DNTP Strategic Realignment Update

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NTP Board of Scientific Counselors Meeting
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Outline

- Previous conversation
- Your feedback
- A refined Vision and Mission
- Taking the bait
- Health Effects Innovation
- Summary
Aspirational Vision

Mission
To evaluate agents of public health concern, by developing and applying tools of modern toxicology and molecular biology.

http://ntp.niehs.nih.gov; April 2015

21st Century Vision
To support the evolution of toxicology from a predominately observational science at the level of disease-specific models to a predominately predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.

A National Toxicology Program for the 21st Century, November 2004
Challenges

• Rapid pace of chemical development

• Growing concerns about non-chemical agents

• Broad stakeholder group with varying needs, concerns, perspectives and constraints (e.g. regulators vs. policy makers vs. toxicologists vs. advocacy groups vs. general public)

• A decision-making community largely still entrenched in low-throughput assays and modeling platforms for which we have some confidence in human relevance

• Significant and growing societal interest in decreasing animal use

• Gap in our ability to ‘predict’ human outcomes in a meaningful way
Strategic Pipeline of Capabilities

Applying our capabilities in deliberate, integrated and complementary ways.

Translational Toxicology Pipeline

Human Health Effects

Knowledge Integration

Chronic in vivo Studies

Short term in vivo Studies

In vitro Studies

Bioactivity Screening

QSAR Profiling

Data / Knowledge Mining

Hypothesis-driven Research

Communicate
• Previous conversation
• Your feedback
• A refined Vision and Mission
• Taking the bait
• Health Effects Innovation
• Summary
• Recent WebEx engagement to gain your input on our strategic direction
  – October 9 NTP BSC meeting
  – WebEx with targeted strategic and rapid response questions

• Targeted strategic questions
  – What are NTP’s unique strengths?
  – What does it mean to be “human relevant”? 
  – How do we build confidence in novel approaches?

• Rapid response questions
  – 3D systems
  – Machine/Deep learning
  – Carcinogenicity testing
• What is NTP’s unique value?
  – Ability to focus on complex challenges for prolonged periods of time
  – Impactful science supporting policy and regulation
  – Opportunity to address chronic health effects
  – Build predictive capabilities

• What does it mean to be human-relevant?
  – Studying things of contemporary human concern/importance
  – Studying things in a relevant human context
    • Modeling human exposure context- quantity, route
    • Demonstrating exposure/outcomes relationships
  – Addressing public confusion
How do we build confidence in non-traditional evidence?

- Demonstrating human relevance
- Understanding mechanisms
  - Toxicologists and pathologists working together
• Rapid responses
  – Opportunity for 3D systems
    • Link between high throughput systems and in vivo studies
    • Build a better comparative understanding of animal and human outcomes
    • Unique role for NTP to demonstrate usefulness
  – Machine/deep learning
    • Not new
    • Deep learning approaches may provide opportunity
    • Concern about the ‘black box’ nature of proprietary deep learning algorithms
  – Carcinogenicity testing
    • Comfort with current approach even with limitations
    • Need to conduct at more human-relevant exposures
    • NTP should play a role in coordinating efforts to reinvent
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Refining the Vision and Mission

• Vision

  – To improve public health through the development of data and knowledge that are translatable, predictive and timely.

• Mission

  – Collaborate with public stakeholders and global partners to identify and address public health issues.

  – Generate and communicate trusted scientific information to support decision making on environmental hazards of public interest.

  – Lead the transformation of toxicology through the development and application of innovative tools and strategies.
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Why are we struggling to become more predictive and how can NTP facilitate getting there?
Progressing the Paradigm

Data/Knowledge Mining → HTP In vitro Screening → Phenotypic In vitro Studies → In vivo Studies → Reporting Health Effects

- In silico modeling
- Mechanism-of-action modeling
- Mode-of-action modeling
- Health outcomes modeling
Fully leveraging ‘pre-animal’ capabilities. Iterative learning of machine/deep learning capabilities leads to hypothesis-driven research. Knowledge integration, chronic in vivo studies, short term in vivo studies, in vitro studies, bioactivity screening, QSAR profiling, data/knowledge mining, and knowledge integration contribute to human-relevant in vitro systems—e.g., 3D complex—communicating human health effects.

Bespoke and human-relevant animal studies.
Evolving Our Portfolio

Goals
- Increase impact
- Improve sustainability
- Increase visibility
- Improve complementarity
Current Programmatic Research

- Mixtures
- Botanical Dietary Supplements
- Polycyclic Aromatic Compounds
- Radiofrequency radiation
- PFAS
- AIDS-related research
- Flame retardants
Increasing DNTP Portfolio Impact: Flagship Initiatives in ‘Health Effects Innovation’
Health Effects Innovation

- Carcinogenicity Testing for the 21\textsuperscript{st} Century
- Developmental Neurotoxicity Modeling
- Cardiovascular Hazard Assessment in Environmental Toxicology
- TBD
- TBD

Goals
- Fill a gap in current capabilities
- Build on existing effort
- Align to NIH model
- Leverage our key strengths and value
Aims of Health Effects Innovation

• Define and build a strategic assessment pipeline for key environmental health effects

• Understand the mechanism of action, mode of action, health effect continuum for these areas

• Increase confidence in the predictivity of MOA assessments

• Align our capability development to problems we’re trying to solve

• Maximize the collective strength of the NTP organization

• Build novel partnerships in and outside NIH
E.g. Impact of CV Morbidity and Mortality

Mortality
Selected Causes of Death

Figure 2. Age-adjusted death rates for selected causes of death for all ages, by sex: United States, 2004–2014

Chart 27-2. The 23 leading diagnoses for direct health expenditures, United States, average annual 2012 to 2013 (in billions of dollars). COPD indicates chronic obstructive pulmonary disease; and GI, gastrointestinal (tract).
Source: National Heart, Lung, and Blood Institute; estimates are from the Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality, and exclude nursing home costs.
E.g. Cardiovascular Health Effects Strategy

Identify human-relevant CV hazard questions

Hypothesis-driven Research

- Knowledge Integration
- Chronic in vivo Studies
- Short term in vivo Studies
- In vitro Studies
- Bioactivity Screening
- QSAR Profiling
- Data / Knowledge Mining

Identify translational biomarkers of chronic CV health effects

- Regulatory and public health stakeholders

Map cardiovascular ‘failure modes’ and agents

- FDA ORISE Fellows

Mine current databases for CV-relevant MOA data

- HESI Cardiac Safety Technical Committee

Define primary mechanistic screening strategy

- Define and test Tier II 3D cardiomyocyte and vascular modeling systems

Communicate

- NHLBI-NIEHS partnership

Contributing projects
- Partners and opportunities

Instrumented animal studies for CV function assessment

- Digital vivarium technology

- NCATS, IQ, NCTR partnerships

Human Health Effects

Short term in vivo Studies

In vitro Studies

Bioactivity Screening

QSAR Profiling

Data / Knowledge Mining

Knowledge Integration

Regulatory and public health stakeholders

NHLBI-NIEHS partnership
• Your feedback has been important to us and is being integrated into our strategic realignment.

• We believe a more deliberate and integrated application of our ‘pipeline’ of capabilities will enable us to improve our rate of progress in reaching our ‘predictive’ aspiration.

• Focus on discrete areas of ‘health effect innovation’ will increase our visibility and impact in biomedical science as well as increase the value of NTP’s efforts to lead a strategic transformation of toxicology.
Thank You!