

Novel Tools and Approaches Program

David M. Crizer, Ph.D.

Division of the NTP

National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting

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NTA Program Members

Members from 5 DNTP branches

Liaison



Alex
Merrick
MTB



Ian
Chen
MTB



David
Crizer
MTB



Rachel
Frawley
STB



Georgia
Roberts
OPO



Greg
Travlos
CMPB



Kristine
Witt
PTB

Ex Officio



Warren
Casey
PTB



Vickie
Walker
IHAB



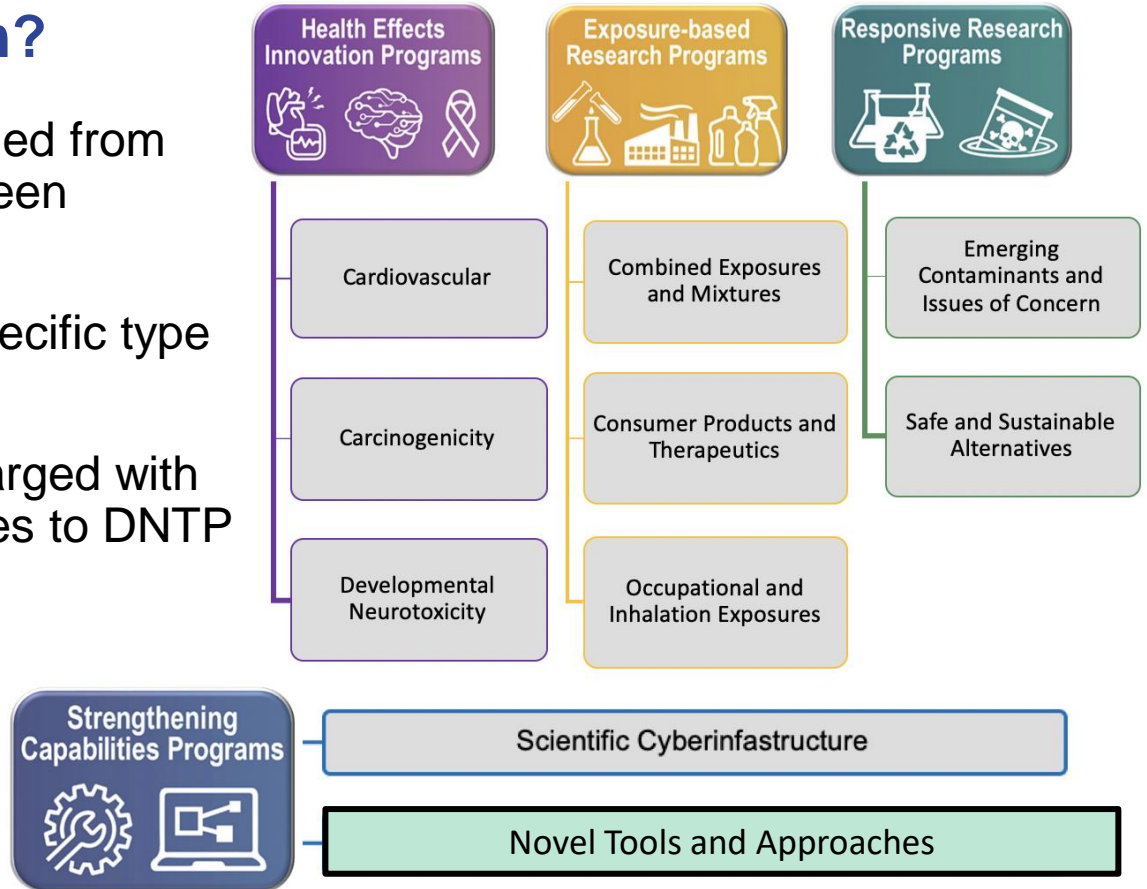
Rick
Paules
PTB

The Novel Tools and Approaches (NTA) Program

What is the NTA Program?

The NTA Program is distinguished from the other programs that have been introduced previously

- NTA is not focused on a specific type of disease or exposure
- NTA is 1 of 2 programs charged with providing special capabilities to DNTP





What is the NTA Program?

NTA is tasked with identifying new and novel testing approaches that may improve DNTP science by

- Increasing testing throughput
- Increasing speed of data acquisition from years to weeks
- Increasing data accuracy and precision
- Providing more in-depth analyses: molecular mode of action (MoA) and benchmark dose (BMD)
- Enhancing human relevance of DNTP studies



Shortfalls in Current NTAs

Human Health
Predictivity

Throughput

Translational
Relevance

To Meet Public Health Needs and Expectations:

Identify

Translatable

Evaluate

NTAs

Predictive

Implement

Timely

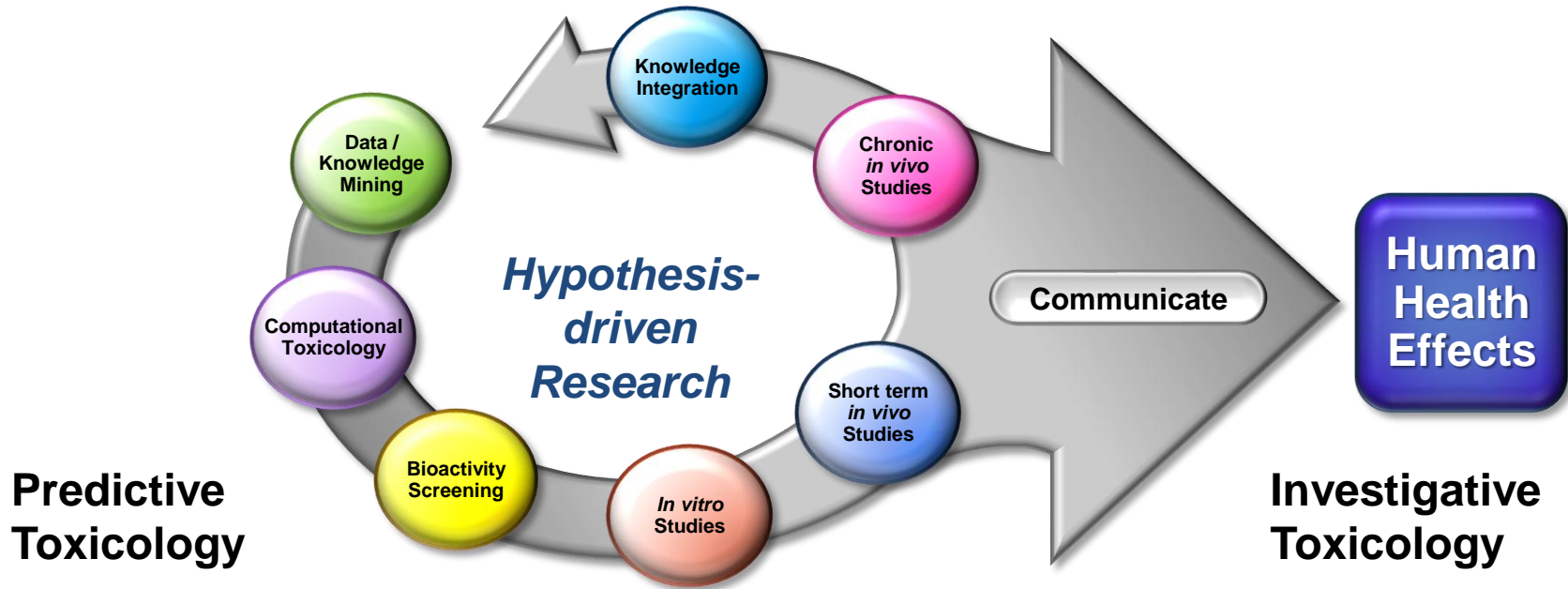
Absence of NTAs

Foster
Development

Meet Needs

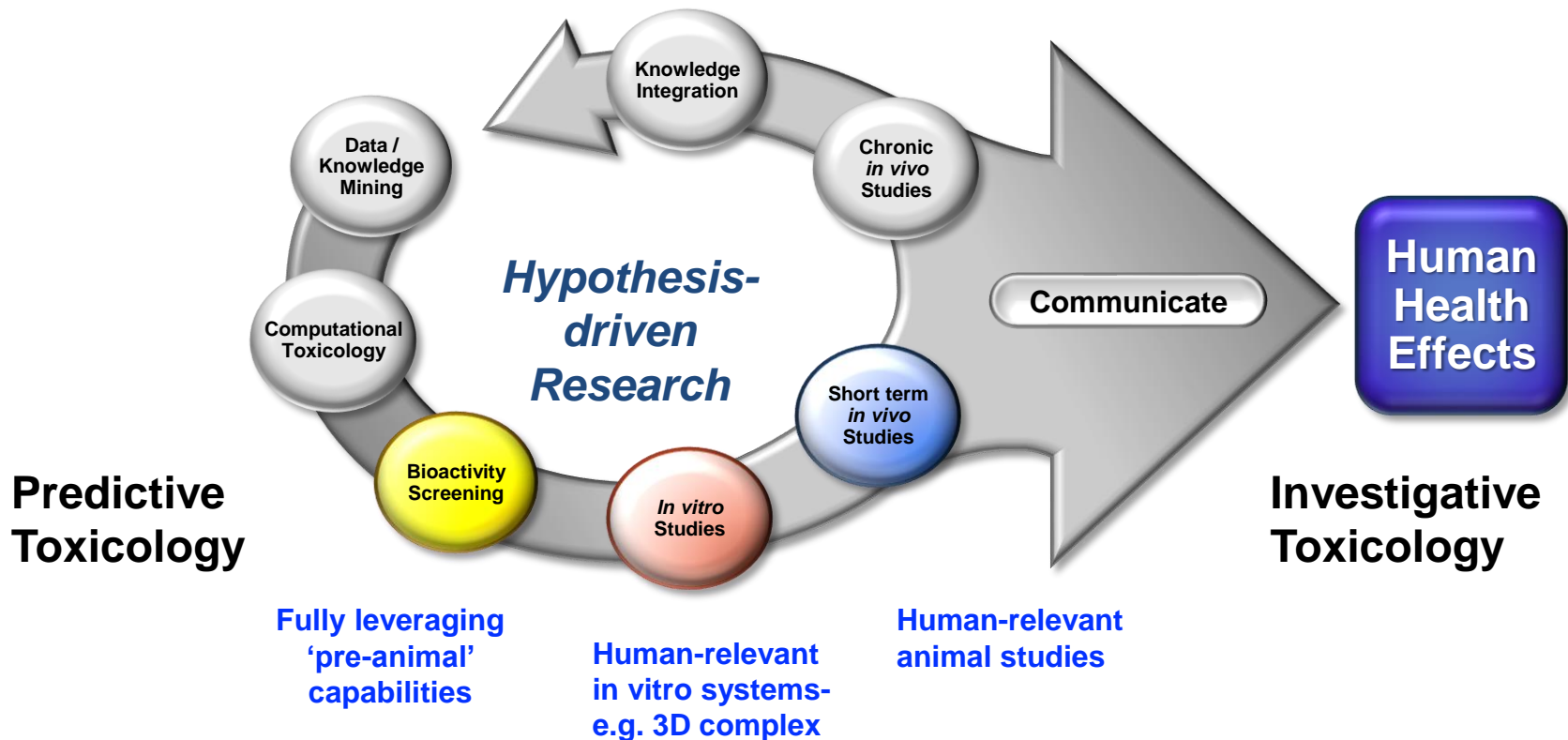


Mission Alignment and Pipeline Engagement



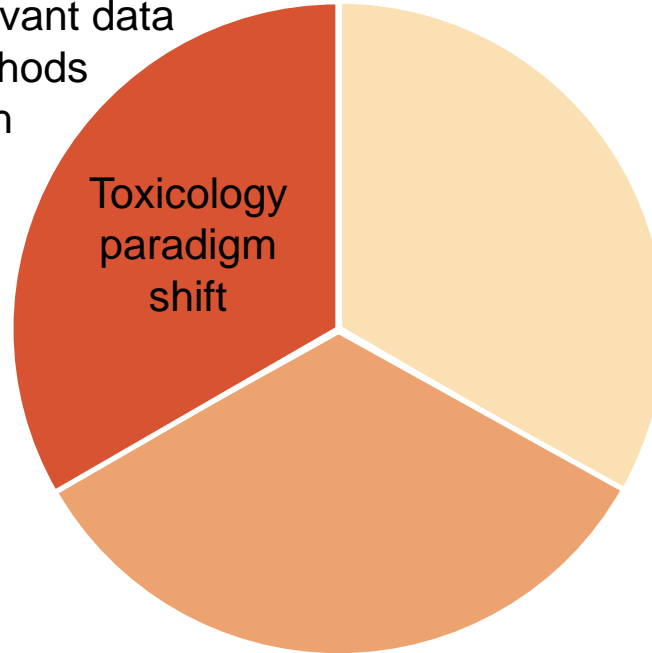


Mission Alignment and Pipeline Engagement



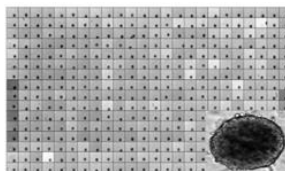
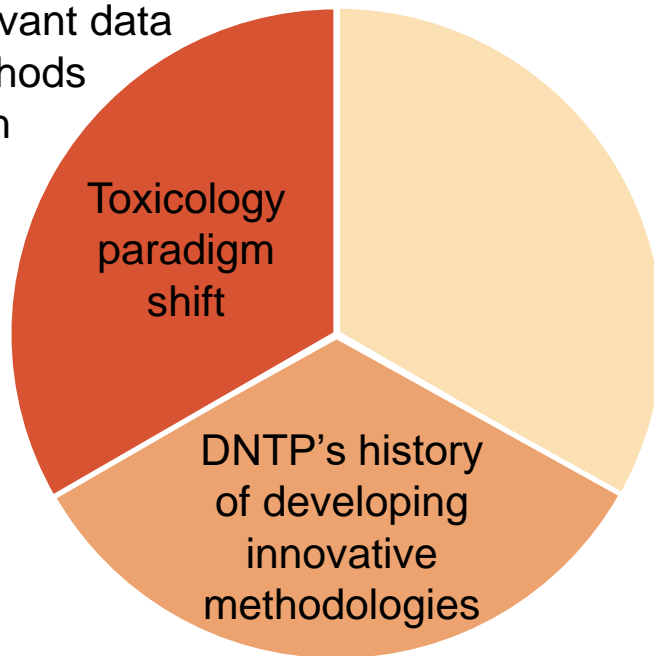


- Rapid, predictive, human-relevant data
- More efficient, innovative methods
- Reduce/refine animal use with focus on *in vitro* models

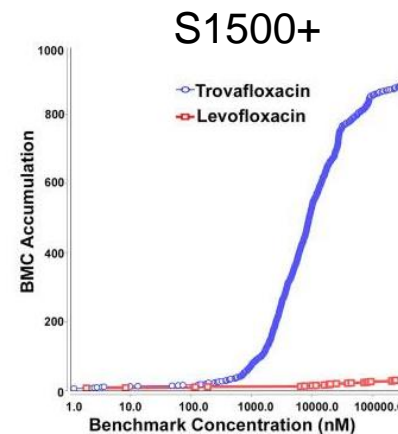




- Rapid, predictive, human-relevant data
- More efficient, innovative methods
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1 vial = 25X
384-well plates

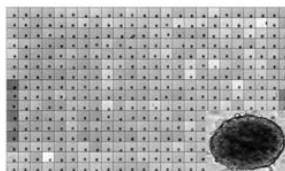
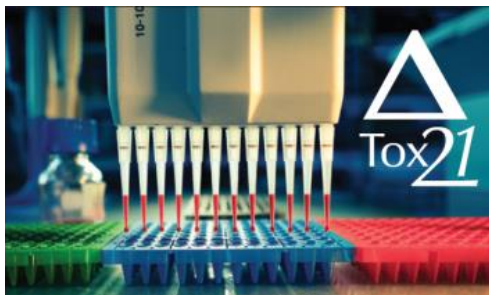
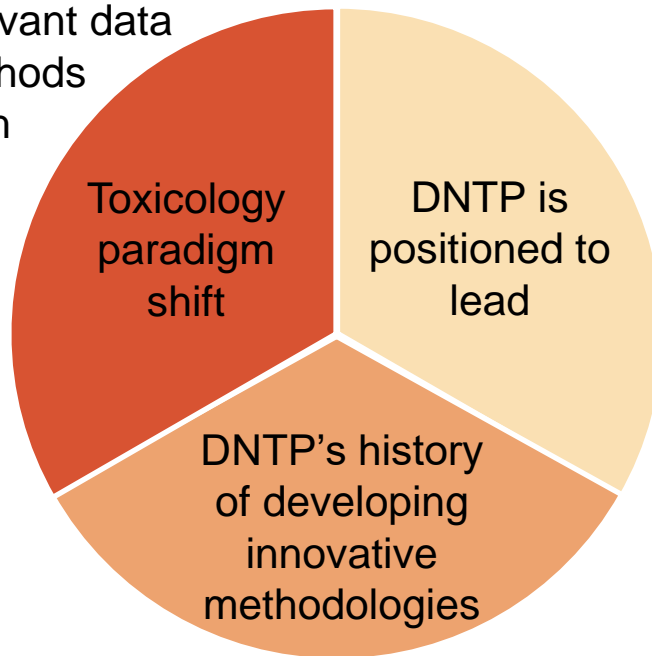




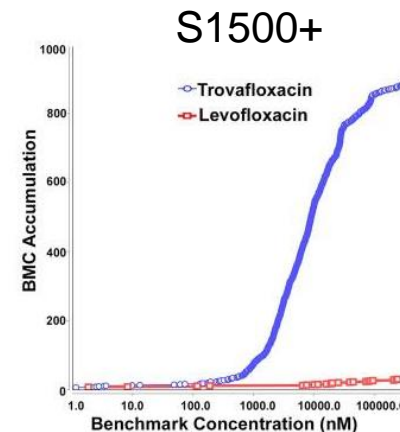
Rationale for NTA

- Rapid, predictive, human-relevant data
- More efficient, innovative methods
- Reduce/refine animal use with focus on *in vitro* models

- Resources
- Broad scientific expertise
- International collaborations



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Addressing the need for human relevant, actionable data

In vitro assays

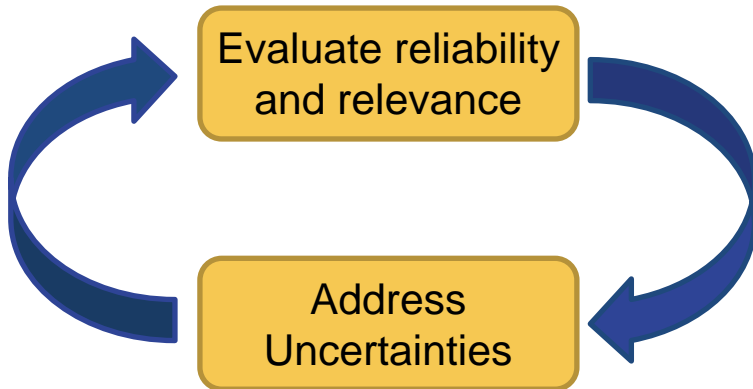
Building Confidence in New Approaches



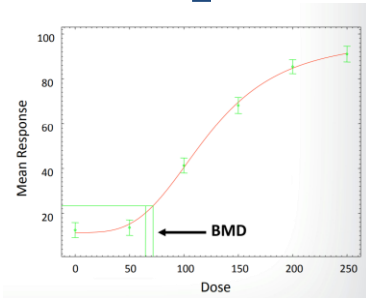
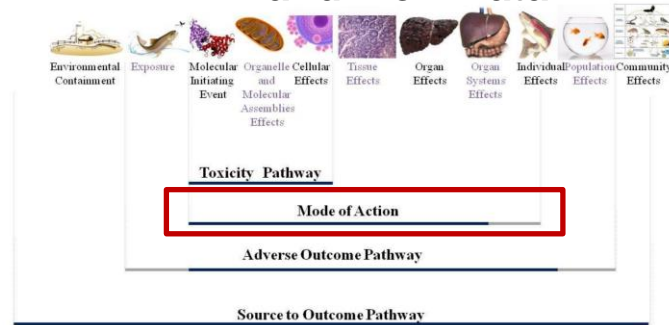
Rapid and Reliable



Hazard Determination



BMD and MoA Data



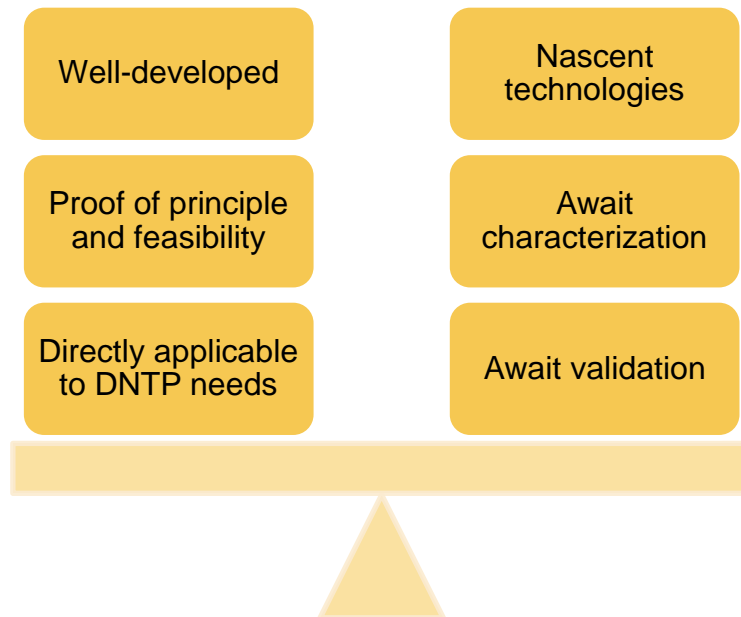
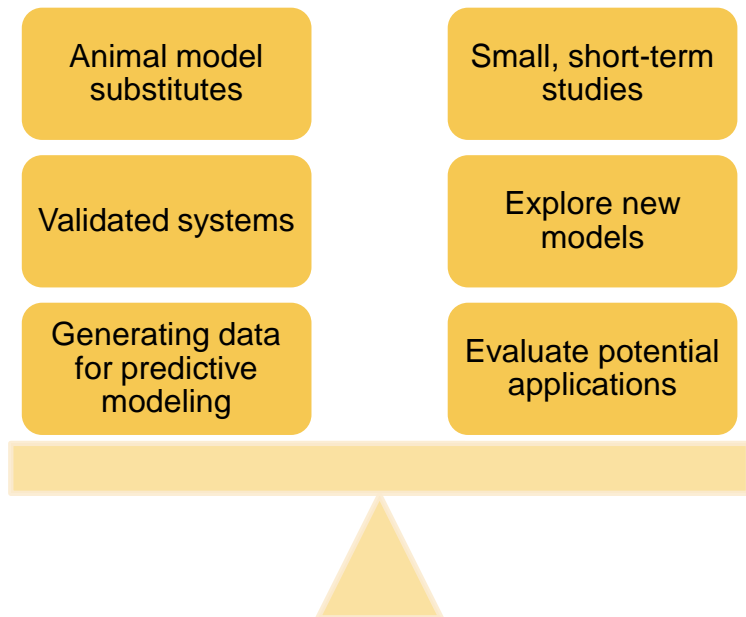
- Translate observations to human exposure
- Data for *in silico* modeling/read-across
- Guide further studies in more complex systems or *in vivo* models



Balancing Risk and Reward

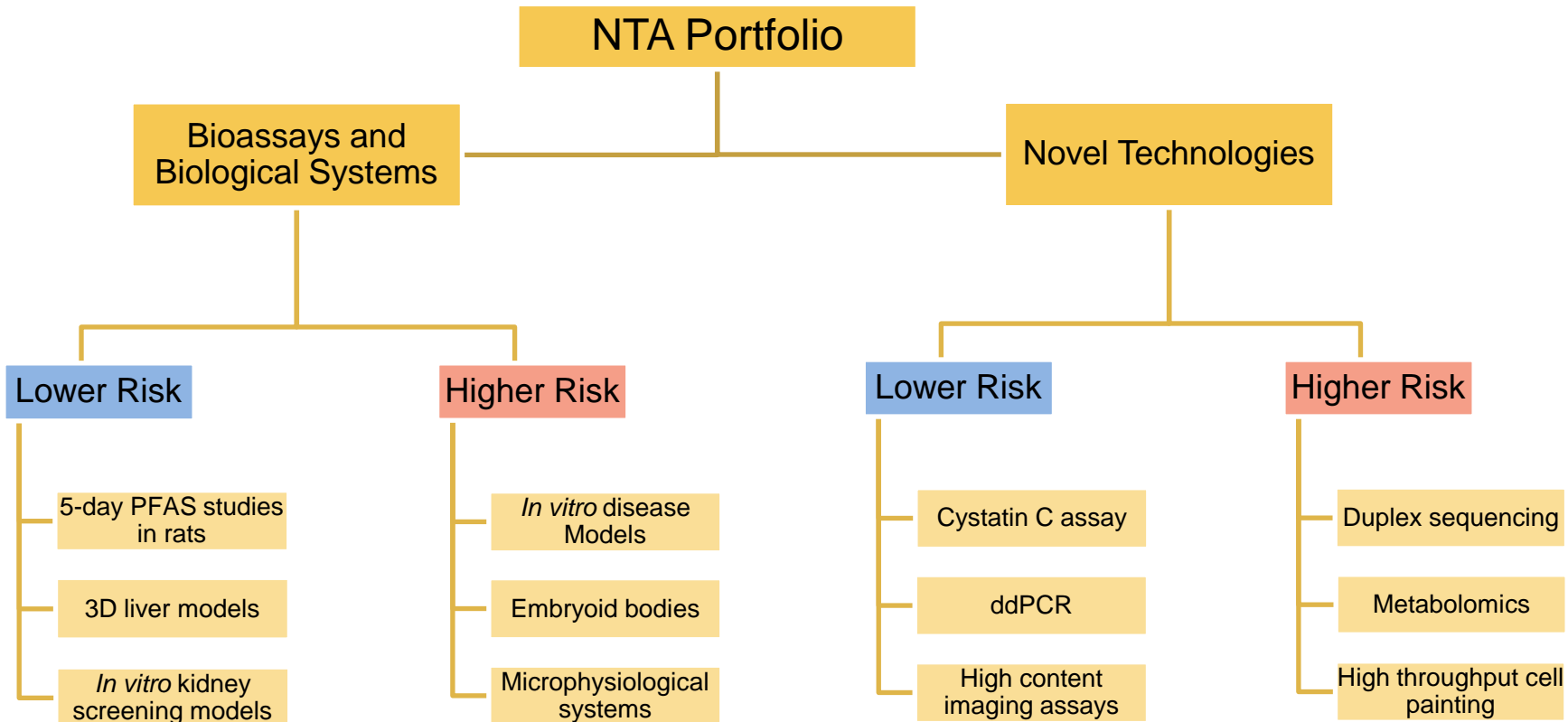
Bioassays and Biological Systems

Novel Technologies





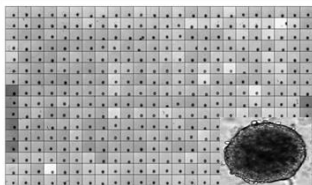
Current Portfolio of 28 Projects



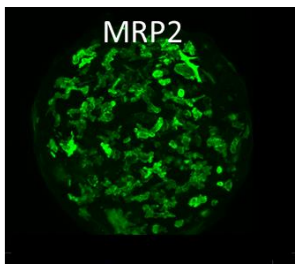


HepaRG Spheroid Model

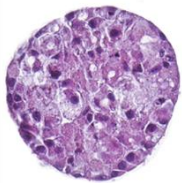
Cost-effective & Highly Differentiated Morphology



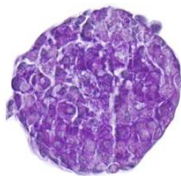
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384-well plates



MRP2



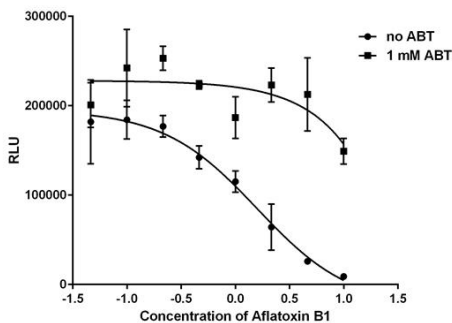
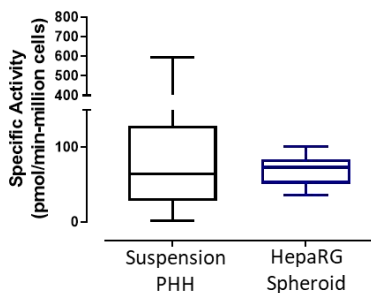
H&E



PAS

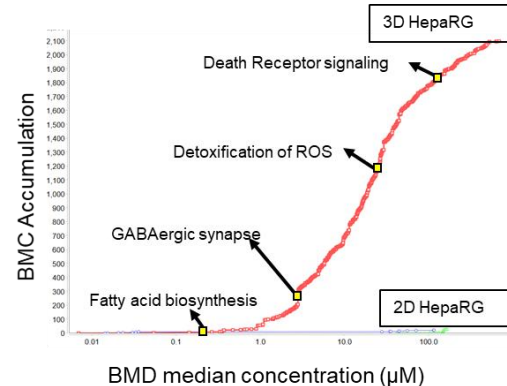
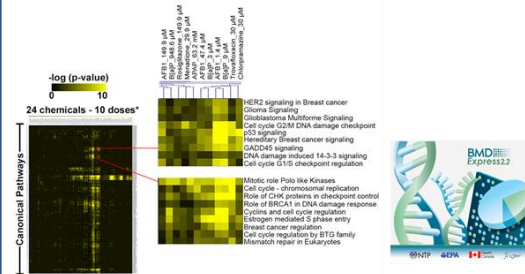
Metabolically Competent

CYP3A4 Enzyme activity



Identifies Metabolism associated Toxicity

Compatible for High-throughput Transcriptomics

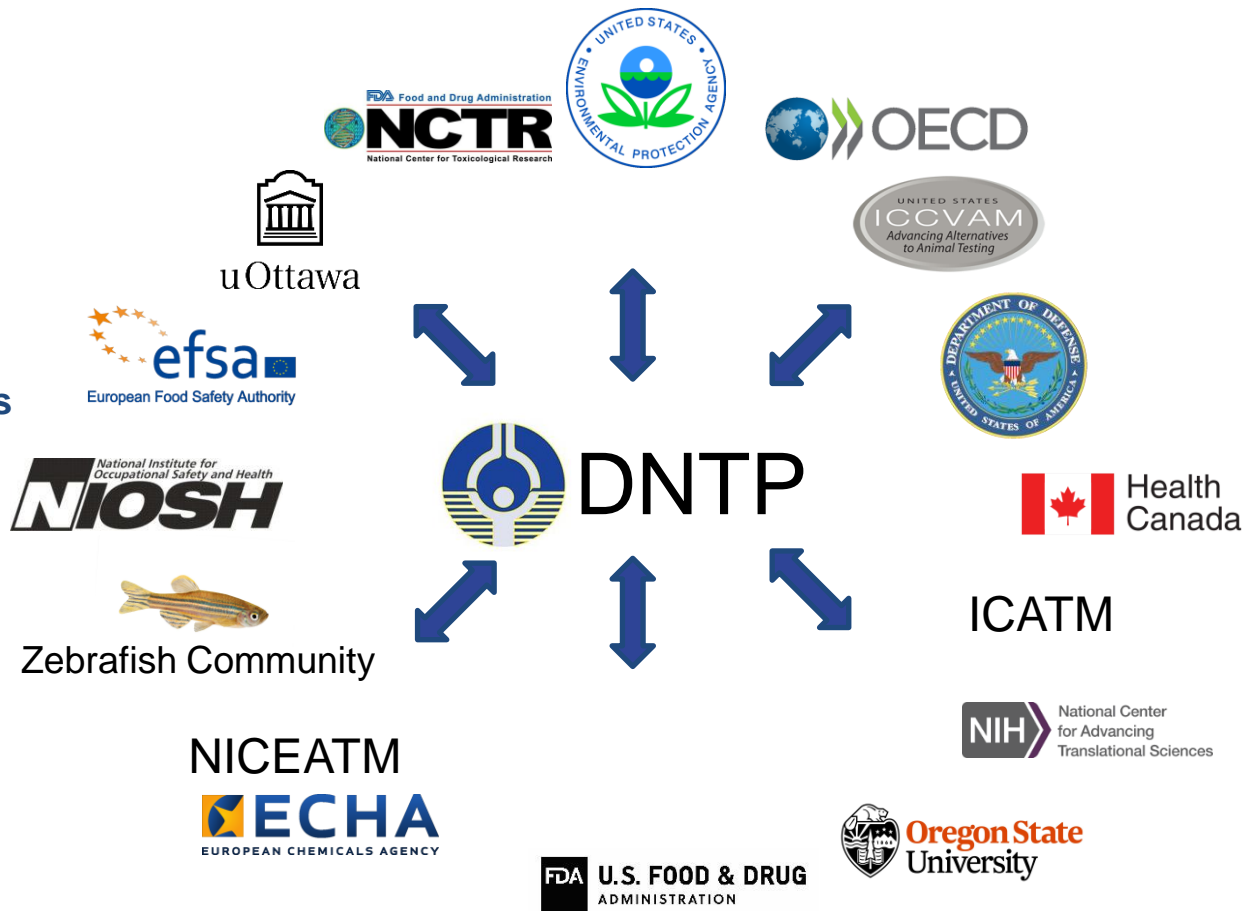


3D HepaRG show robust transcriptomic responses – e.g., Valproic acid exposure



Current Stakeholders

- Regulatory Agencies
- International advisory committees
- Academic laboratories
- Government research centers
- Research specialty communities
- Primary end user of NTAs

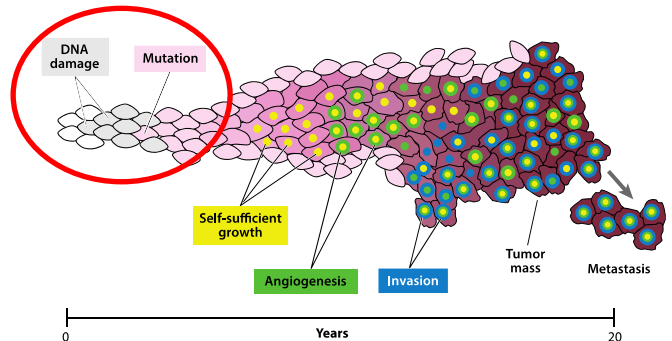




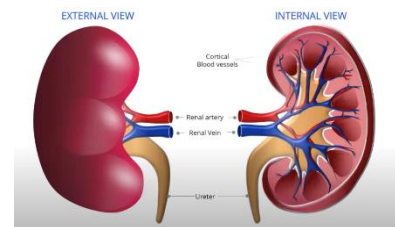
Objectives of the NTA Program

1. Identify and apply promising new technologies and approaches that enhance the efficiency and translational relevance of DNTP hazard assessments

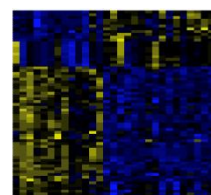
- Duplex sequencing for mutation analysis – applicability to early-stage carcinogenesis



- High throughput Cystatin C measurements for monitoring kidney function in rodent tests



- 5-day animal studies to capture signature transcriptomics changes following chemical exposure

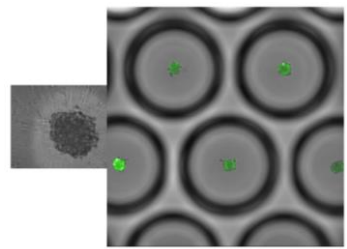




Objectives of the NTA Program

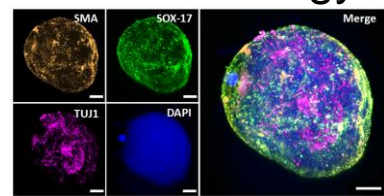
1. Identify and apply promising new technologies and approaches that enhance the efficiency and translational relevance of DNTP hazard assessments
2. Ensure that novel capability development is aligned to contemporary problems that DNTP is attempting to solve

Cardiovascular diseases



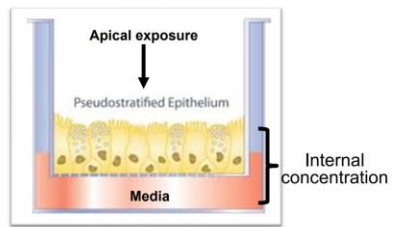
3D iPSC cardiomyocytes

Developmental neurotoxicology



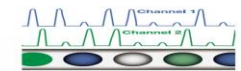
Embryoid bodies

Occupational exposures



Air-liquid interface (ALI)
lung models

Carcinogenesis



ddPCR



Objectives of the NTA Program

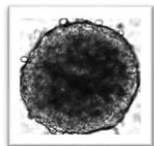
1. Identify and apply promising new technologies and approaches that enhance the efficiency and translational relevance of DNTP hazard assessments
2. Ensure that novel capability development is aligned to contemporary problems that DNTP is attempting to solve
3. Increase confidence in and adoption of NTAs, and foster development when need exists



Future NTA Development Areas

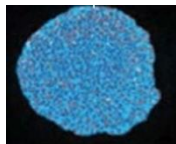
Spheroids and Organoids

3D Liver Models



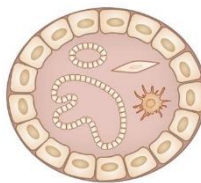
- High-throughput toxicity
- Genotoxicity screening

Neural Spheroids



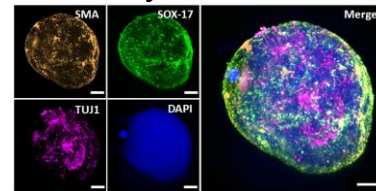
Developmental neurotoxicology

Kidney organoids



renal toxicities

Embryoid bodies

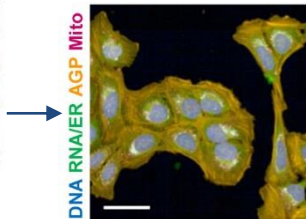


Animal model substitutes

High dimensional data streams

Microphysiological systems

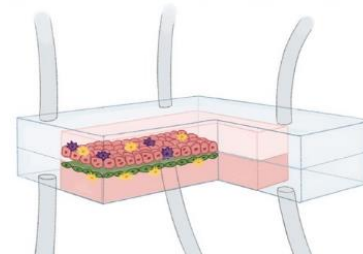
In Vitro Phenotype Screening



Tox21 Projects

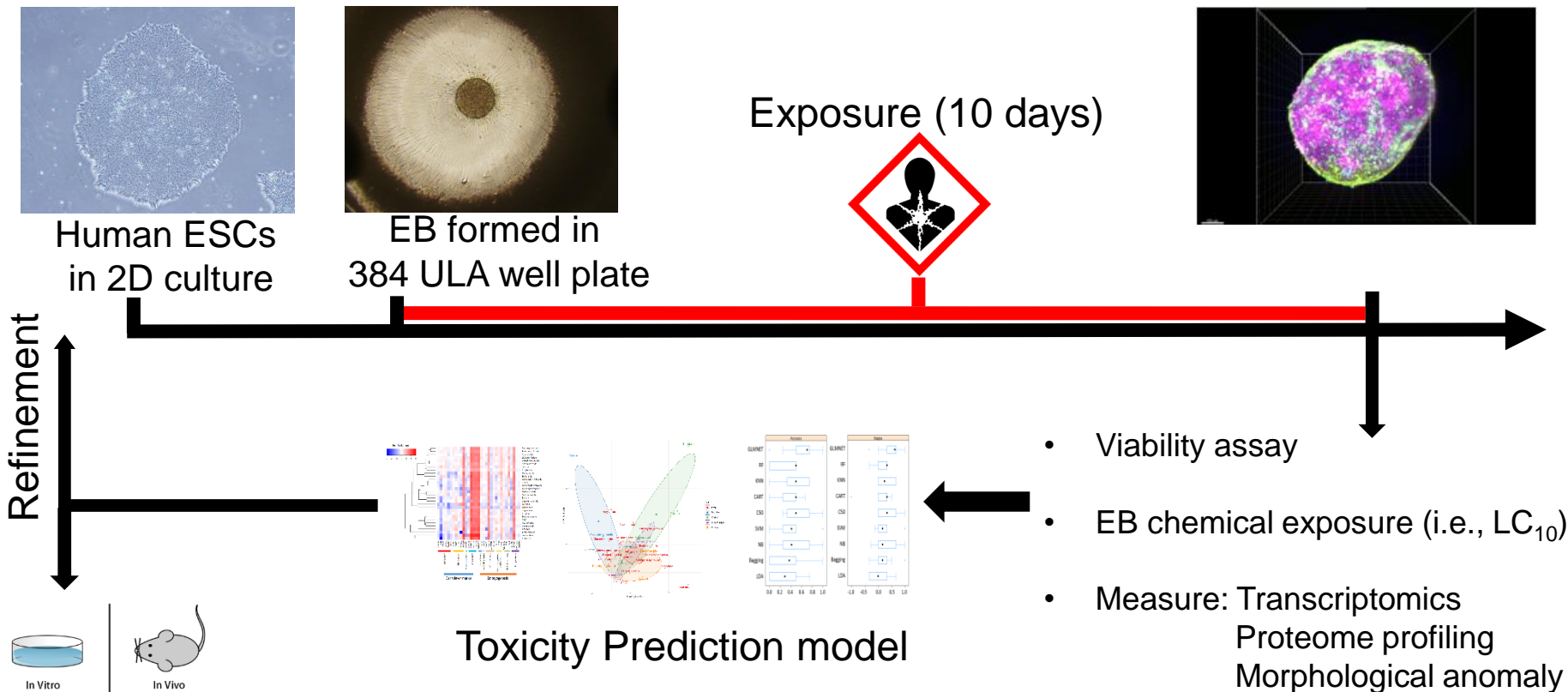


- High-throughput screening
- Complex projects utilizing cutting-edge technologies





Embryoid Bodies (EBs) for High-throughput Teratogen Screening



Prediction validation



Capability realization for 8 current projects



Near Term

Available Now

- 5 day + TempOSeq
- 3D Liver Models
- *In vitro* skin sensitization

Medium Term

1 – 2 years

- Ultra high throughput + S9
- Air-liquid interface
- Lung-on-a-chip

Longer Term

3 – 5 years

- Metabolomics
- Embryoid bodies



NTA Internal and External Connections

Systems Toxicology Branch
(STB)

Cardiovascular Program (CV)

Office of Program Operations
(OPO)

Occupational and Inhalation
Exposures Program (OIE)

Predictive Toxicology Branch
(PTB)

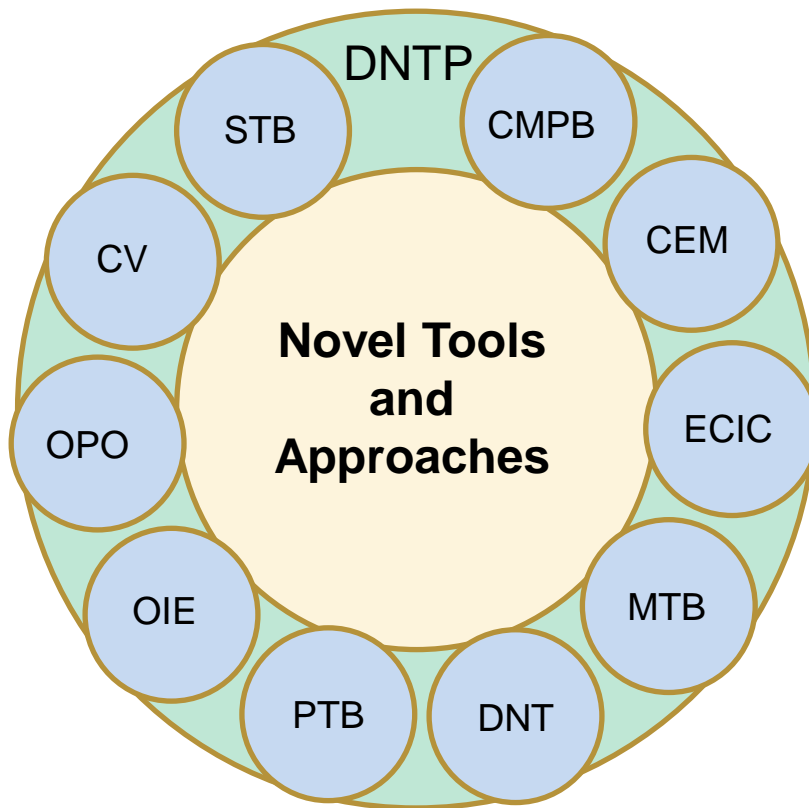
Comparative and Molecular
Pathogenesis Branch (CMPB)

Combined Exposures and
Mixtures Program (CEM)

Emerging Contaminants and
Issues of Concern Program
(ECIC)

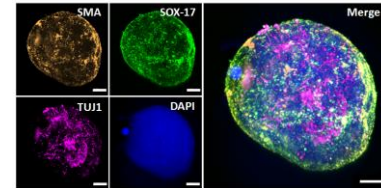
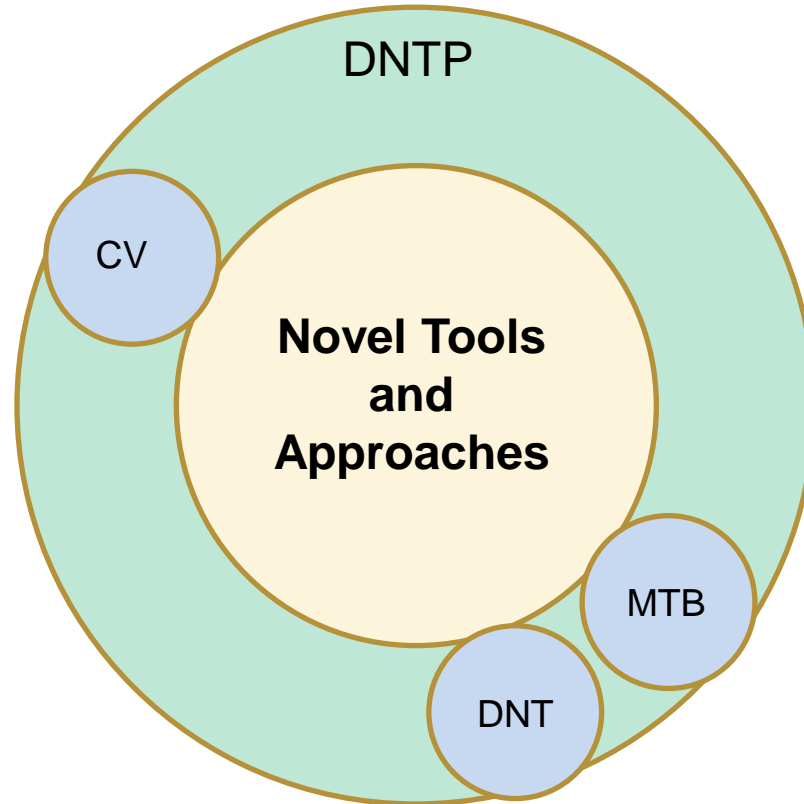
Mechanistic Toxicology
Branch (MTB)

Developmental
Neurotoxicology Program
(DNT)





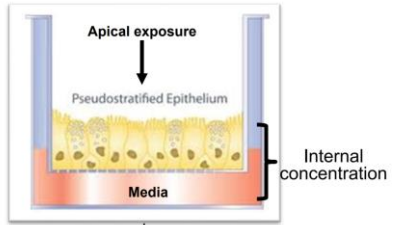
NTA Internal and External Connections



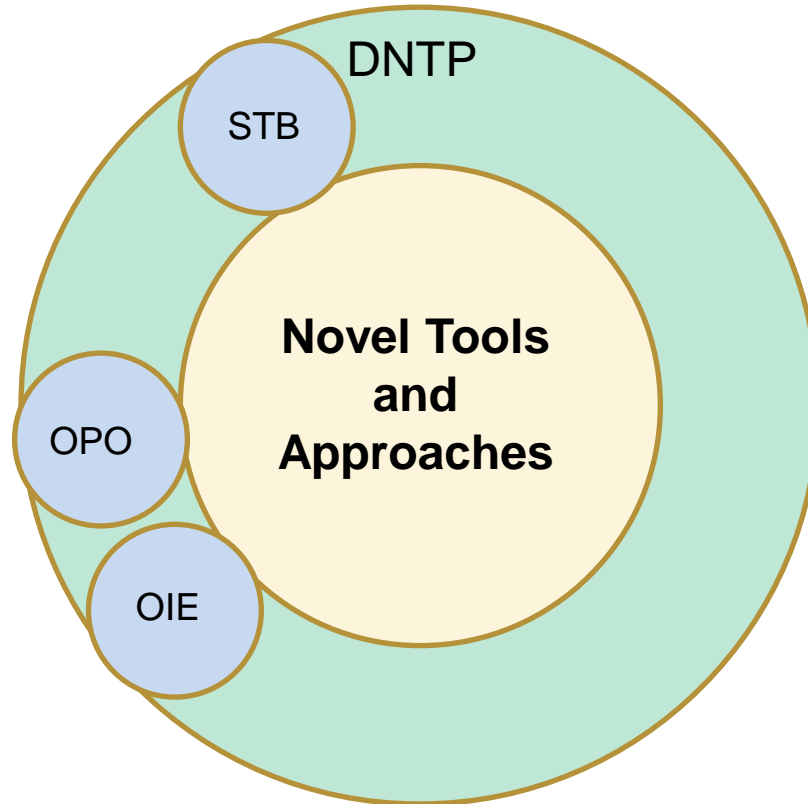
Embryoid bodies



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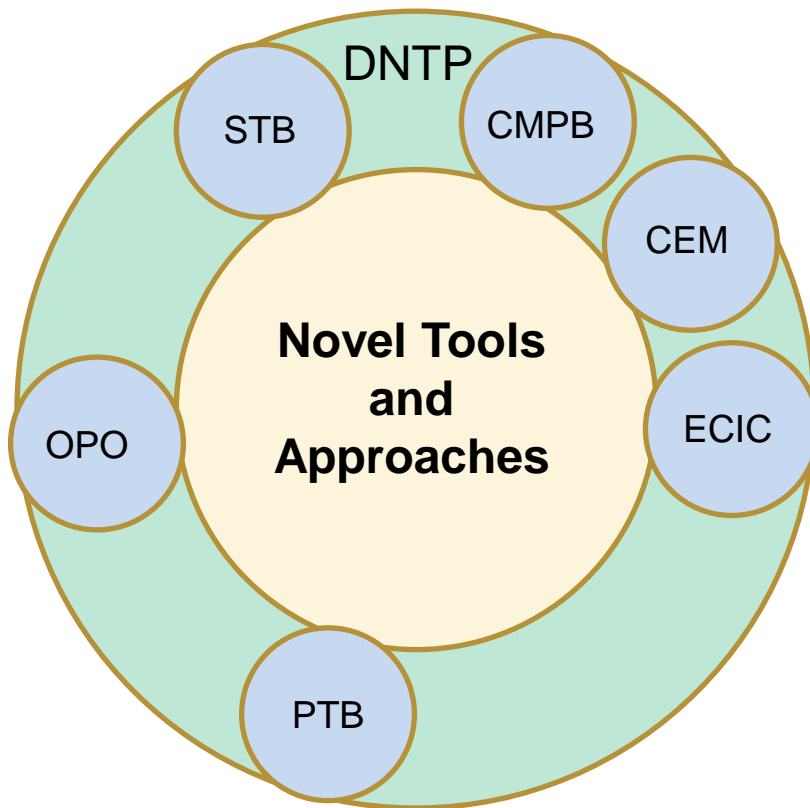


www.atcc.org
Air-liquid interface (ALI)
lung models





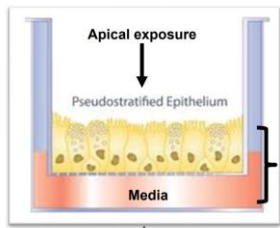
NTA Internal and External Connections



5-day studies
in rats

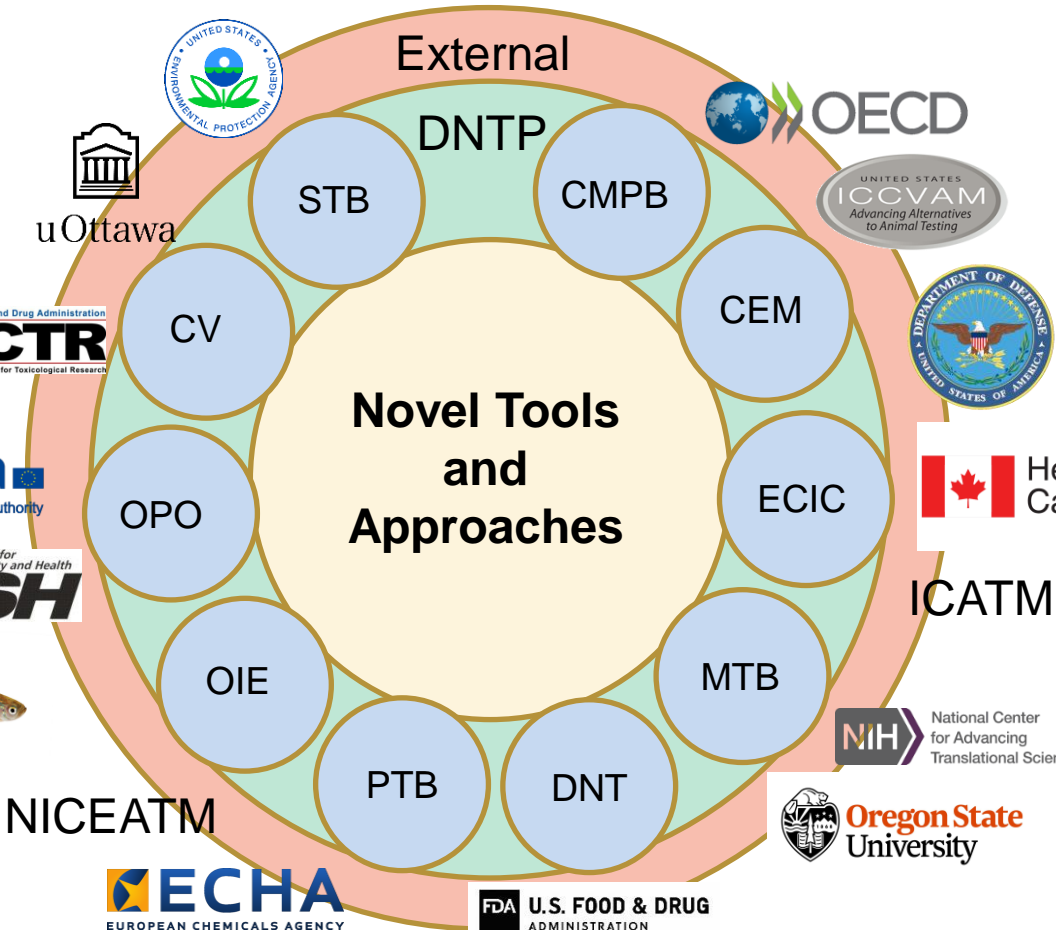


NTA Internal and External Connections

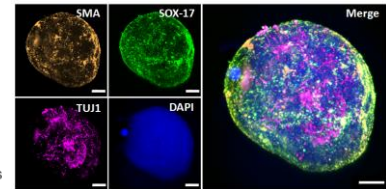


Internal concentration

Air-liquid interface (ALI) lung models
www.atcc.org



5-day studies in rats



Embryoid bodies



How would the BSC suggest the NTA go about identifying promising new technologies that appear to have direct application(s) to DNTP areas of investigation?

Thank You!





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