



**NTP**

National Toxicology Program

# **NIEHS/DNTP Portfolio in Support of NTP**

**Scott Masten, PhD, DABT**

Division of the National Toxicology Program  
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting  
June 17, 2019





- Some NTP basics
- Describing the DNTP portfolio
- Survey of current research
- Shift and alignment
- Structure and focus
- Planning for the future





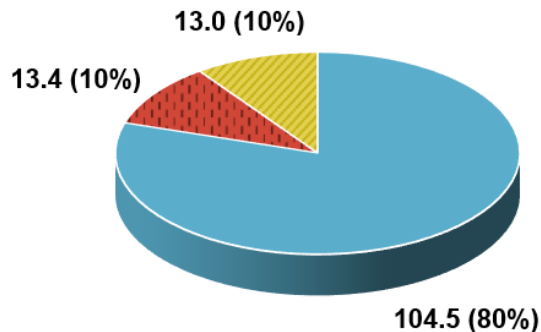
## Organizational Structure and Oversight



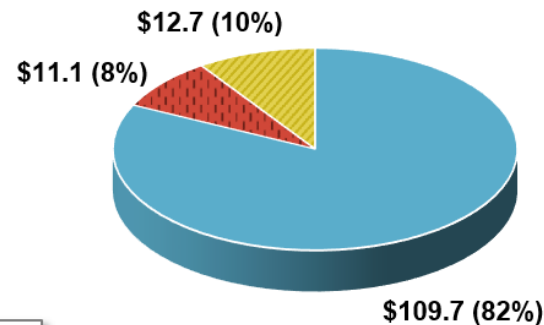


## Funding

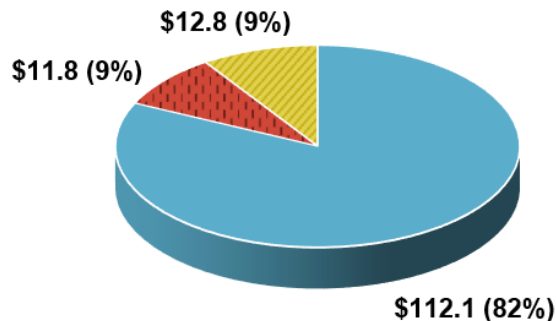
FY 2016 (\$130.9 million)



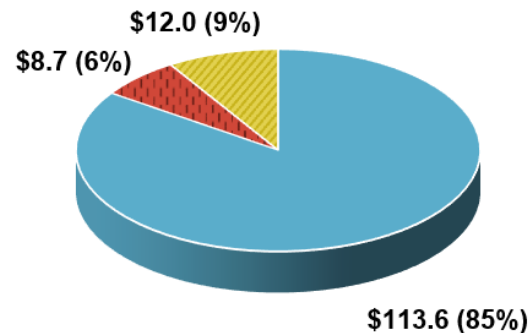
FY 2017 (\$133.5 million)



FY 2018 (\$136.7 million)



FY 2019 (\$134.3 million projected)

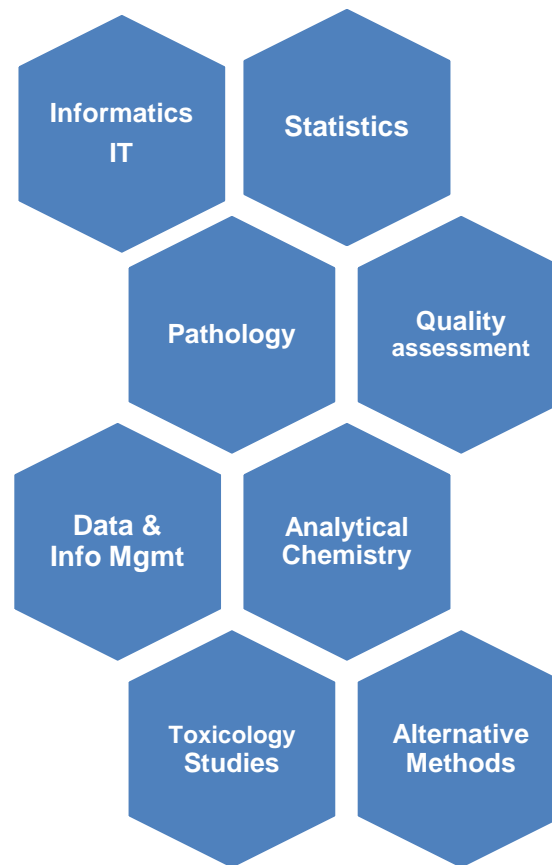




## Capabilities and mechanisms

- NIEHS contracts
  - 30 contracts in FY2018
- In-house research
  - Experimental, computational, evaluative
- Interagency agreements
  - FDA/NCTR
  - CDC/NIOSH
  - NIH/NCATS
  - EPA/NCCT
  - EPA/NCEA
  - DOE/ORNL

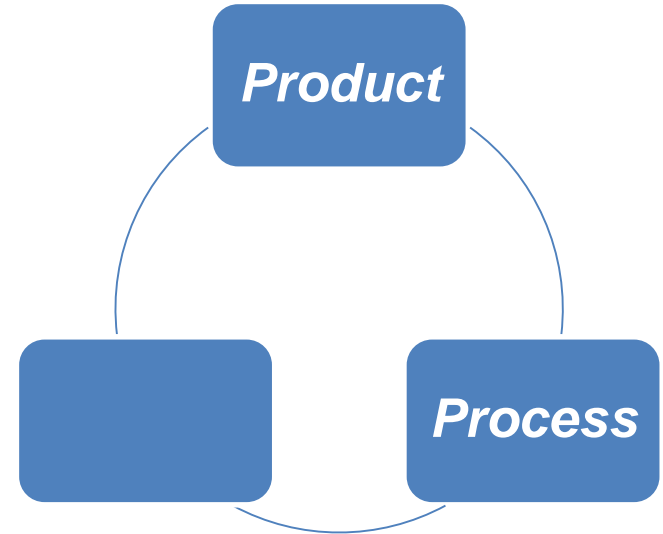
## *Contract Support*





## DNTP Operations

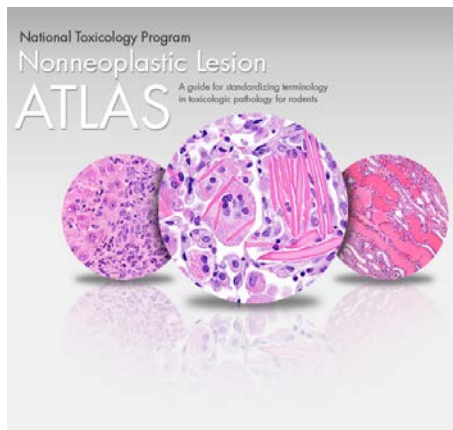
- Project and product centered research
- Shared resources, managed centrally
  - Individual projects/people are not "funded"
- Distributed governance
  - Internal decision-making largely consensus-based
- Teams assembled to include appropriate:
  - Disciplines, expertise, roles





## Primary outputs

- Technical Reports
- Toxicity Reports
- Research Reports
- Monographs
- Report on Carcinogens
- Scientific journal articles



- Data (e.g. CEBS)
- Databases (e.g. ICE)
- Computational tools (e.g. DNT-DIVER)
- Research resources (e.g. Nonneoplastic Lesion Atlas)
- Presentations and posters

CEBS: <https://manticore.niehs.nih.gov/cebssearch/>

ICE: <https://ice.ntp.niehs.nih.gov>

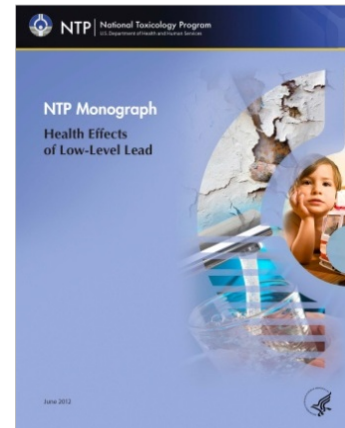
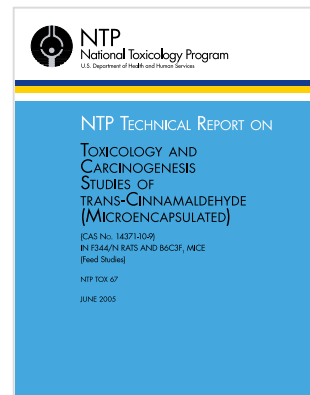
DNT-DIVER: <https://sandbox.ntp.niehs.nih.gov/neurotox/>

NNL Atlas: <https://ntp.niehs.nih.gov/nnl/>



## Examples of NTP products cited by health agencies

- Federal rulemakings
  - EPA dust-lead hazard standards
    - *OHAT Low-Level Lead Monograph (2012)*
- California EPA Proposition 65
  - Cancer hazard determinations
    - *Technical Report on TRIM VX (2016)*
- Health guidance
  - NIOSH List of Hazardous Drugs in Healthcare Settings
    - *14th Report on Carcinogens (2016)*







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## Broadly defined

- Portfolio definition (Oxford)
  - “A range of products or services offered by an organization”
- Portfolio as a unifying concept
  - All scientific activities
- Tangible components
  - Research products, programs, projects, studies
- “Soft” components
  - Advice, consultations, outreach, support, training



## Structure and components

- Organized largely around capability and discipline
- Descriptors
  - Types of substances
  - Types of studies
  - Types of methods/approaches
  - Types of products



- Mammalian toxicology
  - Repeat dose toxicology
  - Carcinogenicity bioassays
  - Immunotoxicology
  - Developmental and reproductive toxicology
  - Neurotoxicology
  - Genetically modified models
- Alternative models
  - Zebrafish
  - HepaRG spheroids
- ADME/Toxicokinetics
- Analytical chemistry
- Bioinformatics
- Biological modeling
- Computational toxicology/QSAR
- Genotoxicity
- Literature scoping
- Molecular pathology
- Systematic review
- Transcriptomics



# Types of Substances Evaluated

- Antimicrobials
- Biological agents
- Botanicals and dietary supplements
- Consumer products
- Cyanotoxins
- Dietary and drinking water exposures
- Endocrine active substances
- Flame retardants
- Food additives/contaminants
- Industrials
- High threat agents
- PAHs
- PFAS
- Metals
- Mixed exposures
- Molds and mycotoxins
- Nanomaterials
- Natural products
- Oil and gas chemicals
- Particles and fibers
- Pesticides
- Physical agents
- Safer alternatives
- Therapeutics



## Project categories

- Research and Testing Activities
  - Toxicology studies
  - Tox21 and biomolecular screening
  - New, revised, or alternative test methods
  - Investigative studies
- Analysis Activities
  - Non-cancer health effects
  - Cancer hazards



## Toxicology studies

- Disposition, metabolism, and toxicokinetics
- Genetic toxicity
- Systems Toxicity
  - Immune, developmental, reproductive
- General toxicology and carcinogenicity
  - 5 days → 2 years
- Toxicogenomics

10-15

40-50

40-50

80-100

15-20



## Tox21 and biomolecular screening

- Develop, apply, and evaluate innovative *high-throughput and/or high-content* approaches to characterize the impact of chemicals on key steps in toxicity pathways
- Ongoing projects
  - Assay development
  - Data analysis
  - Screening/testing

Analysis  
workflows/tools

Predictive model  
development

IVIVE

Reference data  
curation

3-D tissue models

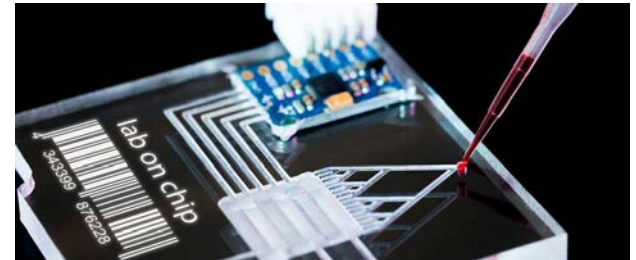
Genomic dose-  
response





## New, revised, or alternative test methods

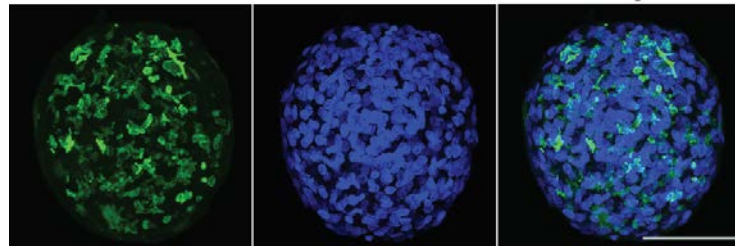
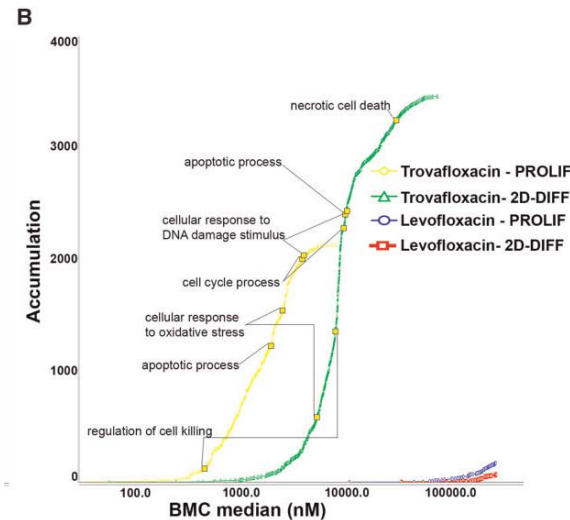
- Development of non-animal approaches
  - Acute systemic toxicity
  - Botulinum neurotoxin testing
  - Cardiotoxicity
  - Developmental toxicity
  - Endocrine disruptor activity
  - Skin sensitization
  - Ocular irritation
- Test method evaluations
  - Electrophilic allergen screening assay
  - OptiSafe
  - EpiAirway™





## Investigative studies

- Agent-specific, targeted research on specific substances of concern to NTP
  - Botanicals, crumb rubber, PFAS, PAHs
- Development of methods and capabilities to advance the NTP mission
  - Metabolomics
  - Complex in vitro systems
  - In vitro imaging and pathology
- Mechanisms of neurotoxicity and the developmental basis of adult disease





## Evaluating non-cancer health effects

- Human health hazard assessments
- Scoping reviews
- Evidence maps
- State-of-the-science evaluations
- Improving systematic review and evidence integration methods



**Neonicotinoid  
Pesticides and  
Adverse Health  
Outcomes**



**Biocides and  
Potential  
Respiratory  
Health Outcomes**



**Inflammation-  
based  
Atherosclerosis**

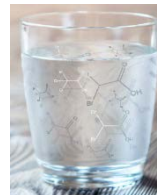


**Traffic-Related Air  
Pollution and  
Children's Health**



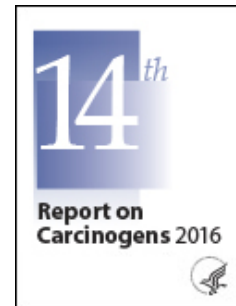
## Evaluating human cancer hazards

- Integrated cancer hazard evaluations
  - Consideration for new editions of the *Report on Carcinogens*
- 14<sup>th</sup> *Report* (2016): 248 listings
- Improving methods for evaluating mechanistic evidence to inform carcinogenicity assessments



**Report on Carcinogens**  
Monograph on  
Haloacetic Acids Found as  
Water Disinfection By-Products

March 2018



**Report on Carcinogens**  
Monograph on  
*Helicobacter pylori*  
(Chronic Infection)

October 2018



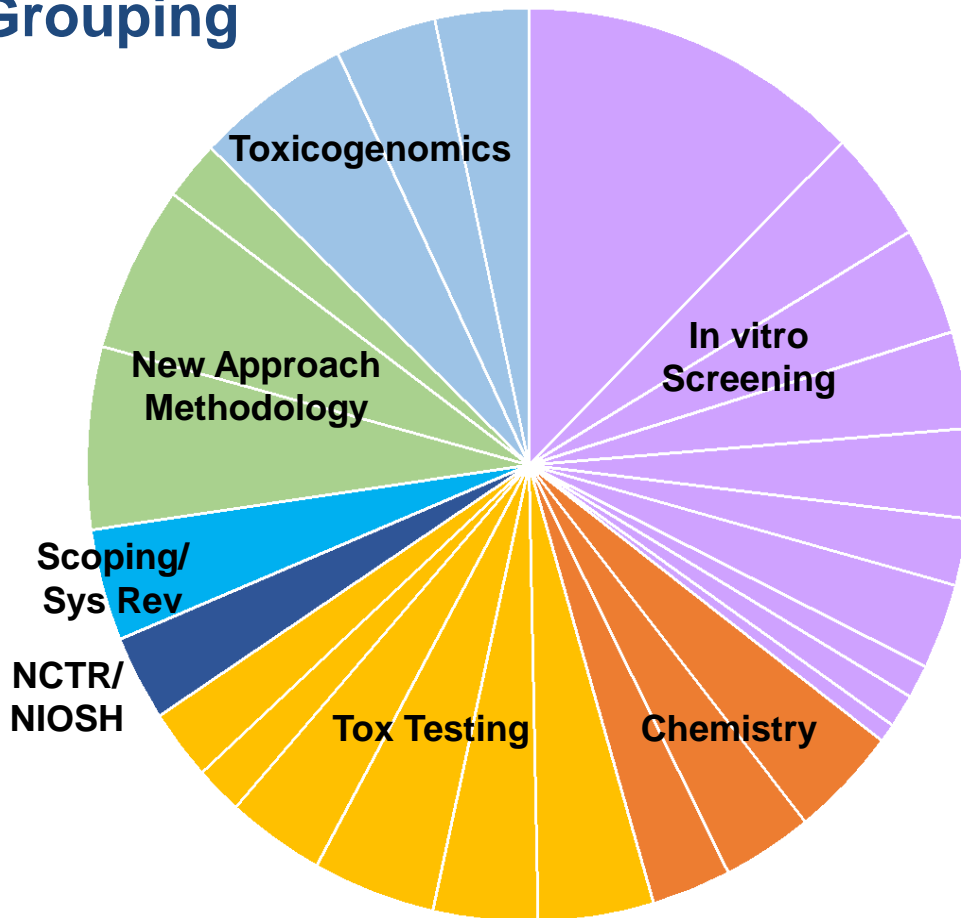
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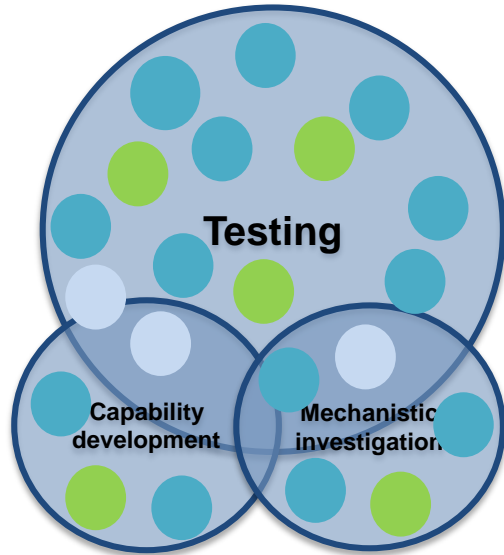
## • All projects – Study Type Grouping

- Counts of test substance x study → not equivalent to level of effort
- N = too many!
- Dissatisfaction with transit time through conduct and reporting pipeline
- Working through prioritization and managed attrition





## Substance-Focused



## Programmatic Strategy

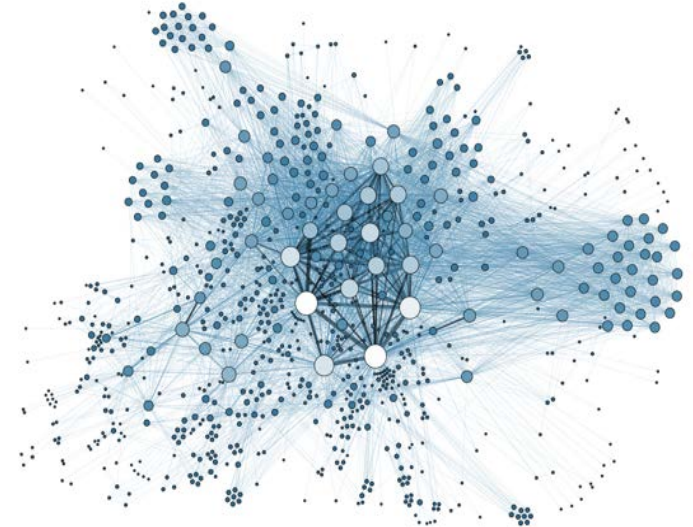


- Focused
- Aligned
- Complementary



## Some things old, some things new

- Broad scientific areas
  - Substance-based hazard evaluations
  - Understanding environmental contribution to human disease
  - Targeted capability development
- Discrete scientific programs
  - Health Effects Innovation Programs
  - Exposure-Based Research Themes
  - Responsive Research







## Targeted capability development

- Directly support/enable scientific initiatives
- Leverage and improve upon existing strengths
- Intentionally developed to fill in blind spots, clear path to application

**High-throughput  
transcriptomics**

**Computational  
toxicology**

**Organotypic  
models**

**In vitro imaging**

**In vitro ADME**

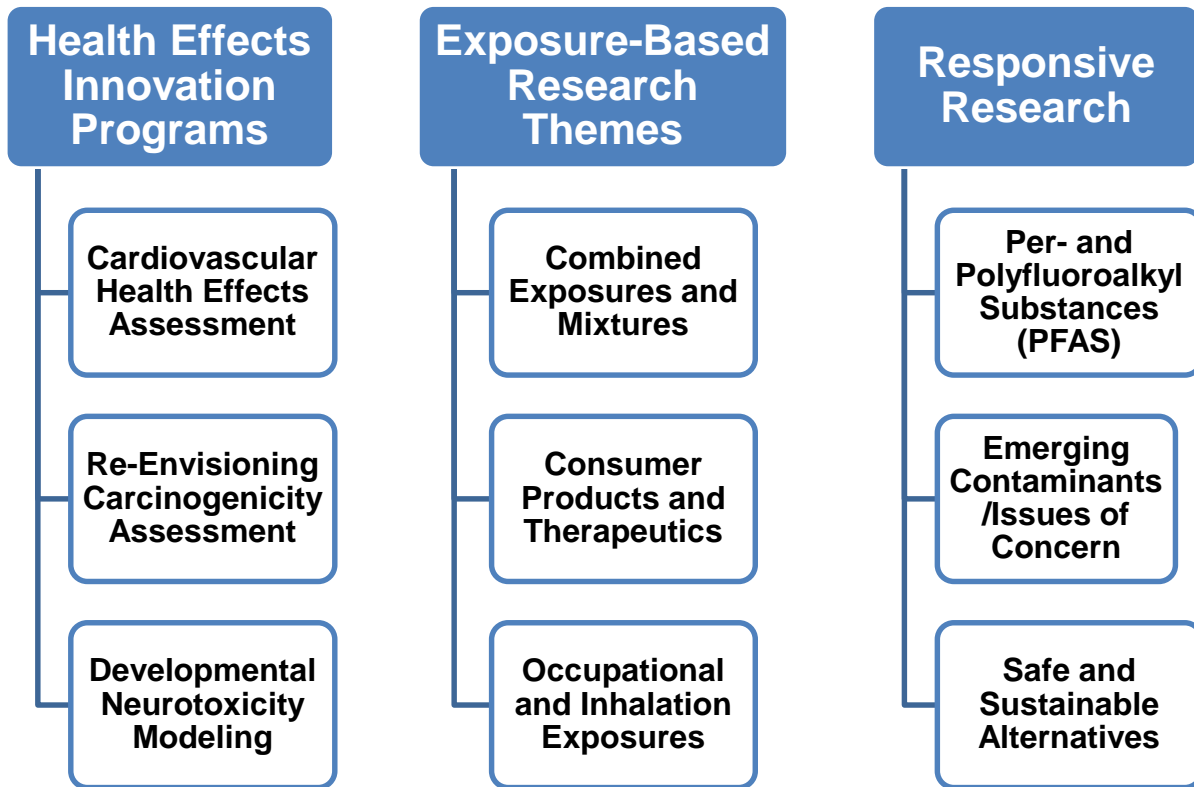
**Evaluating  
confidence in  
NAMs**

**Metabolomics**

**Analytic tool  
development**

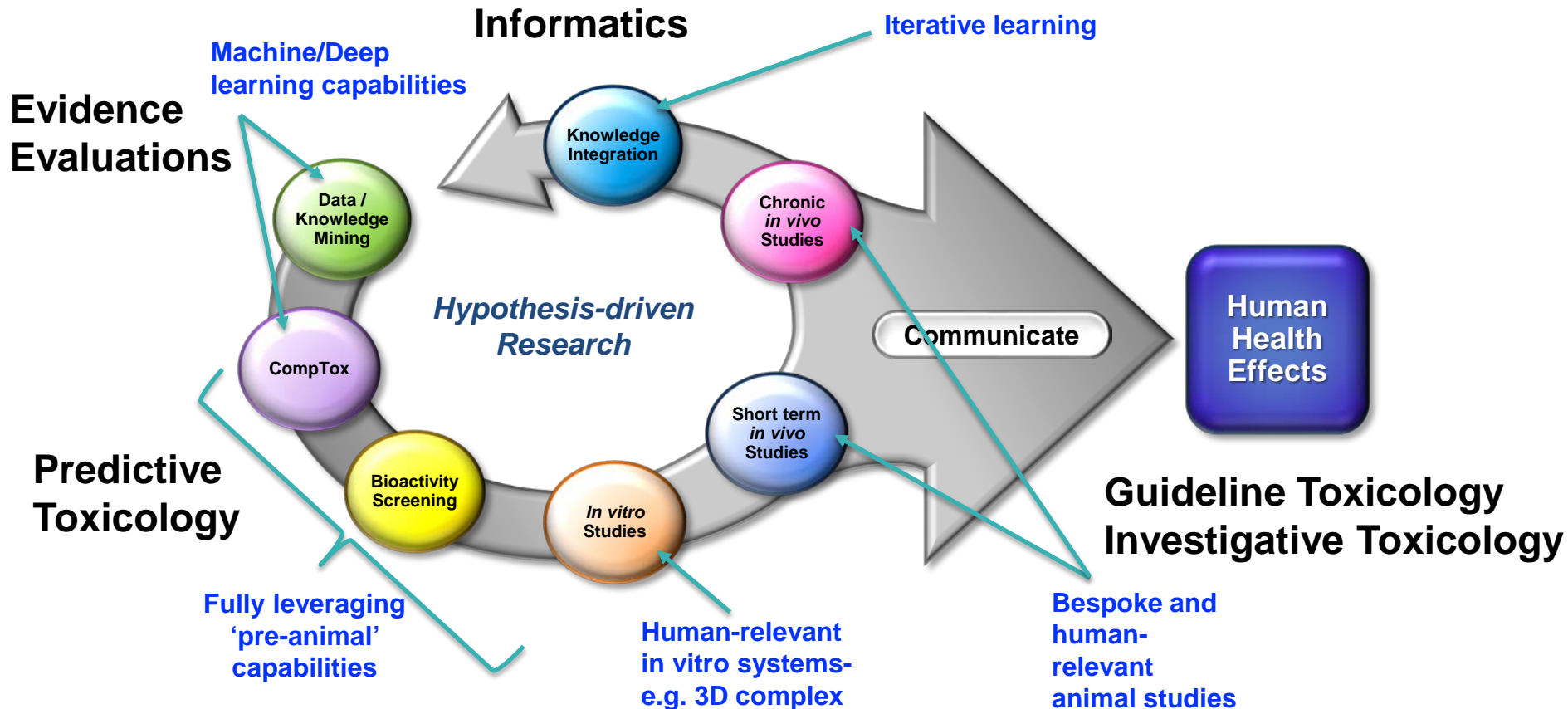


## Strategic Areas of Focus





# DNTP Translational Toxicology Pipeline





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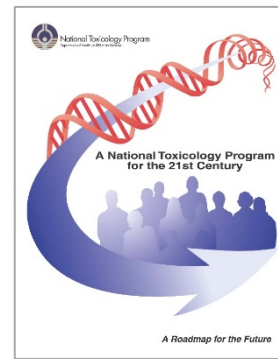


## Portfolio strategic aims

Structure and manage to increase:

- Impact – innovation, prediction, translation
- Integration – across DNTP, NIEHS, “Big NTP”
- Agility – seize opportunities
- Opportunity – build partnerships, leverage resources
- Efficiency – upgrade operations and systems
- Sustainability – effort toward delivering not fixing
- Long-term viability – prepared to tackle tomorrow’s problems

***NTP @ 25***



***NTP @ 40***

***NTP @ 50***



## Commitments, concerns, challenges

- Delivering on current obligations
- Maintaining core capabilities and partnerships
- Fostering disciplined creativity
- Adopting novel mechanisms for engagement and coordination
- Broadening leadership and mentoring skills development
- Expanding range of products: knowledge > decision > action









# Questions and Comments