NTP
National Toxicology Program

Developmental Neurotoxicity Health Effects Innovation Program

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Division of the NTP
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
December 4, 2020

DNT-HEI Program Management Team

Mamta Behl

Laura Hall

Chris McPherson

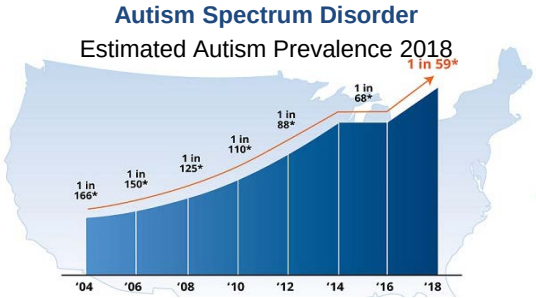
Jeremy Erickson
(New member)

Robert Sills

Nisha Sipes
(prior member: now at USEPA)

Why this?

- Increase in prevalence of neurodevelopmental disorders in the US and globally
  - WHO: 1 in 6 kids diagnosed at birth
- Strategies to evaluate DNT underdeveloped
- *In vivo* DNT Guideline studies primary method of evaluation
  - Require an *apriori* trigger to be run
  - Time & resource intensive
  - Relevance of animal studies for human translation have been questioned
- Compounds with unknown DNT potential remain untested



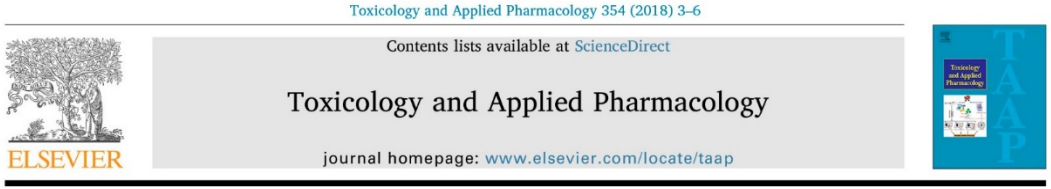
* Centers for Disease Control and Prevention (CDC) prevalence estimates are for 4 years prior to the report date (e.g. 2018 figures are from 2014)
Source: autismspeaks.org, "CDC increases estimate of autism's prevalence by 15 percent, to 1 in 59 children"

Figure Courtesy: Tim Shafer

There is a Need for a New Framework for Assessing DNT

"Our system for evaluating scientific evidence and making decisions about environmental chemicals is broken. We cannot continue to gamble with our children's health"

Project TENDR
Consensus: Targeting Environmental Neuro-Developmental Risks.
Source: http://dx.doi.org/10.1289/EHP358

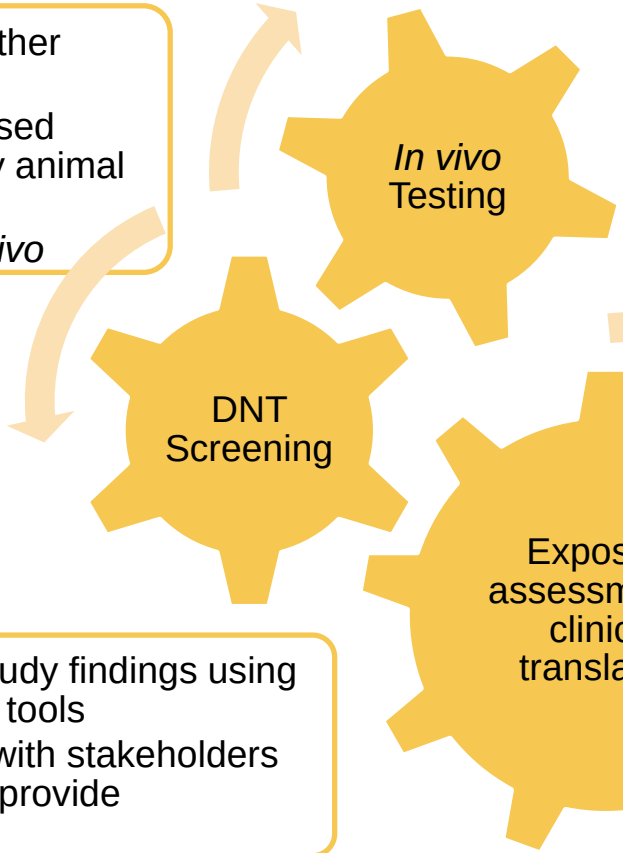

Toxicology and Applied Pharmacology 354 (2018) 3–6
Contents lists available at ScienceDirect
Toxicology and Applied Pharmacology
journal homepage: www.elsevier.com/locate/taap
ELSEVIER

Consensus statement on the need for innovation, transition and implementation of developmental neurotoxicity (DNT) testing for regulatory purposes

Why Us?

- Prioritize compounds for further testing
- Rapid, high-content, cell-based assays, and complementary animal models
- Complement and refine *in vivo*

- Automated behavior
- Neuroimaging
- Novel Biomarkers

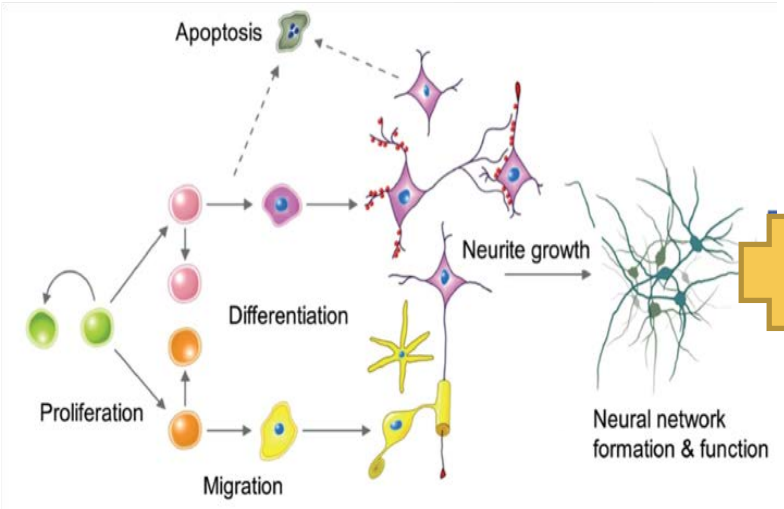


- Cross divisional teams with multi-disciplinary expertise
- Building on past experience

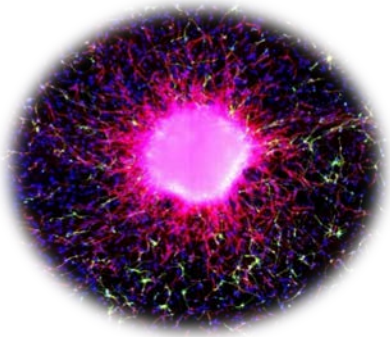
- Integrate exposure with study findings using IVIVE* and computational tools
- Enhance communication with stakeholders to understand issues and provide translatable data

* IVIVE= In vitro in vivo extrapolation

Implement a DNT screening battery that covers key neurodevelopmental events



Human-derived + rodent + zebrafish



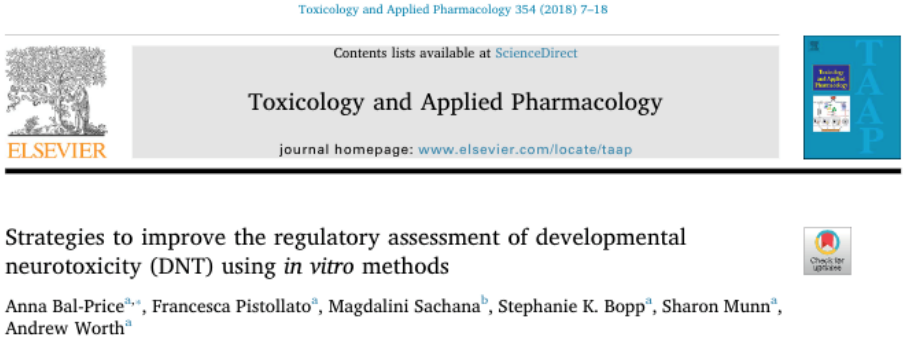
2-D assays **3D- Neurospheres** **Zebrafish**

DNTP's Proposed Battery: Initial Assay Selection

Objective 1: Assay Selection Rationale

What led to selection of the current assays?

- Key neurodevelopmental processes; perturbed →DNT?
- Meet high readiness criteria
  - Biological plausibility
  - Test system description
  - Good robustness
- Implementation for practical applications in industry/regulatory purposes
- High throughput; ready for prime-time

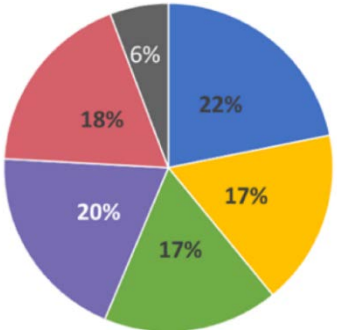


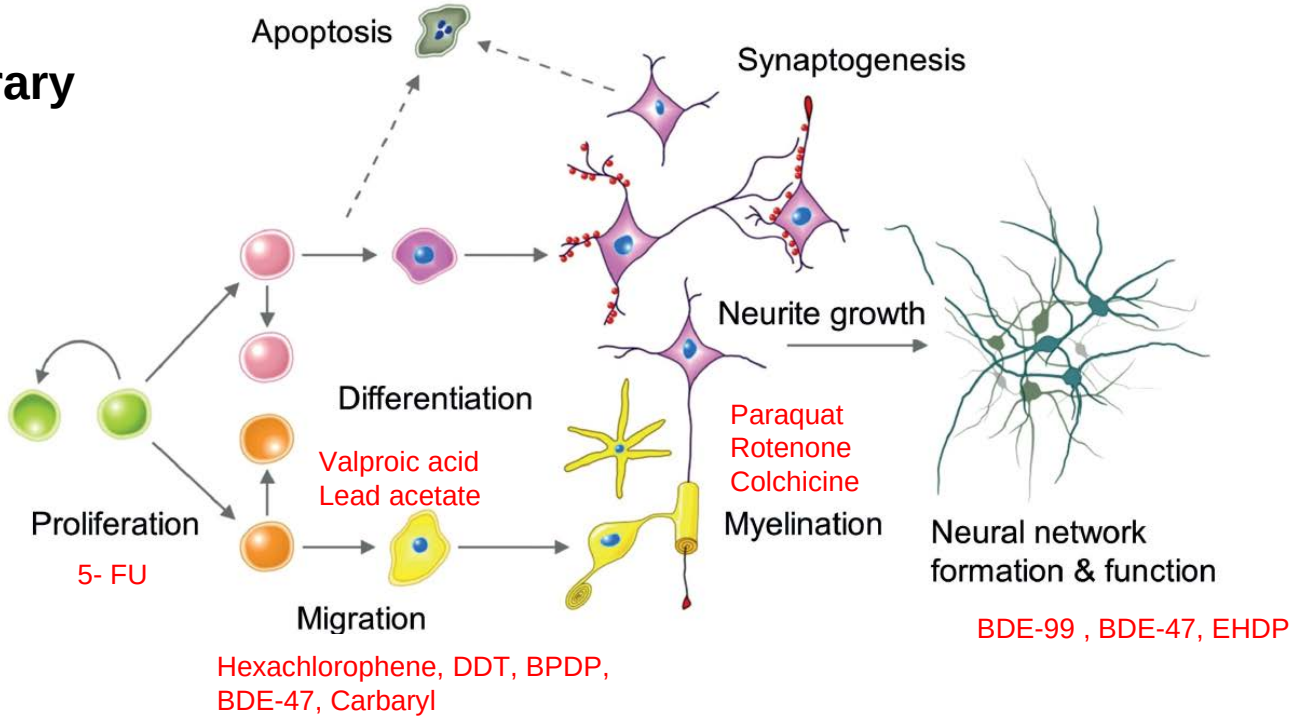
Bal-Price et al., 2018

Objective 1: Building on DNTP's Past Experience

Pilot: DNTP Workshop, 2017

NTP Chemical Library



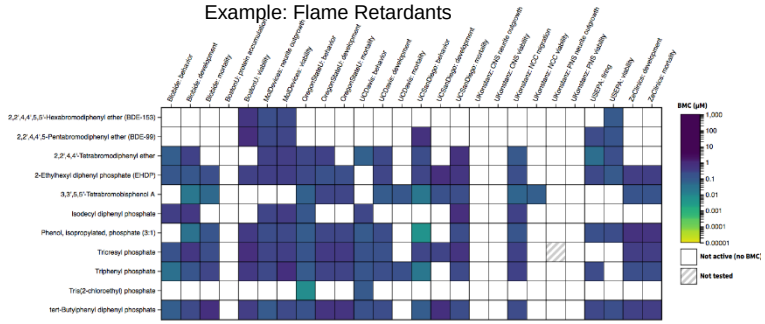


Negatives performed as expected

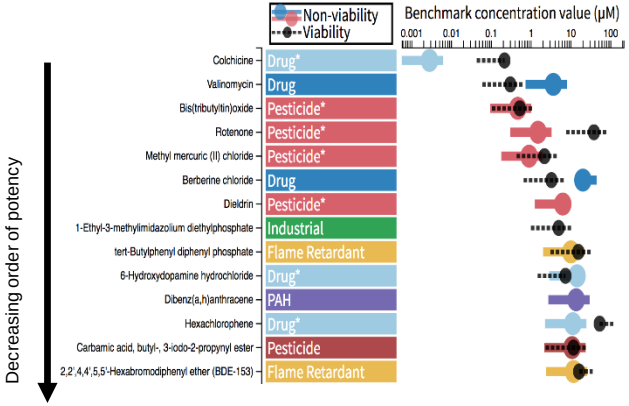
Aschner et al., 2017 & Mundy 2015

Objective 1: Building on NTP's Past Experience

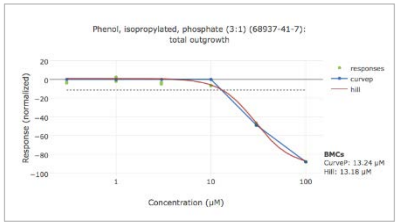
DNT- Data Integration and Visualization Enabling Resource (DNT-DIVER)



Compare activity of compounds/classes across multiple assays



Compare activity of compounds within an assay



Individual dose-response curves

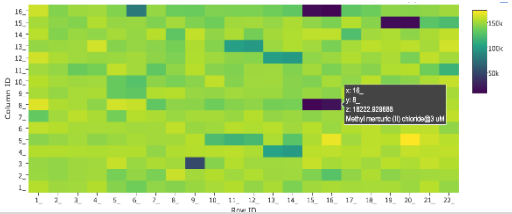
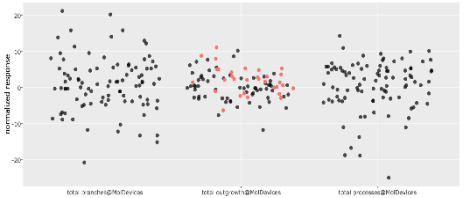


Plate and well level information

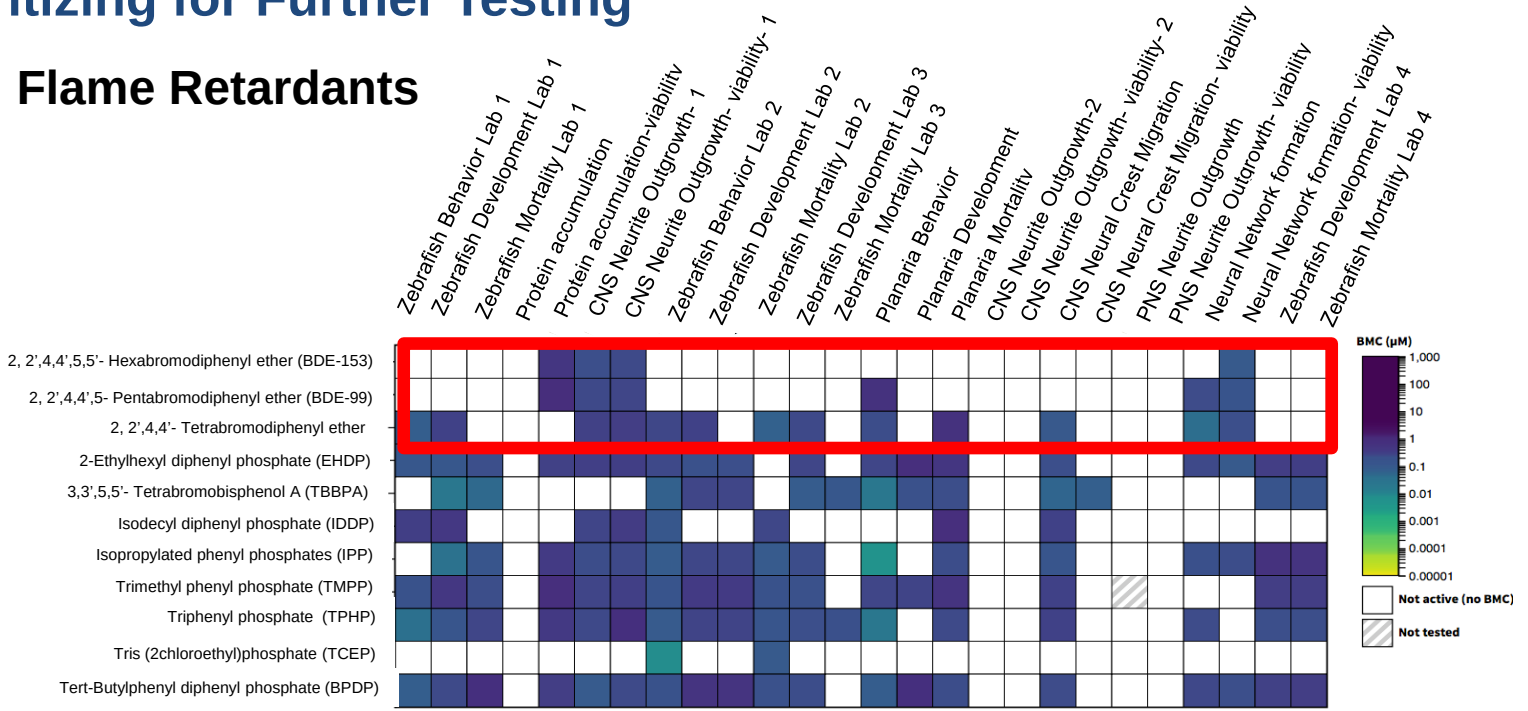


Control variability in assay

https://sandbox.ntp.niehs.nih.gov/neurotox/

Prioritizing for Further Testing

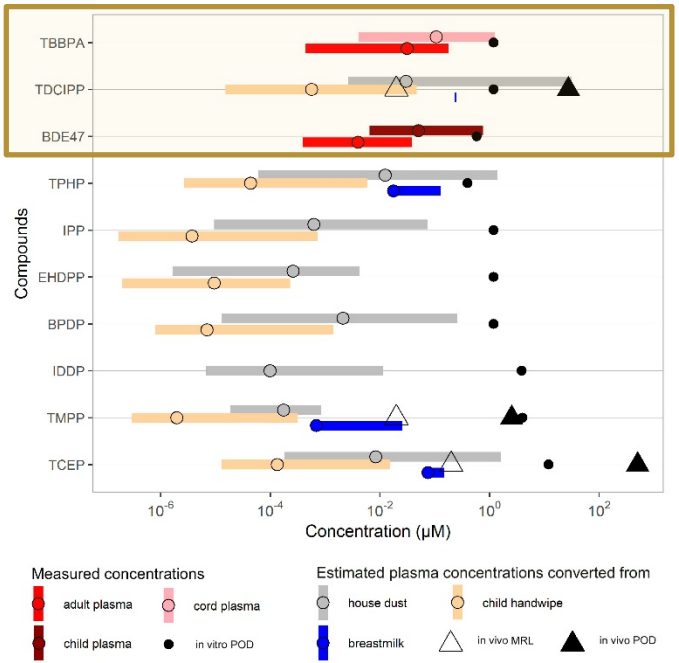
e.g. Flame Retardants



Novel replacements show comparable activity to phased-out compounds

Data publicly available on DNT-DIVER
https://sandbox.ntp.niehs.nih.gov/neurotox/

For use in decision-making



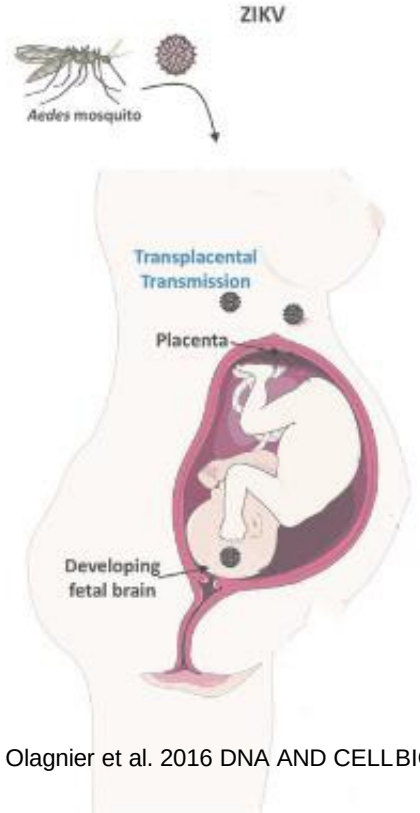
Extensively used/phased-out

Novel Substitutes

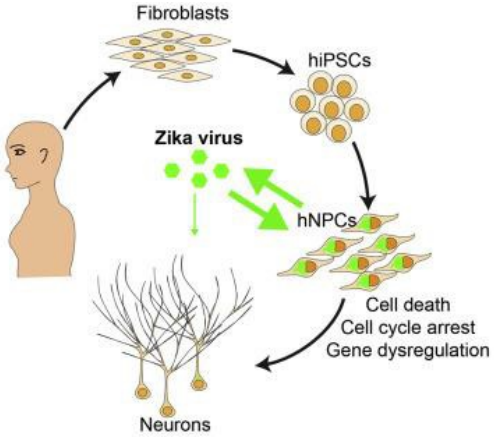
1. Novel substitutes have comparable in vitro activity to older flame retardants
2. In vitro activity within order of magnitude of in vivo point of departure (POD) (when known)
3. Activity lies within range of human exposure (limited exposure data for novel compounds)

Blum et al., (2019) Environ. Sci. Technol. Lett. 6, 638−649

When animal studies may not provide the answer…



Olagnier et al. 2016 DNA AND CELLBIOLOGY



Tang et al. 2016 Cell Stem Cell

Guideline studies did not identify effects in humans

MOA discovered using 3-D neurospheres

- Zika infects hiPSC-hNPC
- Zika infection dysregulates cell cycle and transcription in hNPCs
- Zika infection attenuates hNPC growth and induces apoptosis

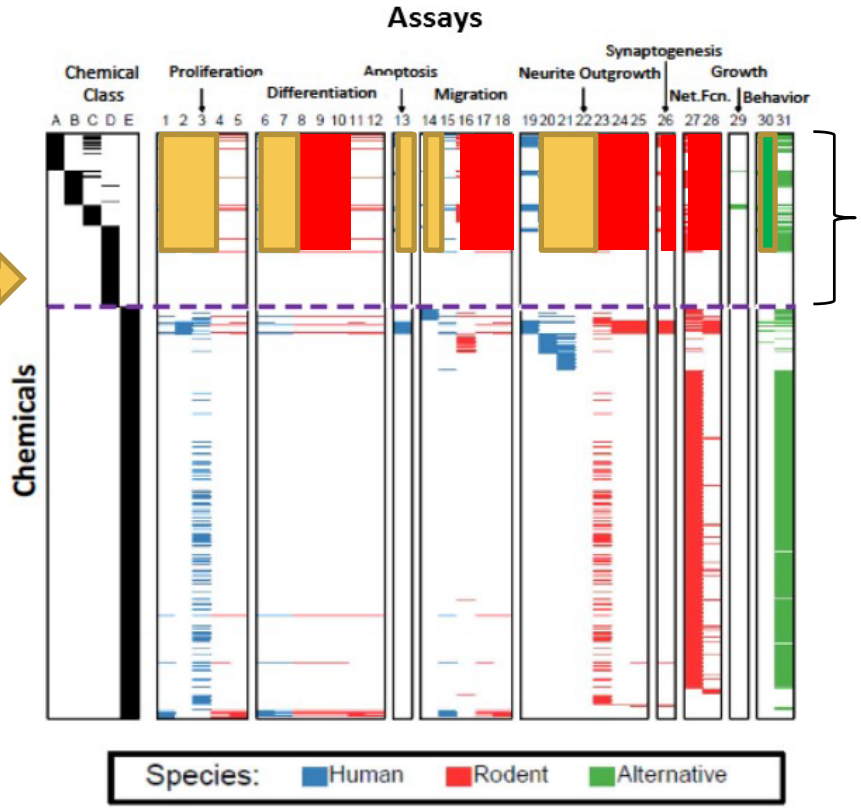
Slide Courtesy: Ellen Fritsche

Objective 1: Global Contribution to DNT

How will our battery fill a global niche?

Assay-specific Compound Lists; Focused on in vivo DNT

Assay 1
Assay 2
Assay3…



Assay Evaluation

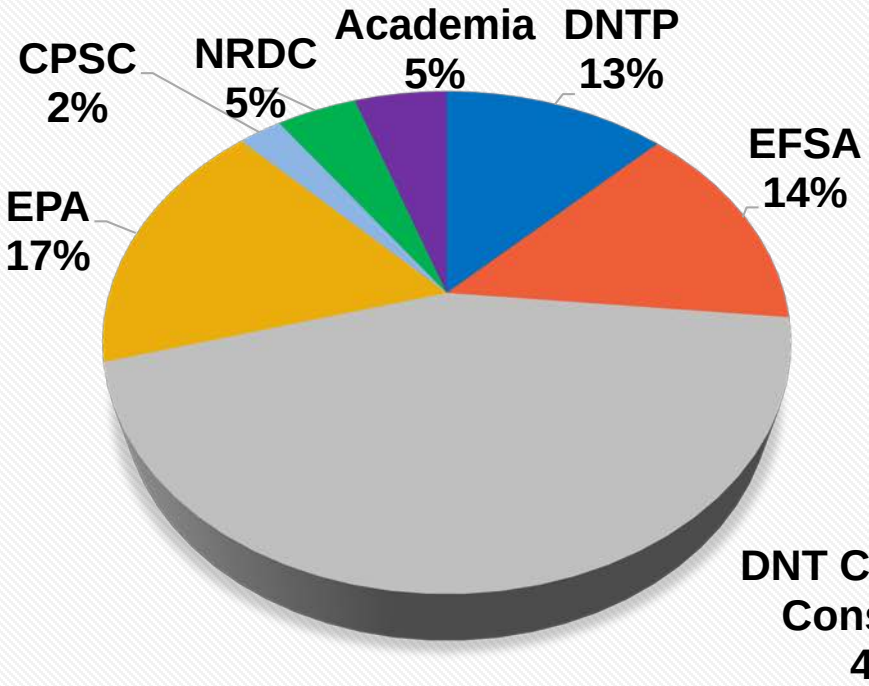
Increase coverage by concerted screening efforts in multiple assays

Address NTP's DNT- related nominations more efficiently

Slide courtesy: Tim Shafer, USEPA

Bal-Price et al., 2018; Sachana et al., 2019

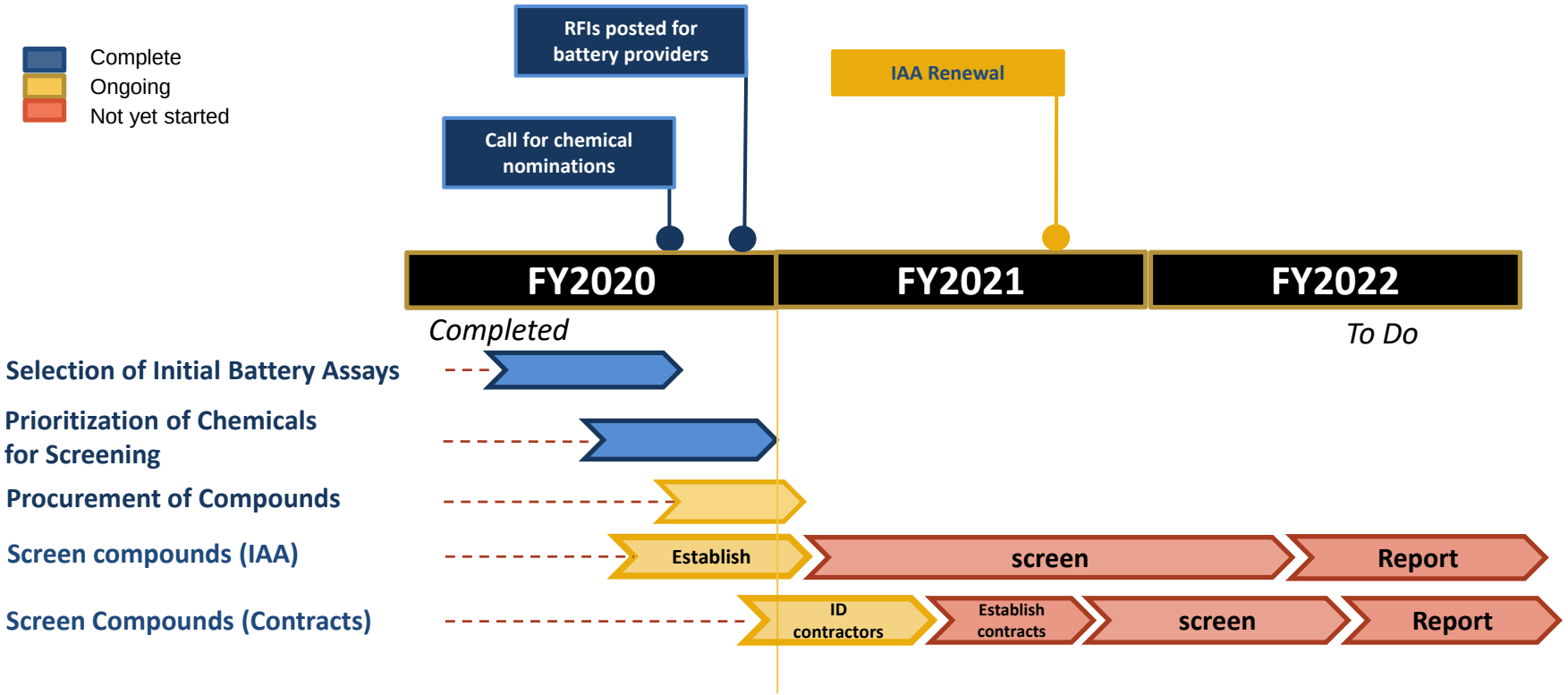
Call for Screening 100 compounds



~ 300 nominations received from ~ 35 individuals representing different sectors

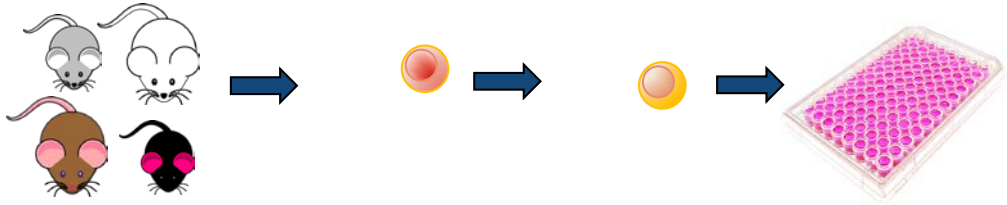
***DNT Consulting Consortium**
R3 Fellows LLC, IDN Consulting, OECD, EFSA, USEPA, Academia, Health Canada

Develop and Implement 7 *in vitro* assays to screen 100 compounds



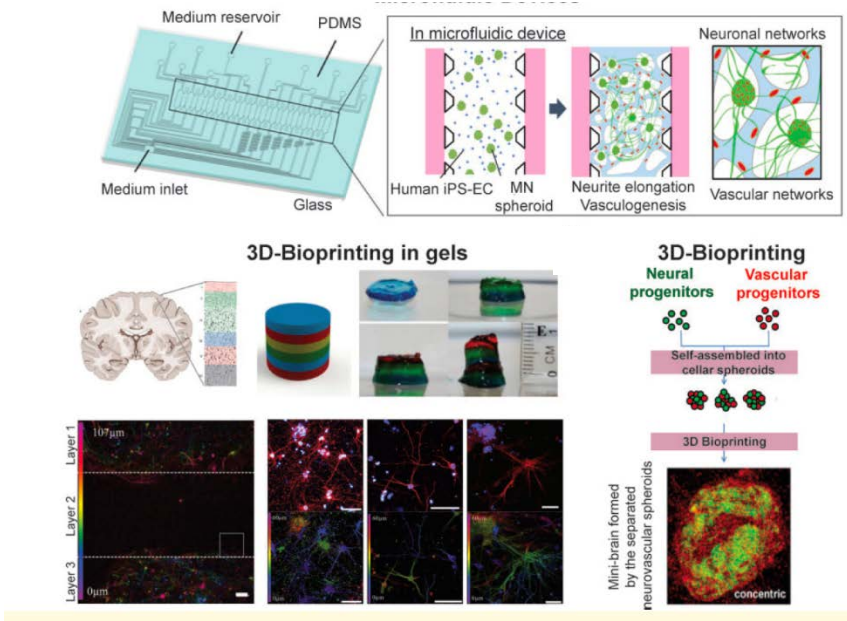
IAA: Inter Agency Agreements

Assess novel DNT assays and technologies: In vitro



♂/♀ DO Mice DO ESCs DO NPCs

Incorporating Genetic Diversity



Microfluidics

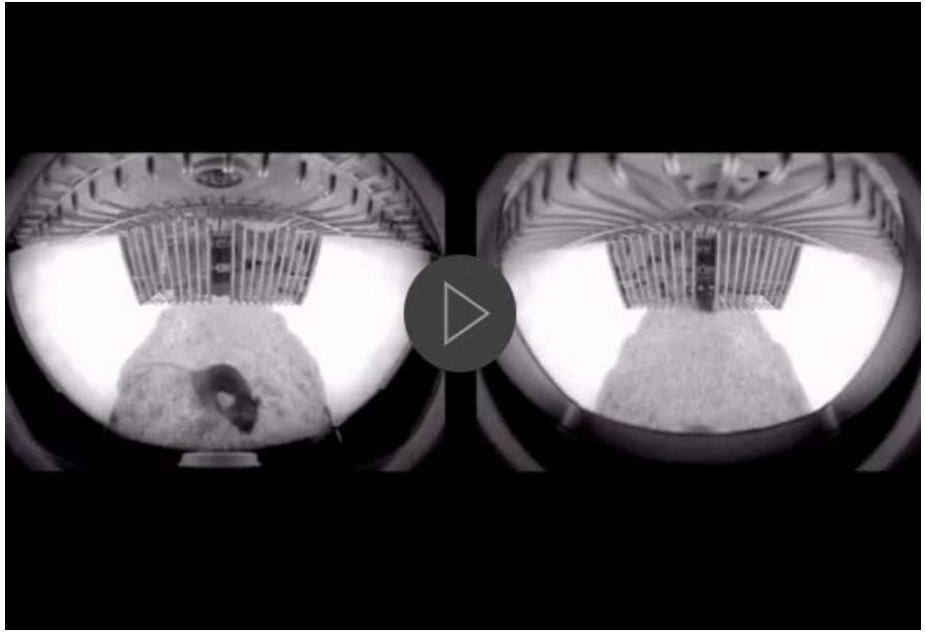
Nikolakopoulou et al., 2020
DO Figure Courtesy: Dahea You

Assess novel DNT assays and technologies: In vivo

- Issue: Clinical observations are the primary diagnostic tool in patients, and yet current rodent evaluations are subjective & often miss critical time-periods (e.g., nighttime)

Linking mechanistic bioactivity to clinical end-points

- Proposed solution: Explore automated 24x7 monitoring- overlay artificial intelligence

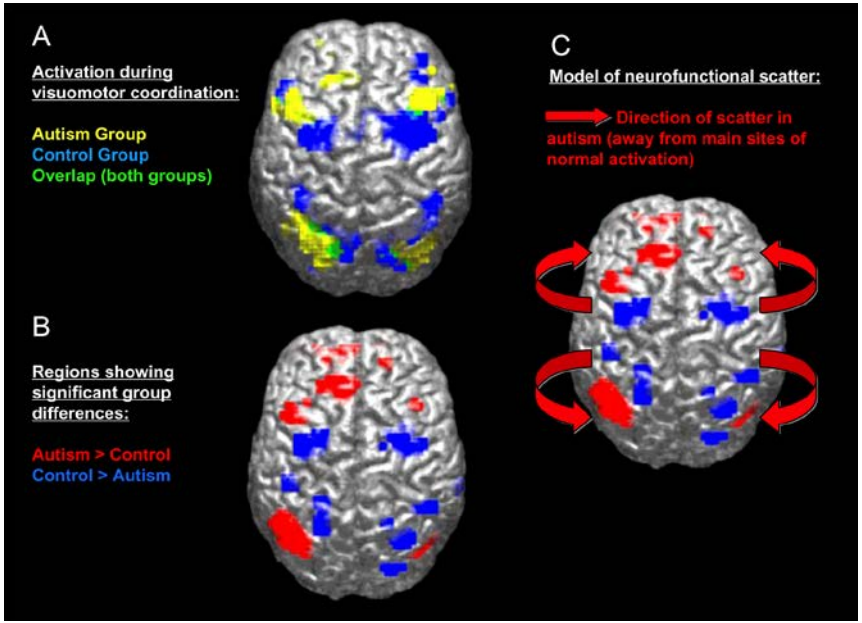


Objective 2

Issue: Representing the entire brain with limited number of histological sections may not be sufficient to capture subtle changes that may occur in neurodevelopmental disorders

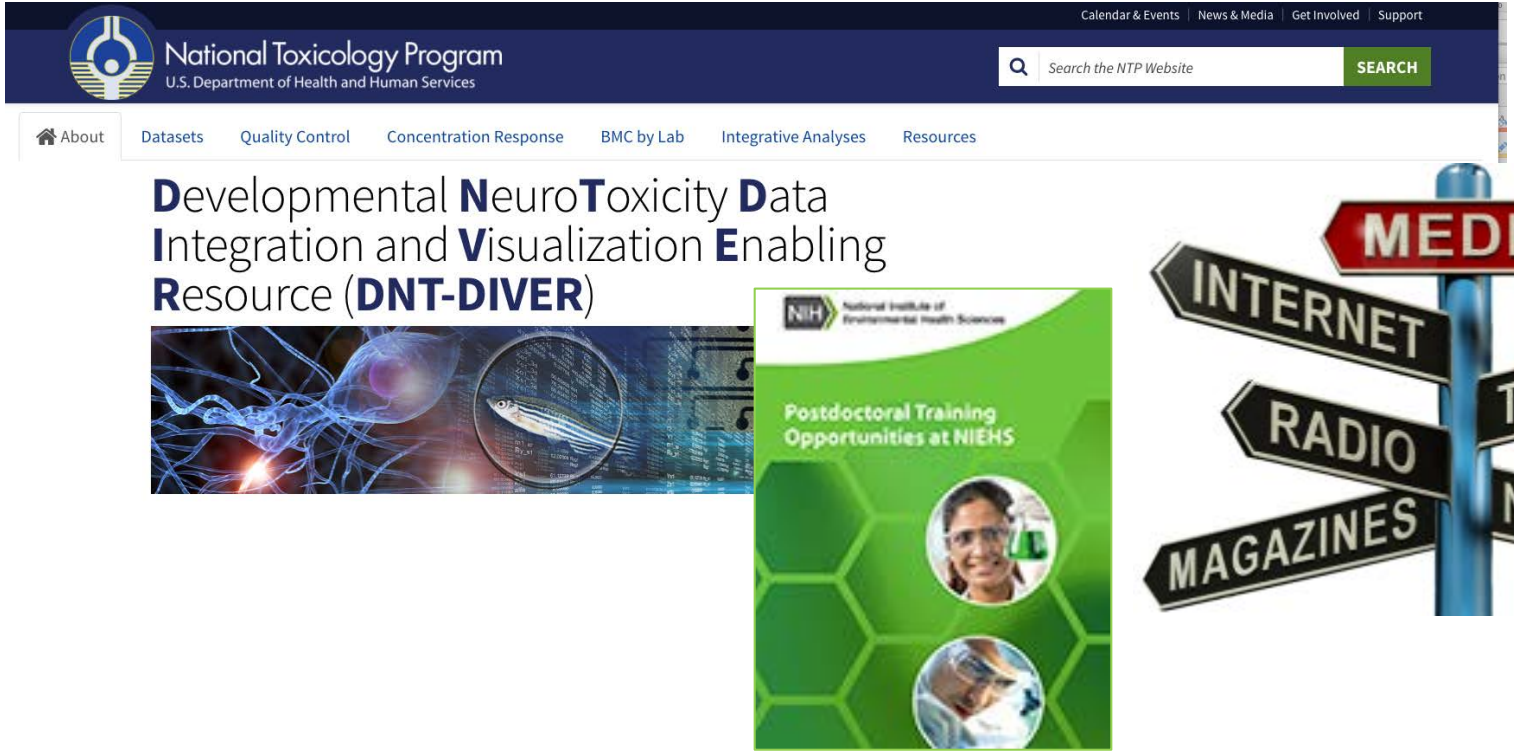
Diffusion tensor connectomics to identify alterations in networks

Proposed Solution: evaluate potential for incorporation of imaging tools to capture structural & functional changes



Journal Pbio 0020267 Autism Mri 5

Establish communication pipelines with stakeholders and public

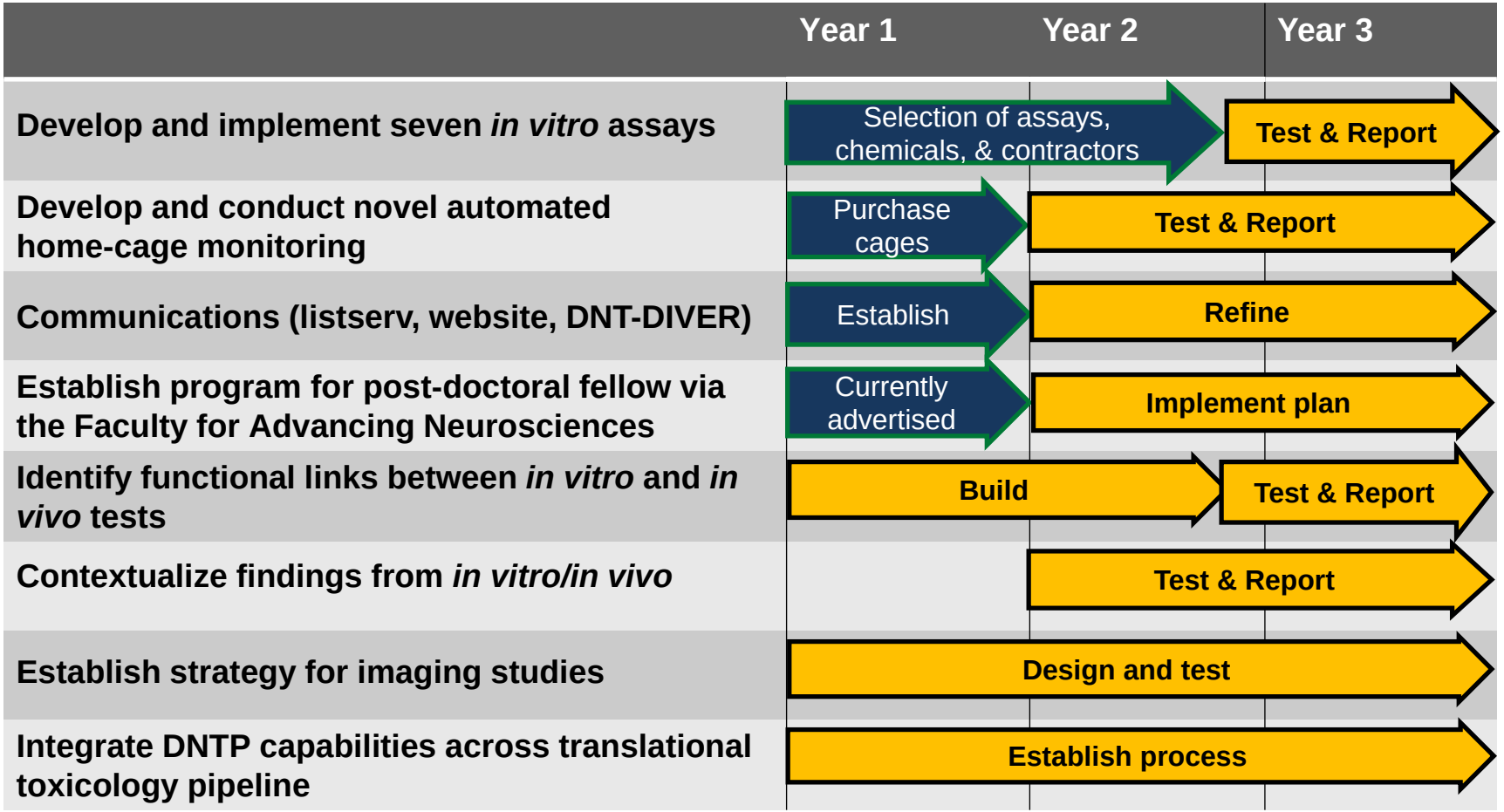


Stakeholder Engagement

…Expanding to include clinicians, industry, advocacy groups..

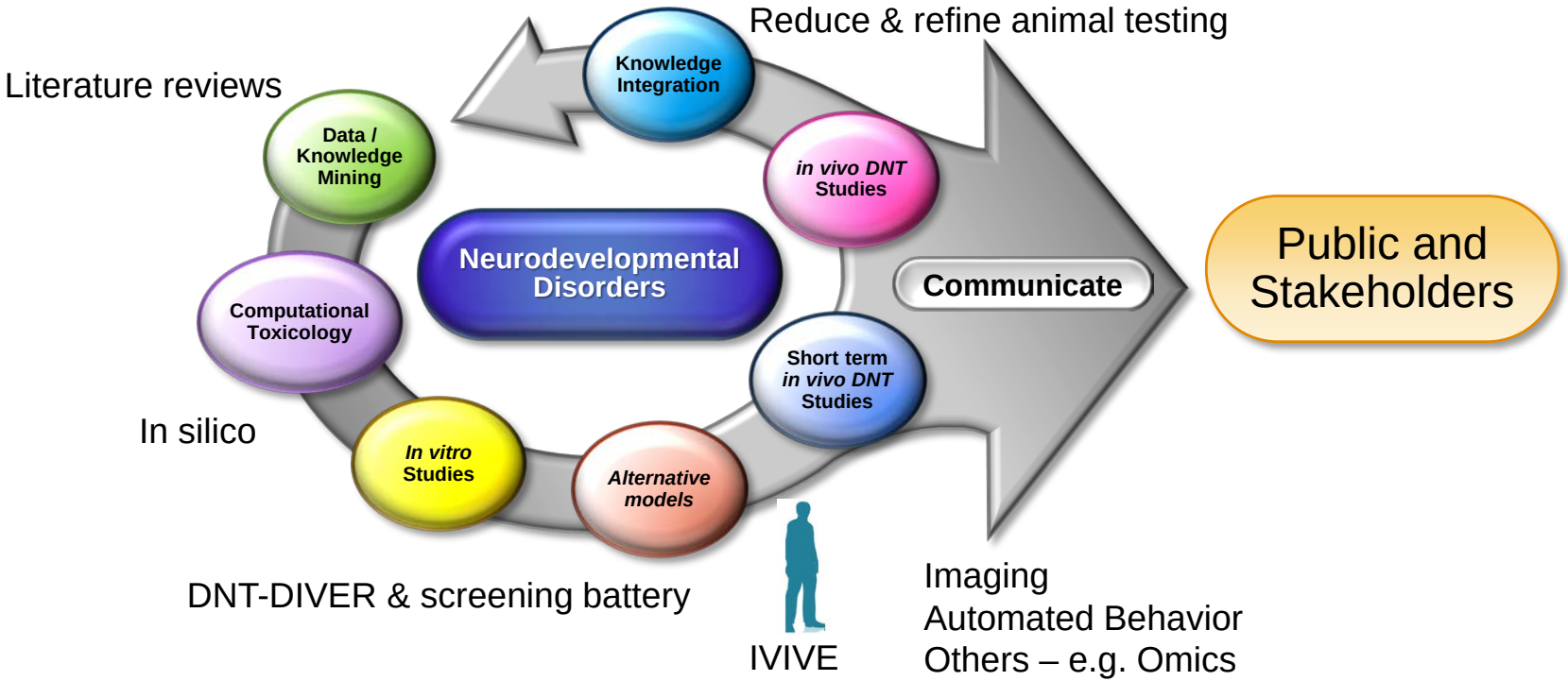
Completed
In process

Program Milestones and Metrics



DNT HEI in DNTP's Translational Toxicology Pipeline

Ultimate goal is to more effectively predict DNT for unknown environmental chemicals to prevent neurodevelopmental disorders



Perspective

There is currently no comprehensive method to evaluate compounds with unknown DNT potential

Compounds remain largely untested and susceptible populations continue to be exposed

Our effort is an initial step in the long journey of preventing neurodevelopmental disorders due to environmental factors

Acknowledgements

NTP
National Toxicology Program

Thank You!

Question 1

What are you most excited about?

Question 2

Please share your insights about the Program regarding:

a. how the objectives address the problem/opportunity
b. the boldness of the approach to achieve the objectives
c. the alignment of the metrics to the desired impact

Question 3

Considering DNTP's capabilities and expertise, what mechanisms do you suggest that we consider to be able to effectively execute against the objectives? With whom might we partner to ensure success?

Question 4

The disease-focused approach of the Health Effects Innovation Programs is novel in toxicology and hazard assessment. What unique challenges are we likely to encounter in taking that approach for developmental neurotoxicity? What near and mid-term deliverables might reinforce our decision to take that approach?

Question 5

A key theme of the NIEHS Strategic Plan is ‘Data to Knowledge to Action’. At what level of detail do we need to characterize neurodevelopmental hazards to enable public health-protective decisions by individuals, regulatory scientists and policy makers? For example, at the level of bioactivity in the developing central nervous system, induction of adverse changes in morphology or function or at the mechanistic level?