- CDDB continued its ongoing collaborations with WHO throughout FY15. Through CDDB's IAA with USAID, the process of collecting and analyzing the world's literature on contraception continued to provide the background for the continuously revised WHO 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.

Staff Membership on Global Health Committees/Working Groups

- **WHO Expert Working Groups for the Medical Eligibility Criteria for Contraceptive Use and the Selected Practice Recommendations for Contraceptive Use**. Member: Trent MacKay, MD, MPH

Point-of-Contact

Dr. Caroline Signore
signorec@mail.nih.gov
301-496-5577

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, health disparities, child development, productivity, behavior, interpersonal violence, natural disasters and development at the population level, using such methods as inferential statistics, natural experiments, policy experiments, statistical modeling, secondary analyses of existing data sets, and gene/environment interaction studies.

Major International Initiatives over the Past Year

Partnership with Mexico. PDB has a special relationship with Mexico as a consequence of the large immigrant population in the United States and supports activities that address health and family welfare. Partnering with the Mexican government, PDB funds and fields the Mexican Family Life Survey, a longitudinal study of Mexican families both in the United States and Mexico.

Social and Behavioral Science Capacity Building. Social and behavioral interventions are critical to prevention of the acquisition of HIV/AIDS and to prevent unwanted, unplanned, and mistimed pregnancies. Yet, social and behavioral science research capacity is limited in low- and middle-income countries (LMICs). In order to strengthen social and behavioral science capacity, NICHD, together with the National Institute of Mental Health and National Institute on Aging, have supported the Partnership for HIV/AIDS Research in Botswana, China, Indonesia, Kenya, Russia, South Africa, Uganda, and Vietnam over the past ten years. PDB funded three sites in the third round of this initiative.

Women's Empowerment. The role of women's empowerment is an important focus of the branch both as it relates to reproductive health risks and outcomes and socio-economic well-being. Studies are being conducted in Bangladesh, India, and various nations in Africa. Where there is greater gender imbalance, women are more susceptible to HIV and unintended pregnancies, as well as to domestic violence. Placing resources in the hands of women has been shown to improve child health and well-being. Studies continue to show that women's education is a powerful predictor of family health and well-being.

Fertility & Family Planning. Fertility and family planning is an important portfolio and supports research in LMICs in addition to domestic studies. Included in this portfolio are high risk behaviors that lead to STDs and AIDS. In 2009, the Branch issued a request for applications (RFA) calling for studies to address the intersection between individuals' and couples' desires to avoid STDs and to plan families. In 2012 and 2013, the Branch was part of an NICHD-wide RFA calling for studies on this topic, in addition to the ongoing studies. The Branch is supporting studies of serodiscordant couples who wish to avoid pregnancy in Rwanda and another study of serodiscordant couples seeking to have children. A study is also being funded in South Africa which examines the relationship between forced or coerced sex and HIV infection.

Youth, Modernization, Generational Change, and Risk. The Branch supports a range of investigator-initiated studies addressing modernization. Projects have a variety of outcomes, including looking at changes in families' consideration of and approval of arranged marriage in India, examining the impact of the introduction of TV into a remote rural area in Vietnam and its impact on adolescent behaviors including physical activity and obesity. We support studies of jobs and unemployment and young men's behaviors in South Africa, generational tensions and HIV risk in Ghana, and one on how young people's understanding of the risk of infection by HIV influences their decisions concerning sexual behavior. We have initiated a study of how providing livelihood support in terms of domestic animal management might improve young people's health and well-being in the Democratic Republic of Congo, and how providing tuition support for school attendance helps young women in Zimbabwe avoid too early marriage, pregnancy, and HIV infection.

Population, Migration, and Environment. Population growth, migration, and environmental change all impact family size and collective and individual health. PDB stimulates and supports research in this area internationally by comparing the status of migrants from China, Mexico, and Puerto Rico and with populations in their home countries. Two studies are examining the HIV risks which male and female migrants from Tajikistan to Russia face in adapting to new environments and jobs, and one study examining the situation of female migrants in Moscow. Other studies address internal displacement in China and Brazil examining the impact of the environment on population health as well as population pressure on environmental integrity. There is growing evidence that growing numbers of households, not growing numbers of people, are the population factor that most strongly affects environmental impacts. One study is looking at how cookstoves, especially poorly ventilated ones in many homes, may influence women's health.

The Indonesian Family Life Surveys (IFLS) and the Malaysian Family Life Surveys (MFLS) were large population samples of households in Indonesia and Peninsular Malaysia that have provided panel data on individuals, households, families, and communities. Topics include family structure, fertility, economic status, education/training, transfers, and migration. The MFLS began in 1976-77, while the IFLS started in 1993. The IFLS study has established that families are very efficient financial institutions that can mobilize resources to meet a variety of emergencies, including tsunamis. Ongoing studies examine a range of economic issues using these data. Currently funded grants address how communities in Indonesia which had been hit by the tsunami are recovering.

Impact of Education Status on Health. The impact of educational status on health was an initiative issued by the Branch. Evidence obtained to date from studies in Europe, Guatemala, India, and Taiwan does not provide a clear pathway linking education to health. However, nutritional status early in life appears to be the actual root of the causal structure that acts by enabling children to obtain a better education and also enjoy better health. See also the section on youth and generational change.

Role of Religious Organizations in HIV Prevention. The role of religious organizations in HIV prevention, a research initiative that began in 2009, continues to produce studies on the importance of religious organizations in Sub-Saharan Africa in communities' responses to the HIV epidemic. People appreciate and welcome the support of faith communities in taking care of the infected and the affected. One investigator wrote a book on *Religion and AIDS in Africa*, which is being widely read.

Social Programs & Economic Interventions. Social programs and economic interventions are being examined to determine the effectiveness of these approaches for improving maternal and child health. Examples of projects include the causal impact of education, age at marriage, and women's control over resources on women and children's health outcomes; the utility of village-level incentives to foster

collective action for improved demand for and access to health services; how corruption can be controlled when subsidizing health products; the impact of primary and secondary education on early fertility and child health; and the channels through which access to education of men and women affects early fertility choices and child health.

International Partnerships

- Joint Working Group on AIDS and Reproductive Health Research in India
- Joint Working Group on AIDS and Research in Russia

Staff Membership on Global Health Committees/Working Groups

None at this time.

Point-of-Contact

Dr. Susan Newcomer
newcomes@mail.nih.gov
301-435-6981

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.

Major International Initiatives over the Past Year

In 2012, the NICHD (FIB and Division of Intramural Population Health Research (DIPHR)) and the Centers for Disease Control and Prevention launched a new program with the South Korean government called the Visiting Scientist Training Award (VSTA). The VSTA Program aims to train Korean epidemiologists in reproductive and perinatal epidemiology and population surveillance. Individuals with faculty appointments are eligible to apply. The first scholar began training in DIPHR in September 2013, and another is expected to begin in 2014. Using this model, the NIH Intramural Program and the Korean National Institute of Health (KNIH) entered into an agreement to sponsor a KVSTA Program for Korean post-doctoral fellows.

International Partnerships

- A letter of intent between NICHD and the KNIH was signed on July 16, 2009 to conduct collaborative research on the genetic basis of infertility and reproductive disorders.

- Ongoing activities include a collaboration with U.S. investigators at Northwestern University and investigators at the KNIH and Ehwa Women's University.

Point-of-Contact

Dr. Louis De Paolo
depaolol@mail.nih.gov
301-435-6970

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, Finland, France, Germany, Greece, Israel, Italy, Mexico, the Netherlands, Spain, Taiwan, 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.

A second study called Positive Outcomes for Orphans (POFO) follows a cohort of 3,000 orphans and abandoned children in Cambodia, Ethiopia, India, Kenya, and Tanzania to examine predictors of positive outcomes such as retention in school, employment opportunities, and civic engagement. It also examines predictors of negative outcomes such as high risk sexual behaviors, drug use, early pregnancy, and engagement in sex trade.

A smaller study building upon the POFO study, is assessing the social and sexual network composition and variability, and determining how network features are associated with low education, income generation, and HIV risk behaviors in orphans and abandoned children. These studies will increase our understanding of the influence of intrapersonal, interpersonal, and community level factors on behavioral and relationship outcomes, HIV risk behaviors, reproductive health, family formation, and academic and social outcomes (education, jobs, and social engagement).

Improving the Health and Well-being of Orphans and Vulnerable Children (OVC) with HIV/AIDS. The Branch supports several outcome evaluation studies in foreign countries to determine if and how services for children affected by HIV/AIDS are having valuable impacts on the children's lives. A study in Uganda implements and evaluates the efficacy and cost-effectiveness of a family-based economic empowerment intervention designed to promote monetary savings for secondary education, to generate family income, and to protect children from future risks. In a second study in Uganda, mediational intervention for sensitizing caregivers is being provided to caregivers of orphans and HIV affected children to heighten caregivers' bonding and sensitivity to serious illness and to improve their children's cognitive and social development. 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.

Mathematics & Science Cognition and Learning, Learning Disabilities. The Branch is supporting the official establishment of an international scientific organization, The Mathematical Cognition and Learning Society (MCLS), in collaboration with math cognition investigators worldwide, with substantial support from European investigators. Kathy Mann Koepke, Scientific Officer, is a founding member on the board. The Branch also sent Dr. Mann Koepke as its branch representative to the International Society for Developmental Psychobiology 48th annual meeting in San Sebastian, Spain from July 20-23, 2015. International presenters and attendees came from five continents, including Asia, Africa, Europe, North America, and South America.

International Partnerships

- The Branch and NICHD have a partnership with the Waltham Centre for Pet Nutrition in the UK. The Centre is a division of Mars, Inc., and is interested in supporting scientifically rigorous research on the influence of pets on child health and human development and the efficacy of animal-assisted interventions and potential mechanisms of that efficacy. With support provided through this public-private partnership, NICHD has been able to fund grants on human-animal interaction (HAI) and hold a series of workshops on key areas and gaps in HAI research. Two of the small grants made to UK institutions are specifically looking at health effects of HAI: one examining asthma prevalence in children living with pets in the home, via secondary data from a major longitudinal study, and one evaluating a dog-bite prevention program. Dr. Layla Esposito leads the NICHD's program on HAI research.

Staff Membership on Global Health Committees/Working Groups

- **Public Law 109-95 (PL 109-95): Assistance for Orphans and Other Vulnerable Children in Developing Countries Act of 2005**. This law was signed on November 8, 2005, to promote a comprehensive, coordinated, and effective response on the part of the U.S. government to the world's most vulnerable children. Dr. Lynne Haverkos is a member of the PL 109-95 Federal Interagency Workgroup and has contributed to the last several annual PL109-95 congressional reports. The role of the working group is to discuss ways in which research might inform the programmatic work of the secretariat and other agencies providing direct assistance to vulnerable children.

- **British Ministry of Health**. Dr. Lisa Freund is working with the British Ministry of Health U.S. liaison, Dr. Stephen Elsby, and a trans-NIH group of interested program officers to discuss and foster progress in developmental behavioral epigenetics research. A jointly supported workshop on Behavioral Epigenetics was held in July 2014 which has resulted in a workshop summary and executive summary for future research activities in this area. These summaries can be found at Behavioral Epigenetics Workshop Summaries. A follow-up workshop is being planned for 2016.

- **World Conference on Learning Disabilities**. Dr. Brett Miller was invited to deliver the opening plenary address at the World Conference on Learning Disabilities in Oviedo, Spain in September 2012. He addressed the progress that has been made in the field of learning disabilities research from the viewpoint of literacy research and indicated some key research topics that continue to challenge the field. He was interviewed by the regional Spanish press and national Spanish television station, and was able to highlight the importance of early identification and intervention for children at risk of learning disabilities.

Point-of-Contact

Dr. Lisa Freund
Lisa.freund@nih.gov
301-435-6879

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, hyperinsuinemia 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, PBNG 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 has 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 Iron**s 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.

Point-of-Contact

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

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 Critical Path Institute held a two-day meeting at the U.S. Food and Drug Administration on neonates. Following that, an International Neonatal Consortia was formed with NICHD representation on the Steering Committee. Discussions on neonatal drug development are underway.

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.

Staff Membership on Global Health Committees/Working Groups

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

Point-of-Contact

Dr. Anne Zajicek
zajiceka@mail.nih.gov
301-435-6865/301-905-7276

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 of HIV and its complications 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), and 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 study offers an extensive database and clinical specimen repository that can be used to explore research questions in the future.

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 63,000 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.

Investigator-initiated research grants: A number of large investigator-initiated research 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-15-107).** 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.

TB in children and pregnant women: The MPID Branch has a special focus on TB in children and pregnant women, and has had several RFA's 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.

- **Enhancing the Capacity for Biomedical Research on Tuberculosis for HIV-Infected Mothers and Children in India (RFA HD-14-025).** NIAID established new Cohort Research Units through collaborations between the U.S. and Indian governments, investigators, and institutions in order to develop longitudinal cohorts of TB patients and their contacts (including patients with HIV and TB co-infection) and fundamental research laboratories. This MPID/NICHD funding opportunity solicited Research Project Grant (R01) applications from institutions/organizations to include HIV-infected and uninfected children and pregnant women with TB exposure, infection, or disease within these recently established programs in India. One grant will be funded that will be looking at the impact of immunologic changes during pregnancy on TB in HIV-infected and HIV-uninfected pregnant women in India.

    - A large study in South Africa is evaluating the impact of TB and its treatment on outcomes in HIV-infected pregnant women and their infants, including HIV transmission, HIV progression, and pregnancy outcome, and will also determine the impact of rifampin-based TB treatment on ART drug concentrations in HIV-infected pregnant women.

    - A clinical trial to assess three drug regimens for the treatment of TB meningitis will start soon in Malawi and India. This trial is the first for TB meningitis since 1986.

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.

- 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.

HIV Prevention and Treatment in Children

- In Botswana, over 3,000 HIV-exposed but uninfected infants were randomized to receive either cotrimoxazole or placebo from four weeks through 15 months to determine if the use of the antibiotic cotrimoxazole may improve survival in infants who are formula fed or after weaning. In addition, breastfeeding infants will be randomized to either breastfeed until six or twelve months of age. Children will be followed prospectively until 18 months of age. The primary endpoint is survival at 18 months comparing all infants in the cotrimoxazole vs. placebo arms, and by randomized duration of breastfeeding. Results should be available soon. In South Africa, a clinical trial is evaluating a simplified, protease inhibitor-sparing strategy among HIV-infected children aged three to five years who were infected despite nevirapine used for PMTCT (and hence likely have nevirapine resistance). The children are initially treated with the protease inhibitor lopinavir/ritonavir, and the study will evaluate changing from lopinavir-ritonavir to a non-nucleoside drug efavirenz vs. staying on the lopinavir-ritonavir regimen.

- 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 HIV-exposed but uninfected children.

- A clinical trial in Kenya is evaluating 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. Immediate start of anti-HIV treatment at the same time as starting treatment of the infection may be associated with increased side-effects, difficulty in administration of several drugs, and increased risk of immune reconstitution inflammatory syndrome. However, these risks may be outweighed by the prompt decrease in viral replication, faster immune recovery, and better control of both HIV infection and coexisting co-infection.

- 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.

HIV in Women

- In Uganda, a study is evaluating the hypothesis that extended repeat HIV testing and enhanced counseling (HTEC) in 1,230 HIV-uninfected women during late pregnancy and breastfeeding can increase and/or sustain risk reduction behaviors and prevent incident sexually transmitted infections and HIV infections among HIV-uninfected pregnant women and that couple HTEC can further enhance this effect. Enhanced counseling will emphasize the concept of a HIV-free and healthy baby and family based on primary prevention, adequate infant feeding, and family planning.

- In 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.

Recent Achievements in International Health

- A clinical trial conducted by MPID-branch funded investigators in South Africa demonstrated that HIV-infected infants, infected despite exposure to single-dose nevirapine to prevent transmission, can initiate treatment with a protease inhibitor but may be able to switch to the cheaper and better tolerated nevirapine after viral replication is controlled (*Lancet Infectious Diseases* 2012;12:521-30). Secondary analyses of this study have demonstrated that continued therapy with lopinavir leads to unfavorable alterations in lipid and triglyceride profile compared to those switched to nevirapine therapy (*Arch Dis Chid* 2013;98:258-64). They have also demonstrated that plasma concentration of lopinavir in children predicts virologic failure in South African children (*Antivir Therr* 2014 Feb 12 epub).

- A clinical trial conducted by MPID-branch funded investigators in Uganda demonstrated that treatment of uncomplicated malaria with artemisinin-based combination therapies in HIV-infected children on ART was safe, but that there was a high risk of recurrent parasitemia following treatment that was significantly lower in HIV-infected infants being treated with lopinavir/ritonavir as compared to nevirapine-based combination regimens (*Clin Infect Dis* 2014 Apr 23 epub).

- An MPID-funded investigator in South Africa is evaluating novel assays for diagnosis of TB in children. She has demonstrated that using the rapid diagnostic test Xpert MTB/RIF assay in stool may hold promise for diagnosis of pulmonary TB in children (*Clin Infect Dis* 2013;57:e18-21). However, the novel approach of using urine to measure mycobacterial lipoarabinomannan, which had shown promise in adults, was not useful for diagnosis of pulmonary TB in children (*Lancet Global Health* 2014;2:e278-84).

- A study in South Africa identified high rates of ARV drug resistance among newly-infected infants, which has significant implications for choice of initial ART in such infants (*AIDS* 2014; 28:1673-8).

- A pilot study in South Africa of an innovative family-based intervention for young adolescents found the intervention improved mental health, youth behavior, HIV treatment knowledge, and adherence to medication among HIV-infected youth (*AIDS Care* 2014;26:1-11). MPID is now funding a larger scale evaluation of this intervention.

- A study in Kenya recruited HIV-1 uninfected couples undergoing voluntary HIV testing. 228 women had cervicovaginal secretions collected for concentrations of human neutrophil defensins (HNP) 1-3, LL-37, lactoferrin, human beta-defensins (HBD) -2, and secretory leucocyte protease inhibitor (SLPI) measured by enzyme linked assays and compared between women who were using depot medroxyprogesterone acetate (DMPA), non-hormonal contraceptives, oral contraceptives, and hormonal implants. Compared to non-hormonal users, DMPA users had significantly higher mean levels of human neutrophil peptides (HNP) and lactoferrin, suggesting that there may be mucosal susceptibility to infection. DMPA may affect innate immune defenses and should be further investigated on HIV-1 acquisition risk. (*JAIDS* 2015;69(1):1-10)

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

Point-of-Contact

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

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. These efforts include:

- Studies of the continuum of psychosocial, behavioral, and physiological influences that impact child health outcomes in trauma, injury, and acute care
- Projects that explore short- and long-term consequences of acute traumatic experiences, such as natural and man-made disasters, all acute forms of child maltreatment, violence, and exposure to violence
- Research linking pediatric emergency and critical care medicine and science to the epidemiology, prevention, and treatment of childhood physical disabilities and
- Research on prevention, treatment, management, and outcomes of physical and psychological trauma and the surgical, medical, psychosocial, and systems interventions needed to improve outcomes for critically ill and injured children across the developmental trajectory

Major International Initiatives over the Past Year

None to report at this time.

Recent Achievements in International Health

None to report at this time.

International Partnerships

None to report at this time.

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

Point-of-Contact

Dr. Valerie Maholmes
maholmev@mail.nih.gov
301-496-1514

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 that affects an estimated 50 to 100,000 women each year. It is estimated that as many as two million women have untreated obstetric fistula in Asia and Sub-Saharan Africa. Obstetric fistula is the result of obstructed labor and causes constant leaking of urine and/or feces. Women with obstetric fistula can be successfully treated with surgery most often, but even then, are often not reintegrated into the community. The small amount of research in this area has focused on treatment approaches without considering the success of the woman's reintegration into her family and community. An essential step toward understanding reintegration is to develop an appropriate measurement tool of reintegration success, as none currently exist. The GHDB has funded a study with the goals of better understanding the process of family and community reintegration post fistula surgery; to modify and pilot test in Uganda a measurement tool to assess long-term success of family and community reintegration among women post-fistula surgery, and to assess the feasibility of long-term follow-up among this group utilizing mobile phone technology.

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 been cut. There are still immigrant communities in the United States carrying out this procedure or taking care of women who have had this procedure, so this remains both an international and domestic area of research for GHDB.

Recent Achievements in International Health

- The study on obstetric fistula above is nearing completion.

International Partnerships

- U.S. Agency for International Development (USAID), Mary Ellen Stanton

Staff Membership on Global Health Committees/Working Groups

- The Obstetric Fistula International Research Advisory Group funded by USAID to FistulaPlus, GHDB Staff: Dr. Susie Meikle

Point-of-Contact

Dr. Susie Meikle
meikles@mail.nih.gov
301-273-8541

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. Our 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

Neural Tube Defects (NTDs). A collaborative study of NTDs and oral facial clefts between NICHD and the Health Research Board of Ireland/Trinity College Dublin/NHGRI.

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.

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.

Genetic Factors in Birth Defects. An international collaboration with investigators from the Denmark will evaluate genetic factors in birth defects.

Recent Achievements in International Health

- **Neural Tube Defects:** Recent work has identified two new genetic variants associated with plasminogen. A genetic variant in the gene for dihydrofolate reductase, which is important in absorbing folic acid to prevent NTDs, was shown not to interfere with normal folic acid absorption. Low maternal choline status had been postulated to be a risk factor for NTDs. Choline concentrations were shown to be no different in women carrying an affected fetus than in women with unaffected fetuses. Similarly, low maternal iron status had been suggested as a risk factor for NTDs, but women carrying affected fetuses had concentrations no different than women carrying unaffected fetuses.

- **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.

- 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

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

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

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

Point-of-Contact

Enrique F. Schisterman, Ph.D., M.A.
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 and to determine how to apply such knowledge to illuminate developmental origins of health and disease and help ensure that women and men have good reproductive health, that children are born healthy, and that people develop to live healthy and productive lives.

The DIR research program utilizes a multidisciplinary environment to investigate the physics, chemistry, and biology of cells, the processes that govern and regulate cellular function, and the effects when these processes fail.

Ten research programs, comprised of roughly 78 units and sections, constitute the NICHD DIR. The Division includes a total of 72 tenured and tenure-track investigators, over 300 postbaccalaureate, clinical, and postdoctoral fellows and graduate students, and a total administrative and staff complement of approximately 1,200.

The research of the DIR 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?

The majority of the DIR laboratories are located on the NIH campus in Bethesda, Maryland, or in nearby Rockville. An additional research facility is located in Poolesville, Maryland. The Program in Perinatal Research and Obstetrics is based in Detroit, Michigan.

Program on Developmental Endocrinology and Genetics

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

Name of Lab: Section on Endocrinology and Genetics, NICHD

Name of Program: Program on Developmental Endocrinology and Genetics (PDEGEN)

Mission of Program/Lab

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, and others in Brazil

Selected Publications with International Collaborators

1. 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.

2. 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.

3. Zilbermint M, Xekouki P, Faucz FR, Berthon A, Gkourogianni A, Schernthaner-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.

4. 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.

5. Trivellin G, Daly AF, Faucz FR, Yuan B, Rostomyan L, Larco DO, Schernthaner-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.

6. 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.

7. 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.

8. 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

9. 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.

10. 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.

11. 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]*

12. 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*

13. 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.*

14. 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 and phosphodiesterases and related genes 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

- Sisi Liu, Pre-doctoral Visiting Fellow
  Shaw College
  Lianyunggang City, China

- Paraskevi Salpea, Ph.D., Postdoctoral Visiting Fellow
  Kapodistrain University of Athens
  Cholargos, Greece

- Nikolaos Settas, Ph.D., Postdoctoral Visiting Fellow
  University of Athens
  Department of Genetics
  Athens, Greece

- Chaido Stathopoulou, MRes Visiting Fellow
  Imperial College London, UK
  (BSc Genetics, University of Leeds, UK)
  Translational Medicine

- Eva Szarek, Ph.D., Postdoctoral Visiting Fellow
  University of Adelaide
  Tarnow, Poland

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

International Partnerships

Memoranda of Understanding with:

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

Staff Membership on Global Health Committees/Working Groups

None at this time.

Point-of-Contact

Dr. Fabio Rueda Faucz
fabio.faucz@nih.gov
301-451-7177

Program in Cellular Regulation and Metabolism (PCRM)

Section on Molecular Morphogenesis (Yun-Bo Shi)

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, 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, they have recently collaborated 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.

In their studies of thyroid hormone regulation of Xenopus metamorphosis, they 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.

In conjunction with researchers at the University of Dundee in the United Kingdom, they have generated a conditional knockout mouse line to investigate the role of a transporter for thyroid hormone and amino acids that they had 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, their collaboration with Wuhan University on the global developmental expression profiles has revealed genetic programs underlying the developmental divergence between mouse and human embryogenesis.

Finally, in collaboration with researchers at Wuhan University, they 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, they have successfully transformed Staphylococcus aureus cells 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.

Relevant Publications:

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. 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.

12. 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.

13. 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.

14. 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.

15. 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).

16. 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.

17. 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)

18. Song, E.-Q., Hu, J., Wen, C.-Y., Tian, Z.-Q., Yu, X., Zhang, Z.-L., **Shi, Y.-B**., and Pang, D.-W. (2011) Fluorescent-Magnetic-Biotargeting Multifunctional Nanobioprobes for Detecting and Isolating Multiple Types of Tumor Cells. *ACS Nano*. 5(2), 761-70.

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*, in press.

Section on Eukaryotic Transposable Elements (Henry Levin)

Work conducted under this Section to generate dense maps of transposon insertions in fission yeast was carried out in conjunction with Dr. Kwang-Lae Hoe at the Department of New Drug Discovery and Development in Chungnam National University in the Republic of Korea. This study resulted in a novel approach to identify the functions of eukaryotic genes based upon dense maps of transposon integration. The method has the potential to identify interactions between genes and to identify which genes are targeted by specific drugs.

Relevant Publication:

1. Guo Y, Park JM, Cui B, Humes E, Gangadharan S, Hung S, Fitzgerald PC, Hoe KL, Grewal SI, Craig NL, Levin HL., Integration Profiling of Gene Function with Dense Maps of Transposon Integration. *Genetics*, In Press.

Section on Protein Biosynthesis (Thomas Dever)

Work from this Section on protein kinase regulation of cellular protein synthesis conducted in conjunction with Frank Sicheri at the Lunenfeld-Tanenbaum Research Institute and University of

Toronto and with Susumu Katsuma at the University of Tokyo has elucidated a novel mechanism employed by baculovirus to inhibit cellular protein kinases that regulate protein synthesis.

Relevant Publication:

1. Baculovirus protein PK2 subverts eIF2α kinase function by mimicry of its kinase domain C-lobe. Li JJ, Cao C, Fixsen SM, Young JM, Ono C, Bando H, Elde NC, Katsuma S, Dever TE, Sicheri F. Proc Natl Acad Sci U S A. 112:E4364-73, 2015.

Dr. Dever in collaboration with with Venki Ramakrishnan at the MRC Laboratory of Molecular Biology and Cambridge University in England is co-mentoring a graduate student conducting structure-function studies of the ribosome and the mechanism of cellular and viral protein synthesis.

Section on Nutrient Control of Gene Expression (Alan Hinnebusch)

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.

Relevant Publications:

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.

Section on Neuronal Connectivity (Chi-Hon Lee)

Work in this section on dissecting visual circuits carried out in conjunction with researchers from the University of Sheffield in England and Dalhousie University in Canada 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. Work in collaboration with researchers from Tata Institute of Fundamental Research in India has led to new insight in neural circuit assembly and dendrite development.

Relevant Publications:

1. 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 (in press).

2. 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.

3. 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.

4. Meinertzhagen, I.A and Lee, C.-H. The Genetic Analysis of Functional Connectomics in *Drosophila*. Advances in Genetics, 80, 99-151, 2012.

5. 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.

6. 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.

Section on Environmental Gene Regulation

Name of Investigator: Gisela Storz

Name of Lab: Section on Environmental Gene Regulation

Name of Program: Cell Biology and Metabolism Program

Mission of Program/Lab

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

Major International Initiatives in 2015

None at this time.

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. It is anticipated that he will fulfill all of the requirements for a Ph.D. degree within the next year and a half.

International Partnerships

None at this time.

Staff Membership on Global Health Committees/Working Groups

None at this time.

Point-of-Contact

Dr. Gisela Storz
storz@helix.nih.gov
301-402-0968

Section on Child and Family Research (SCFR)

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

Name of Lab: Child and Family Research Section, Office of Scientific Director, NICHD

Name of Program: Office of the Scientific Director

Mission of Program/Lab

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
- 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 2014 to present, 44 reports dealing with international or cross-cultural samples and collaborations were published.

1. Bornstein, M.H., & Esposito, G. (2014). 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. (in press). Mothers' and fathers' parenting practices with their daughters and sons in low- and middle-income countries. Monographs of the Society for Research in Child Development

3. Bornstein, M. H., Putnick, D. L., Bradley, R. H., Deater-Deckard, K., & Lansford, J. E. (in press). Gender in low- and middle-income countries: Introduction. Monographs of the Society for Research in Child Development

4. Bornstein, M. H., Putnick, D. L., Bradley, R. H., Deater-Deckard, K., Lansford, J. E., & Ota, Y. (in press). Gender in low- and middle-income countries: General methods. Monographs of the Society for Research in Child Development

5. Bornstein, M. H., Putnick, D. L., Bradley, R. H., Lansford, J. E., & Deater-Deckard, K. (2015). Pathways among caregiver education, household resources, and infant growth in 39 low- and middle-income countries. Infancy, 20, 353-376.

6. Bornstein, M. H., Putnick, D. L., Cote, L. R., Haynes, O. M., & Suwalsky, J. T. D. (2015). Mother-infant contingent vocalizations in eleven countries. Psychological Science, 26, 1272-1284.

7. Bornstein, M. H., Putnick, D. L., Deater-Deckard, K., Lansford, J. E., & Bradley, R. H. (in press). Gender in low- and middle-income countries: Reflections, limitations, directions, and implications. Monographs of the Society for Research in Child Development

8. Bornstein, M. H., Putnick, D. L., Lansford, J. E., Deater-Deckard, K., & Bradley, R. H. (in press). A developmental analysis of caregiving modalities across infancy in 38 low- and middle-income countries. Child Development

9. Bornstein, M. H., Putnick, D. L., Lansford, J. E., Pastorelli, C., Skinner, A. T., Sorbring, E., Tapanya, S., Uribe Tirado, L. M., Zelli, A., Alampay, L. P., Al-Hassan, S. M., Bacchini, D., Bombi, A. S., Chang, L., Deater-Deckard, K., Di Giunta, L., Dodge, K. A., Malone, P. S., & Oburu, P. (2015). Mother and father socially desirable responding in nine countries: Two kinds of agreement and relations to parenting self-reports. International Journal of Psychology, 50, 174-185.

10. Bornstein, M. H., & Suwalsky, J. T. D. (2014). Risco e resiliência na adoção: Um estudo longitudinal de crianças adotadas em circunstâncias ótimas [Risk and resilience in adoption: A longitudinal study of children adopted under optimal circumstances]. In M. Matias & M. Paulino (Eds.), A Criança no Processo de Adoção: Realidades, Desafios e Mudanças [Children in the Adoption Process: Realities, Challenges and Changes] (pp. 160-184). Prime Books: Lisboa.

11. Bradley, R. H., & Putnick. D. L. (in press). The role of physical capital assets in young girls' and boys' mortality and growth in low- and middle-income countries. Monographs of the Society for Research in Child Development

12. Cote, L. R., Bornstein, M. H., Kwak, K., Putnick, D. L., & Chung, H. J. (in press). The acculturation of parenting cognitions: A comparison of South Korean, Korean immigrant, and European American mothers. Cross-Cultural Psychology,

13. De Houwer, A., & Bornstein, M. H. (in press). Balance patterns in early bilingual acquisition: A longitudinal study of word comprehension and production. In J.C. Treffers-Daller & C. Silva-

Corvalán (Eds.), Language Dominance in Bilinguals: Issues of Measurement and Operationalization (pp. xx-xx). Cambridge: Cambridge University Press.

14. De Houwer, A., Bornstein, M. H., & Putnick, D. L. (2014). A bilingual-monolingual comparison of young children's vocabulary size: Evidence from comprehension and production. Applied Psycholinguistics, 35, 1189-1211.

15. De Pisapia, N., Serra, M., Rigo, P., Jager, J., Papinutto, N., Esposito, G., Venuti, P., & Bornstein, M. H. (2014). Interpersonal competence in young adulthood and right laterality in white matter. The Journal of Cognitive Neuroscience, 26, 1257-1265.

16. 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 Sciences, 112, 9310-9315.

17. Esposito, G., Nakazawa, J., Ogawa, S., Stival, R., Putnick, D. L., & Bornstein, M. H. (2015). Using infrared thermography to assess emotional responses to infants. Early Child Development and Care, 185, 438-447.

18. Esposito, G., Nakazawa, J., Ogawa, S., Stival, R., Kawashima, A., Putnick, D. L., & Bornstein, M. H. (2014). Baby, you light-up my face: Culture-general physiological responses to infants and culture-specific cognitive judgments of adults. Plos One

19. Esposito, G., Nakazawa, J., Venuti, P., & Bornstein, M. H. (in press). Judgment of infant cry: The roles of acoustic characteristics and sociodemographic characteristics. Japanese Psychological Research.

20. 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, 6, 264. doi: 10.3389/fpsyg.2015.00264.

21. 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, 43-50.

22. 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.

23. Ferguson, G. M., Desir, C., & Bornstein, M. H. (2014). "Ayiti Cheri": Cultural orientation of early adolescents in rural Haiti. The Journal of Early Adolescence, 34, 621-637.

24. 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.

25. Gartstein, M. A., Putnick, D., 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., Goetz, 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, 6, 1060. doi: 10.3389/fpsyg.2015.01060.

27. Hendricks, C., Lansford, J. E., Deater-Deckard, K., & Bornstein, M. H. (2014). Associations Between Child Disabilities and Caregiver Discipline and Violence in Low-and Middle-Income Countries. Child Development, 85, 513-531.

28. 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, 46, 1023-1038.

29. Lansford, J. E., Deater-Deckard, K., Bornstein, M. H., Putnick, D. L., & Bradley, R. H. (2014). Attitudes justifying domestic violence predict endorsement of corporal punishment and physical and psychological aggression towards children: A study in 25 low- and middle-income countries. Journal of Pediatrics, 164, 1208-1213.

30. 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.

31. 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. (in press). Individual, family, and culture level contributions to child physical abuse and neglect: A longitudinal study in nine countries. Development and Psychopathology.

32. Lansford, J. E., Sharma, C, Malone, P. S., Woodlief, D., Dodge, K. A., Oburu, P., Pastorelli, C, Skinner, A. T., Sorbring, E., Tapanya, S., Uribe Tirado, L. M., Zelli, A., Al-Hassan, S. M., Alampay, L. P., Bacchini, D., Bombi, A. S., Bornstein, M. H., Chang, L., Deater-Deckard, K., & Di Giunta, L. (2014). Corporal punishment, maternal warmth, and child adjustment: A longitudinal study in eight countries. Journal of Clinical Child and Adolescent Psychology, 43, 670-685.

33. Lansford, J. E., Woodlief, D., Malone, P. S., Oburu, P., Pastorelli, C., Skinner, A. T., Sorbring, E., Tapanya, S., Uribe Tirado, L. M., Zelli, A., Al-Hassan, S. M., Alampay, L. P., Bacchini, D., Bombi, A. S., Bornstein, M. H., Chang, L., Deater-Deckard, K., Di Giunta, L., & Dodge, K. A. (2014). A longitudinal examination of mothers' and fathers' social information processing biases and harsh discipline in nine countries. Development and Psychopathology, 26, 561-573.

34. Longobardi, E., Rossi-Arnaud, C., Spataro, P., Putnick, D. L., & Bornstein, M. H. (2015). Children's acquisition of nouns and verbs in Italian: Contrasting the roles of frequency and positional salience in maternal language. Journal of Child Language, 42, 95-121.

35. Longobardi, E., Spataro, P., Putnick, D. L., & Bornstein, M. H. (in press). Noun and verb production in maternal and child language: Continuity, stability, and prediction across the second year of life. Language Learning and Development

36. Putnick, D. L. & Bornstein, M. H. (in press). Girls' and boys' labor and household chores in low- and middle-income countries. Monographs of the Society for Research in Child Development

37. 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.

38. Putnick, D. L., Bornstein, M. H., Breakstone, D. A., & Suwalsky, J. T. D. (2014). Mother-child emotional availability across cultures: Findings from western and non-western countries. In H. Selin (Ed.), Parenting Across Cultures: Childrearing, Motherhood and Fatherhood in Non-Western Cultures. Series: Science Across Cultures: History and Practice, Vol. 7 (pp. 475-487). New York: Springer.

39. Putnick, D. L., Bornstein, M. H., Lansford, J. E., Malone, P. S., Pastorelli, C., Skinner, A. T., Sorbring, E., Tapanya, S., Uribe Tirado, L. M., Zelli, A., Alampay, L. P., Al-Hassan, S. M., Bacchini, D., Bombi, A. S., Chang, L., Deater-Deckard, K., Di Giunta, L., Dodge, K. A., & Oburu, P. (2015). Perceived mother and father acceptance-rejection predict four unique aspects of child adjustment across nine countries. Journal of Child Psychology and Psychiatry, 56, 923–932.

40. Skinner, A. T., Bacchini, D., Lansford, J. E., Godwin, J., Sorbring, E., Tapanya, S., Uribe Tirado, L. M., Zelli, A., Alampay, L. P., Al-Hassan, S. M., Bombi, A. S., Bornstein, M. H., Chang, L., Deater-Deckard, K., Di Giunta, L., Dodge, K. A., Malone, P. S., Miranda, M., Oburu, P., & Pastorelli, C. (2014). Neighborhood danger, parental monitoring, harsh parenting, and child aggression in nine countries. Societies, 4, 45-67.

41. Tamis LeMonda, C. S., & Bornstein, M. H. (2015). Infant word learning in biopsychosocial perspective. In S. Calkins (Ed.), Handbook of Infant Development: A Biopsychosocial Perspective (pp. 152-185). New York: Guilford Press.

42. 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. (in press). Hostile attributional bias and aggressive behavior in global context. Proceedings of the National Academy of Science.

43. Tomlinson, M., Bornstein, M. H., Marlow, M., & Swartz, L. (2014). Imbalances in the knowledge about infant mental health in rich and poor countries: Too little progress in bridging the gap. Infant Mental Health Journal, 35, 624-629.

44. Winstanley, A. V., Sperotto, R. G., Putnick, D. L., Cherian, S., Bornstein, M. H., & Gattis, M. (2014). Consistency of maternal cognitions and principles across the first five months following preterm and term deliveries. Infant Behavior and Development, 37, 760-771.

Recent Achievements in International Health

Bornstein MH, Putnick DL, Cote LR, Haynes OM, Suwalsky JT. Mother-Infant Contingent Vocalizations in 11 Countries. *Psychological Science*, 2015.

- Mother-infant vocal interactions serve multiple functions in child development, but it remains unclear whether key features of these interactions are community-common or community-specific.

- We examined rates, interrelations, and contingencies of vocal interactions in 684 mothers and their 5½-month-old infants in diverse communities in 11 countries: Argentina, Belgium, Brazil, Cameroon, France, Israel, Italy, Japan, Kenya, South Korea, and the United States.

- Rates of mothers' and infants' vocalizations varied widely across communities and were uncorrelated. However, collapsing the data across communities, we found that mothers' vocalizations to infants were contingent on the offset of the infants' non-distress vocalizing, infants' vocalizations were contingent on the offset of their mothers' vocalizing, and maternal and infant contingencies were significantly correlated. These findings point to the beginnings of dyadic conversational turn taking. Despite broad differences in the overall talkativeness of mothers and infants, maternal and infant contingent vocal responsiveness is found across communities, supporting essential functions of turn taking in early-childhood socialization.

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

International Partnerships

See above.

Staff Membership on Global Health Committees/Working Groups

None at this time.

Point-of-contact:

Dr. Marc H. Bornstein
Marc_h_bornstein@nih.gov
301-496-6832

Section on Molecular Neurobiology

Name of Investigator: Dr. Andres Buonanno

Name of Lab: Section on Molecular Neurobiology (SMN)

Name of Program: Office of the Scientific Director

Mission of Program/Lab

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 I, 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.

Staff Membership on Global Health Committees/Working Groups

None reported.

Point-of-Contact

Andres Buonanno, Ph.D.
buonanno@mail.nih.gov
301-496 0170

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

- Dr. Richard Greenwald, R24HD065703, "Translation of Rehabilitation Engineering Advances and Technology (TREAT)"
- Dr. Richard Macko, 5R01HD068712-05, "Effects of Early Exercise on Muscle and Cardiovascular Health after Stroke"
- Dr. David Ostry, R01 HD75740 "Training-Induced Plasticity in Human Motor and Sensory Systems"
- Dr. Mark Ruegsegger, R25HD074840, "Multidiscipline Design Projects with Outreach to Persons with Disability"
- Dr. Terrence Sanger, R01HD081346, "Multi-Center Trial of Augmented Sensory Feedback in Children with Dyskinetic CP"
- Dr. Marco Santello, 1R21HD081938-01 "Soft Synergy Based Artificial Hand for Prosthetic Applications"
- Dr. Lynn Snyder-Mackler, 5R37HD037985-13, "Dynamic Stability in the ACL Injured Knee"

Staff Membership on Global Health Committees/Working Groups

- None at this time.

Point-of-Contact

Dr. Ralph Nitkin
R21e@nih.gov
301-402-4206