February 15th, 2019

RE: Request for Information (RFI): NICHD Strategic Plan Fiscal Years 2020-2024
Notice Number: NOT-HD-18-031

We thank the NICHD for undertaking a revision of their strategic plan to respond to the important challenges and exciting opportunities to improve child health and human development, and for the opportunity to provide input on the proposal. As a scientific society comprised of a diverse set of developmental biologists, we have both highly relevant expertise to offer and a vested interest in the outcome. We applaud the broad focus of the proposed research themes, and are excited by the impact of translational research on human health. We are particularly excited about including the ever-increasing ways for human pluripotent stem cells to model aspects of human development and generate disease models. However, we are concerned that the crucial role of fundamental research in model organisms is not adequately emphasized in this proposal. Two major research directions in developmental biology, regeneration and birth defects, are also not clearly represented.

The overarching goal of the NIH has always been to improve human health. It is important to realize that in many cases, the most appropriate route to understanding human biology, including human development, is to study model organisms. The deep conservation of fundamental biological processes and their genetic underpinnings makes study of a wide variety of organisms, both vertebrate and invertebrate, potentially appropriate given the question at hand. From genetic screens in *D. melanogaster* and *C. elegans*, to knockout mice, to the manifold uses of GFP, experiments in model organisms have been central to an array of Nobel Prize-winning work in recent decades. Indeed, thousands of such fundamental studies, many funded by the NICHD, provided crucial insights to our understanding of human embryonic development.

Looking forward, the impact of work in animal systems will clearly continue. Recent work in zebrafish uncovered a pathway likely involved in preeclampsia. The methodology and concepts undergirding both stem cell biology and regenerative medicine arose, and continue to arise, from work from developmental biologists studying model organisms. Organoids and synthetic embryoids, derived from both human and animal tissue, offer great promise to decipher the fundamentals of tissue patterning, embryogenesis and organogenesis. We posit that the technological advances in genome editing, sequencing, imaging and cell culture methods make investigations of model systems particularly effective and synergistic with human studies.

We urge the NICHD to revise the language describing these overarching research themes, as described below. These changes will make it clear how fundamental research in developmental biology is vital to achieving long-term improvements in human health. This will ensure that scientists, legislators and the public continue to view fundamental research as a central part of the NICHD mission.

1. **Understanding early human development**

We have two major concerns with the language used to describe this important goal. First, we are concerned
that the goal does not emphasize the key roles that animal models must continue to play here. Second, we are concerned that the language used here puts an undue emphasis on the role of sequencing approaches, at the expense of other crucial modes of investigation. For example, massive advances in the labeling and visualization of cellular components and in optogenetics now allow the long-term imaging and manipulation of all cells in organisms over extended periods of developmental time, thereby providing a spatial and temporal architecture of the embryo that is essential to make sense of the vast new amounts of single-cell sequencing data. Again, these methods, which are increasingly utilized to interrogate human development in organoids, have historically and continue to be developed by biologists studying animal models.

We advise that this goal be broadened, and suggest the following revision.

This goal includes the study of fundamental developmental processes across the animal kingdom, using existing and emerging technologies, as well as the development of novel platforms, tools, and techniques to characterize the early stages of development. This work will capitalize on rapid advances in microscopy, nucleic acid sequencing, proteomics and computational analysis to elucidate critical developmental processes such as cell differentiation through gene regulatory networks, morphogenetic cell behaviors, and the behavior of complex developmental systems at the molecular, cellular, tissue and organismal level. This work will be enhanced by research on the influence of environmental exposures on early development, which may help to identify potential targets for prevention. This research area provides opportunities to understand at a cellular level what developmental factors contribute not only to typical development but also to infertility, miscarriage, stillbirth, birth defects, and other congenital conditions.

2. Setting the foundation for a healthy pregnancy and lifelong wellness

The study of birth defects should also be emphasized in this section, as the CDC estimates that these defects represent the leading cause of death for children under one year of age and remain among the top five causes of death for children of all ages. Many birth defects are genetic and there is increasing evidence of links between birth defects and childhood cancers, both of which are acknowledged by the NIH Director’s Office’s Gabriella Miller Kids First Pediatric Research Initiative. Accordingly, as prenatal genetic testing has grown more sophisticated, improving prenatal diagnosis and treatment of birth defects should be a primary goal of the NICHD. We further note that directed experimentation in animal models is now a gold-standard approach for functional validation of genetic variants. Such validation is essential, as the pathogenic impact of most variants identified in human patients is unknown and cannot be predicted by computer algorithms at this time. Moreover, animal disease models enable effective screening for candidate therapeutics in the context of a whole organism.

To incorporate these important directions, we suggest the following revision.

This goal is focused on the developmental origins of postnatal health for mothers and children, including the origin, diagnosis and prenatal treatment of birth defects, and development of early indicators of risk for threats to maternal health during pregnancy, such as preeclampsia, gestational diabetes, post-partum hemorrhage, and placental anomalies. It also includes understanding how these pregnancy-related conditions contribute to maternal mortality and influence health and wellbeing later in life. Research in this area aims to determine the biological underpinnings of these conditions and potential targets for intervention by studying genotypic, phenotypic, exposure, and other biomarkers. This work will incorporate new and/or existing datasets to better understand the course and complications of pregnancy that contribute to health outcomes for woman and child through adulthood, and therefore includes efforts to build infrastructure necessary to collect and curate relevant patient datasets and foster necessary collaboration between clinicians and researchers. It also includes work to functionally validate human genetic variants in model animal systems. Continued study of the placenta, including non-invasive methods to determine placental health, will play a key role in this opportunity. This work will inform
new prevention strategies by considering prenatal genetic testing, lifestyle factors (e.g., maternal weight, substance misuse, etc.), exposure to infectious diseases, nutrition, and other influences during pregnancy that promote health or lead to disease at the very earliest stages of life. Understanding the contributors to morbidity and mortality will help to identify and validate targets for preventing preterm birth and related adverse events. Testing of early interventions, both domestically and globally, will be a vital component of this research opportunity.

3. **Promoting Gynecological, Andrological, and Reproductive Health**

   This research theme aims to “improve basic biological understanding of the male and female reproductive organs” and to “seek to identify modifiable factors to solve infertility both through basic science”, and yet does not include the possibility of model animal systems contributing to these goals. We see clear roles for animal research in elucidating the fundamental biology of gonad formation, and for testing potential interventions that seek to remedy infertility.

   We suggest the following revision to this theme.

   There is an opportunity to improve basic biological understanding of the male and female reproductive organs; knowledge that may lead to treatments for conditions that affect them. NICHD is interested in the use of integrated genetic and phenotypic exposure data to understand the fundamental biology of gonad formation, in humans and animal systems, as well as the underlying mechanisms of conditions such as endometriosis, fibroids, pelvic pain, vulvodynia, pelvic organ dysfunction, undescended testes, cryptorchidism, varicocele, and other factors that affect urogenital health. We will maintain a focus on the science of pediatric gynecology, especially as it relates to congenital conditions or complex pediatric gynecologic conditions. Understanding the basic biology of healthy reproductive development, especially the role of menstruation and endometrial biology in health processes, will lead to new avenues for addressing gynecologic conditions. Ensuring options to allow women and men to manage their fertility, as well as determining the causes of and developing solutions for infertility, will continue to be an area of focus for NICHD. The institute will seek to identify modifiable factors to solve infertility both through basic science, as well as through an examination of clinical and epidemiologic data on treatments used prior to assisted reproductive technologies.

4. **Identifying Sensitive Time Periods to Optimize Health Interventions**

   This goal aims to guide interventions by understanding “sensitive time periods in which an exposure to a disease or event - or the use of a particular intervention - will have the greatest impact. NICHD aims to identify the timing and mechanisms of plasticity in early developmental stages”. Realizing this exciting goal could be accelerated through studies of animal models, which will be particularly informative for assessing plasticity at the levels of molecules, tissues and cells.

   We suggest the following revision:

   This opportunity focuses on change brought on by normal development or by injury or disease. For our efforts to be successful, there is a need to understand sensitive time periods in which an exposure to a disease or event—or the use of a particular intervention—will have the greatest impact. NICHD aims to identify the timing and mechanisms of plasticity in early developmental stages in humans and animal models. The plasticity of systems, whether molecular, cellular, motor, cognitive, or behavioral, will be a key component of this work. Investigations of the mechanisms that determine the initiation and termination of these sensitive time periods, including different periods during development and gestation, will be a novel and transformative area of science. In addition, identification of sensitive time periods after disease or injury when plasticity is high will inform the timing of prevention and management, including early interventions for intellectual, developmental, and
learning disabilities and therapeutic approaches in critical care and rehabilitation settings. Exploring factors that can promote health during these sensitive time periods, such as gene therapy, drug treatment, nutrition, sleep, or behavioral interventions, will be a key component of this effort. Including very early exposures, whether to infectious disease, to early language interventions, or to technologies or digital media will help us to understand the impact of the environment on the health of the developing child. Finally, looking at social determinants, in conjunction with biological factors, that influence these sensitive time periods will enhance our ability to target interventions.

Yours Sincerely,

Lilianna Solnica-Krezel  
Washington University, St. Louis MO  
SDB President 2018-19

John Wallingford  
UT Austin, Austin TX  
SDB President 2017-18

Alejandro Sanchez Alvarado  
Stowers Institute, Kansas City MO  
SDB President 2019-20

Robb Krumlauf  
Stowers Institute, Kansas City MO  
SDB President 2015-16

Mark VanDoren  
Johns Hopkins University, Baltimore MD  
SDB Treasurer

Ondine Cleaver  
UT Southwestern, Dallas TX  
SDB Secretary

David McClay  
Duke University, Durham NC  

Martin Chalfie  
Columbia University, New York NY  

Angela DePace  
Harvard Medical School, Boston MA  
SDB Chair of Public Affairs

Ida Chow  
SDB Executive Director