NTP
National Toxicology Program

Report of the NTP Associate Director: NTP Activities for the National Children's Study Funding Redirect

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National Children's Study (NCS) History

- Children's Health Act of 2000
  - Directed the NIH National Institute of Child Health and Human Development to establish a consortium to:
    - Plan, develop, and implement a prospective cohort study to evaluate the effects of chronic and intermittent exposures *(broadly defined to include factors such as air, water, diet, sound, family dynamics, community, and cultural influences)* on child health and human development
    - Investigate basic mechanisms of developmental disorders and environmental factors that influence health and developmental processes
- NCS Study
  - Vanguard study: pilot launched in 2009
  - Main study: (goal of 100,000 children – prenatal through 21 years old) never initiated

ACD Working Group Review

- Persistent concerns led to:
  - NCS being put on hold
  - Evaluation by an NIH Advisory Committee to the Director (ACD) working group
- Working Group's finding:
  - "while the overall goals [of examining how environmental factors influence health and development] are meritorious and should be a priority for future scientific support**, the NCS, as currently outlined, is not feasible."**
- Working Group's recommendation:
  - NIH should **"champion and support new study designs, informed by advances in technology and basic and applied research**...that could make the original and overall goals of the NCS more achievable, feasible and affordable."

NCS Discontinued

THE NIH DIRECTOR

The NIH Director

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Statement on the National Children's Study

December 12, 2014

In July of this year, I charged a working group of my Advisory Committee to the Director (ACD) with evaluating whether the National Children's Study (NCS) as currently outlined is feasible, especially in light of increasing and significant budget constraints. The NCS was envisioned as a longitudinal, observational study examining the effects of a broad range of

I and my leadership team have had time to consider this report over the last few weeks. Based on the working group's findings and internal deliberation, I am accepting the ACD findings that the NCS is not feasible.

Furthermore, NIH leadership and stakeholders have had concerns about the study, and those concerns were echoed in a report by the National Academies (NAS), issued in June 2014. As a result, I placed the launch of the Main Study on hold until critical questions regarding next steps could be answered to ensure that this important area of research is pursued in the most rigorous manner.

Today, the ACD considered the final report of the NCS working group. The report concluded that the overall goals of examining how environmental factors influence child health and development are meritorious and should continue to be a priority for future scientific support, but that the NCS as currently designed is not feasible.

FY15 Appropriation

- $165M appropriated for NCS
- Bill and Report Language direct NIH to maintain the mission and goals of the NCS, with flexibility on how to carry this out

Redirection of NCS Funds

- Remain true to the original intent of the NCS – address questions at the intersection between pediatric health and the environment
- Three initiatives:
  - **Initiative 1**: Develop tools that would enhance studies of environmental influences of pediatric diseases
  - **Initiative 2**: Study the influence of environment on *in utero* development with the goal of identifying the "seeds" of future diseases and conditions
  - **Initiative 3**: Expand examination of environmental influences on later child development by leveraging extant programs

Tox21 Developmental Toxicity Program

- **NCATS/NIEHS** – Expand the NCATS/NIEHS/EPA/FDA Tox21 program to include developmental toxicology
- Goals:
  - Comprehensively test the 10,000 chemical collection on developmental pathways (e.g., Sonic Hedgehog, Wnt, Notch, bone morphogenic proteins, TGF beta, MAP/ERK, Hippo, and HDACs) and cellular phenotypes
  - Create dynamic maps of the patterns of gene expression that drive normal differentiation of stem cells and study the potential for disruption by chemicals
  - Determine the critical parameters needed to standardize use of the zebrafish for developmental biology screening

NTP Activities for NCS Redirect

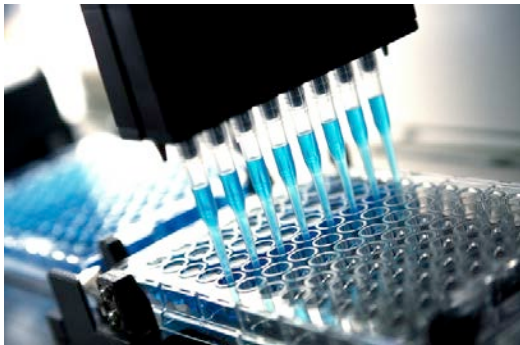
NICEATM: Database of ~100 Developmental Toxicants

- Goal: Identify reference developmental toxicants in rodents and humans
  - Include subtle effects (embryo-fetal death, growth retardation, functional impairment, etc.)
  - Capture detailed data from references: MoA, ADME, physical / chemical properties, species, dose levels, timing of exposure, *in vitro* data, etc.
- Progress: Identified ~220 potential chemicals based on literature / experience
- Process: External Information Group vetted list of chemicals
  - Recommended additional chemicals and reduced list to manageable number, while covering breadth of mechanisms of [illegible] outcomes

NTP Activities for NCS Redirect

NTP Lab: Metabolism and High-Throughput Screening (HTS)

- Goal: Develop metabolically competent models for high-throughput / mid-throughput screening
  - Characterize models for metabolic competency compared to suspension hepatocytes
  - Promising results with hepatocyte spheroids
- Goal: *In vitro* to *in vivo* extrapolation (IVIVE)
  - Characterize the uncertainty in current IVIVE approaches
  - Evaluate *in vitro* disposition of chemicals and compare to *in vivo* disposition
- Progress: Iterative and multiyear project facilitated with purchase of LC/MS



NTP Activities for NCS Redirect

Biomolecular Screening Branch: Development of a HTS-Transcriptomics Platform

- Goal: Conduct targeted transcriptomic interrogation of human, mouse, rat, and zebrafish cellular lysates
  - Develop a mid- to high- throughput transcriptomics technology for measuring the expression levels of a set of ~2500 human, mouse, rat, and zebrafish “sentinel” genes
  - Demonstrate performance by measuring gene expression levels in extracts from different sample types, each treated with developmental toxicants identified by NICEATM at multiple doses, in triplicate
- Progress: Human and mouse gene sets complete

NTP Activities for NCS Redirect

Tox21 Approach to Development

- Goal: Conduct transcriptomic studies to map patterns of gene expression during development
  - Determine if ES and iPSC-like cells from Diversity Outbred (DO) mice show differences in developmental gene expression patterns
  - Map transitions of neuronal precursor cells (NPC) to neurons, astrocytes, and oligodendrocytes
  - Identify specific genetic loci or genes that contribute to potential diversity in the developmental process
  - Treat NPC lines with selected chemicals in extended dose response
  - Identify specific genetic loci or genes that contribute to diversity in the response to neurotoxicants
- Progress: DO gene expression studies underway

Systematic Evaluation of Zebrafish in Toxicology

- Goals:
  - Provide the scientific basis on which to make a programmatic decision regarding use of zebrafish in toxicological screening of chemicals to which humans are exposed during development
  - Provide fundamental knowledge on the use of zebrafish in toxicology to support further research endeavors by the academic community
- Progress: Survey of current methodologies underway

DNTP: Data Streams and Informatics Support

- Goals:
  - Provide *in vitro* informatic infrastructure for screening tools for Tox21 development projects
  - Provide support for data and analysis of studies using stem cells, alternative models, metabolism, high transcriptomic screening, and data streams
  - Provide storage and tracking of data and samples from NCS-redirect projects
- Progress:
  - Additional computer software and hardware, freezers, and license for PharmaPendium purchased

Questions