Looking Forward: Innovation in the NIEHS Division of the National Toxicology Program

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Division of the NTP
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
December 8, 2021
“Lead the transformation of toxicology through the development and application of innovative tools and strategies.”
Centralized budget and contract management; enhancing our future planning and project management capabilities

Developed a strategic portfolio management framework

Modernizing our data infrastructure

Re-invented our BSC engagement; increased the efficiency of our review processes

Centralized our administrative support organization; developed a workforce development framework

Office of Program Operations
Deputy Director for Program Operations
Office of Portfolio Strategy
Office of Data Science
Office of Policy, Review, and Outreach
Deputy Director for Policy & Communication
Office of Workforce Development and Operations
Systems Toxicology Branch
Comparative and Molecular Pathogenesis Branch
Mechanistic Toxicology Branch
Predictive Toxicology Branch
Integrative Health Assessments Branch
Built computational tools that enhance our use of bioactivity data; expanded Tox21; leadership in adoption of NAMs

Added new capabilities and research focus; grew existing capabilities

Increased the efficiency of pathology review; expanded training program

Enhanced assessment of life-stage susceptibility; expanded study type portfolio

Expanded literature-based assessment capabilities
Translational Toxicology Pipeline

It's not just about having the tools but also how you use them!

Concept introduced in 2018

Fundamental changes
- purposeful integration
- iterative learning
- informed progression
- hypothesis-driven
Translational Toxicology Pipeline 2021

- Human Health Effects
- Computational Analysis
- Data / Knowledge Mining
- Bioactivity Screening
- Simple In Vitro Systems
- Complex In Vitro Systems
- Animal Studies
- Human Studies
- Integrated Health Assessments
Innovating the Translational Toxicology Pipeline

Incremental → Disruptive

- AI-based automated knowledge mining
- Systems-based HTP screening
- Computational Analysis
- Data / Knowledge Mining
- Computational screening
- Bioactivity Screening

Decision frameworks
- Integrated Health Assessments
- Human health assessments
- Histopathology AI/ML

In vitro models of human disease
- Modeling host susceptibility/vulnerability

Human Studies
- Animal Studies
- Integrative physiological monitoring

Multi-scale computational modeling
- Simple In Vitro Systems
- Complex In Vitro Systems

Incremental → Disruptive Decision frameworks
• Leveraging informatics to support evidence-based decisions
  – Identify, adapt, and develop a toolbox of informatics approaches to advance our ability to turn data into knowledge for understanding health effects from environmental exposures
  – Improve workflow, reduce manual workload, identify tools for the range of DNTP users
  – Support synthesis through identification and categorization to better link mechanism to experimental and epidemiological data
Bioactivity data sources

EPA's ToxCast- 1800 chemicals, 700+ assays

Tox21- 10K chemicals, 70+ assays
**CV-relevant Bioactivity Targets**

<table>
<thead>
<tr>
<th>Slice</th>
<th>Target name</th>
<th>Effect</th>
<th>Reference</th>
<th>Slice Color</th>
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<tr>
<td>1</td>
<td>ADR</td>
<td>Adenosine Receptor</td>
<td>Vasodilation, alterations in BP</td>
<td>Bozes et al., 2012</td>
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<td>ADH</td>
<td>Adrenergic Receptors</td>
<td>Altered BP levels</td>
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<td>CHRM</td>
<td>Cholinergic Receptors</td>
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<td>Bozes et al., 2012</td>
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<td>DRD</td>
<td>Dopamine Receptor</td>
<td>Altered BP and HR, Vascular relaxation</td>
<td>Bozes et al., 2012</td>
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<td>5</td>
<td>ENDR</td>
<td>Endothelin Receptor</td>
<td>Altered BP, Can exert adverse effects during pregnancy</td>
<td>Bozes et al., 2012</td>
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<td>HTB</td>
<td>Serotonin Receptor</td>
<td>Altered BP, Potential cardiac valve pathology</td>
<td>Bozes et al., 2012</td>
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<td>AVPR</td>
<td>Vasopressin Receptor</td>
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<td>Bozes et al., 2012</td>
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<td>HRR</td>
<td>Histamine Receptor</td>
<td>Positive inotropy</td>
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<td>DOR</td>
<td>Opioid Receptor</td>
<td>Altered BP and Cardiac contractility</td>
<td>Bozes et al., 2013</td>
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<td>CHRNA3</td>
<td>Cholinergic Receptors</td>
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<td>Bozes et al., 2012</td>
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<td>11</td>
<td>SCN1A</td>
<td>Voltage-gated Sodium Channel</td>
<td>Slow conduction; prolonged QRS interval</td>
<td>Bozes et al., 2012</td>
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<td>12</td>
<td>CACNA1C</td>
<td>Voltage-Gated Calcium Channel</td>
<td>Altered BP, QT prolongation, Arrhythmia</td>
<td>Bozes et al., 2012</td>
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<td>13</td>
<td>KCNH2</td>
<td>Potassium Voltage Gated Channel</td>
<td>QT prolongation</td>
<td>Bozes et al., 2012</td>
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<td>14</td>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
<td>Altered BP, Cardiac Ischemia</td>
<td>Touys &amp; Herrmann, 2018</td>
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<td>15</td>
<td>Vascular Tissue</td>
<td>Vascular Tissue</td>
<td>Myocardial ischemia, cardiac Arrhythmias</td>
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<td>Oxidative Stress</td>
<td>Oxidative Stress</td>
<td>Cellular Hypertrophy, Cardiac Cell Death</td>
<td>Takimoto &amp; Kass, 2007</td>
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<td>17</td>
<td>Mitochondrial Dysfunction</td>
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<td>Cardiac dysfunction, Cardiomyopathy</td>
<td>Marin-Garcia, 2008</td>
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<td>Tissue Factor</td>
<td>Tissue Factor</td>
<td>Altered BP and ventricular hypertrophy</td>
<td>Bode &amp; Mackman, 2015</td>
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<td>Phosphodiesterase</td>
<td>Altered BP in cardiac contractility, HR and BP</td>
<td>Bozes et al., 2012</td>
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<td>MAO</td>
<td>Monoamine Oxidase</td>
<td>Altered BP</td>
<td>Bozes et al., 2012</td>
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<td>e-NOS N-terminal kinase</td>
<td>Vascular injury, cardiac hypertrophy</td>
<td>Muslin, 2008</td>
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<td>Tks5A</td>
<td>Tyrosine Kinase</td>
<td>Altered BP, LV dysfunction, conduction abnormalities,</td>
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<td>Tks5A</td>
<td>Tyrosine Kinase</td>
<td>QT prolongation</td>
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<td>24</td>
<td>Aromatase Protein</td>
<td>Estrogen metabolism</td>
<td>Ischemic heart disease</td>
<td>Kohsroub-Khavar et al., 2012</td>
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<td>Acetylcholinesterase</td>
<td>Altered BP</td>
<td>Bozes et al., 2012</td>
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<td>26</td>
<td>COX</td>
<td>Cyclooxygenase</td>
<td>Myocardial infarction; Alteration in BP, Ischemic stroke</td>
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<td>27</td>
<td>ER Alpha</td>
<td>Estrogen receptor Alpha</td>
<td>Abnormal cardiac contractility, cardiac hypertrophy</td>
<td>Pagach, Blenc, Dragoone, Leiger, &amp; Lehmann, 2016</td>
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<td>28</td>
<td>NR3C1</td>
<td>Glucocorticoid receptor</td>
<td>Perlsamen Proliferator</td>
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<td>29</td>
<td>PPAR G</td>
<td>Activated Receptor Gamma</td>
<td>Cardiac hypertrophy, Atherosclerosis</td>
<td>Das &amp; Chakrabarti, 2006</td>
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<td>THR</td>
<td>Arylhydrocarbon receptor</td>
<td>Endothelial dysfunction, Atherosclerosis</td>
<td>Wu et al., 2011</td>
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<td>AKT</td>
<td>Activator protein-1</td>
<td>Atherosclerosis</td>
<td>Meijer et al., 2012</td>
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<td>NFIB</td>
<td>Hypoxia Inducible Factor</td>
<td>Ischemic disease</td>
<td>Semenza, 2004</td>
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<td>33</td>
<td>TGFb</td>
<td>NFkappa B</td>
<td>Atherosclerosis</td>
<td>Floridolf et al., 2019</td>
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<td>34</td>
<td>TP53</td>
<td>Tumor Protein p53</td>
<td>Altered in cardiac function</td>
<td>Merzer &amp; Bennett, 2006</td>
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<td>ICAM-1</td>
<td>Intercellular adhesion molecule</td>
<td>Markers of endothelial dysfunction</td>
<td>Boyd et al., 2008</td>
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<td>IL6</td>
<td>Interleukin 6</td>
<td>Markers of inflammation and oxidative stress</td>
<td>Chu et al., 2020</td>
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<td>37</td>
<td>e-PA</td>
<td>Tissue Type plasminogen activator</td>
<td>Markers of endothelial dysfunction</td>
<td>Mason, 2017</td>
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<td>38</td>
<td>PAI-1</td>
<td>Tissue plasminogen activator inhibitor</td>
<td>Markers of endothelial dysfunction</td>
<td>Mason, 2017</td>
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<td>39</td>
<td>NPA</td>
<td>Natriuretic peptide A</td>
<td>Release in response to elevation in LV filling pressure and wall stress</td>
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<td>40</td>
<td>SAA1</td>
<td>Serum amyloid A2</td>
<td>Direct promotion of vascular dysfunction through vascular tissues</td>
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<td>41</td>
<td>SLC6A4</td>
<td>Serotonin transporter</td>
<td>Abnormalities</td>
<td>Bozes et al., 2012</td>
</tr>
</tbody>
</table>

**References:**
Uses: marine anti-fouling paints, antifungal, plastics stabilizer

- **Oxidative stress**: HepG2; AC50 = 0.097 uM
- **Mito Dysfunction**: MMP in HepG2; AC50 = 0.086 uM
- **Tissue Factor**: LPS-activated HUVECs; down-regulation; AC50 = 0.012 uM
- **Endothelial cell activation**: activated HUVECs; down-regulation; AC50 = 0.010-0.029 uM
- **PAI-1**: bronchial epi cells; down-regulation; AC50 = 0.023 uM
- **ICAM-1**: cytokine-activated HUVECs; down-regulation; AC50 = 0.014 uM
Complex In Vitro Systems

- Metabolic activation of toxicity
- Hepatic filtration & metabolism
- Cellular & molecular mechanisms of pathophysiological response
- Human translation

Human Microphysiological System Exploration & Qualification
- Assays & Analytics
- Application & Human Translation

- Cardiovascular injury
- Cellular & molecular mechanisms of pathophysiological response
- Human translation

- Renal toxicity of the proximal tubule
- Proximal tubule transport & metabolism
- Renal clearance & bioaccumulation
- Human translation

Lin et al. 2019
In Vitro Models of Human Disease

- Disease state susceptibility (Hypertrophic Cardiomyopathy, Long QT syndrome, dilated cardiomyopathy etc.)
- Inflammation
- Fibrosis
- Hypoxia, I/R injury

- Hepatocellular carcinoma (HCC)
- Susceptibility from non-alcoholic fatty liver disease, hyperglycemia
- Fibrosis
- Genetic disorders & metabolism
- Interindividual susceptibility

- Renal proximal tubule
  - Chronic hyperglycemia
  - Hypoxia
  - Dehydration & CKDu
  - Fibrosis

- Renal cell carcinoma (RCC)
- Genetic disorders
Data Integration and Modeling

- HTS • Multi-Omic • Microbiome

- Translation
- Prediction
- Genome-Scale
- Kinetic
- Sex as a biological variable
- Population variability and susceptibility
CV Hazards of HIV Therapeutics

SD Rats dosed by gavage beginning at GD6

Test agent = HIV triple drug combination
Dobutamine = beta-adrenergic agonist; positive inotrope
dP/dt+ = measure of contractile performance
dP/dt- = measure of myocardial relaxation

Vehicle Group

- no DOB
- 1 mg/Kg/min DOB
- 3.3 mg/Kg/min DOB
- 10 mg/Kg/min DOB

High Dose Group

- no DOB
- 1 mg/Kg/min DOB
- 3.3 mg/Kg/min DOB
- 10 mg/Kg/min DOB

Dams @ weaning

Test agent = HIV triple drug combination
Dobutamine = beta-adrenergic agonist; positive inotrope
dP/dt+ = measure of contractile performance
dP/dt- = measure of myocardial relaxation
CV Hazards of HIV Therapeutics

SD Rats dosed by gavage beginning at GD6

Pups @ weaning

Test agent = HIV triple drug combination
Dobutamine = beta-adrenergic agonist; positive inotrope
dP/dt+ = measure of contractile performance
dP/dt- = measure of myocardial relaxation
• Tox21 partner project testing an *in vitro* DO panel of unique neural progenitor cell lines for determining empirically based toxicodynamic variability factors.
  
  – Variability in cytotoxicity data, was comparable to that seen with human cells lines
  
  – Current work using cell painting data in over 100 DO cell lines to investigate sub-cytotoxic effects that can be quantified using high content imaging.

• Utility of DO to assess population variability *in vivo* for select agents for hazard ID, characterization and dose-response
  
  – JAX collaboration for short term toxicity studies in DO mice

Unpublished data provided by Alison Harrill (NICHD)
Integrative Physiological Monitoring

Animal study outcomes can be significantly improved by contextualizing mechanistic outcomes in a dynamic and continuous assessment of physiology and behavior

• Utilizing a holistic approach that is
  – Integrative
    • Expanded focus beyond a single organ system
  – Translational
    • Focused on translational clinically relevant endpoints
  – Continuous and automated
    • Leveraging emerging technologies to collect more data in an automated way
• Collaboration with DIR investigators and other ICs
  – Establishment of a dedicated animal research core at NIEHS
Artificial Intelligence in Toxicologic Pathology

- Artificial Intelligence (AI) now routinely used in diagnostic toxicologic pathology
- Automated, faster, reduce costs, improve diagnostic accuracy, consistency, and workflow
- Being used to screen, detect, and diagnose histopathological lesions
- Establishing an AI Core in CMPB to use this innovative technology for DNTP/NIEHS
  - PhD contractor scientist hired to provide expertise
  - Initiated a continuing education seminar series in AI in summer 2021
- Completed a study developing and training an AI algorithm to diagnose mouse lung tumors
Linking Exposures to Disease

DoD Serum Repository (DoDSR)

65,000,000 serum specimens collected longitudinally

Molecular Signatures: Proteomics, Metabolomics, cfcDNA, Epigenetics, Mutations

Understand

Exposures

VA Longitudinal Exposure Record (ILER) Database
- The Airborne Hazards and Open Burn Pit Registry
- The Gulf War Registry
- The Depleted Uranium Follow-Up Program
- The Toxic Embedded Fragment Surveillance Center
- The Agent Orange Registry
- The Ionizing Radiation Registry

Pre-Neoplastic Pathobiology

Predict

Disease outcomes

Automated Central Tumor Registry (ACTUR)

DNTP TTP
• There is a long history of innovation at DNTP where we’ve actively and continuously refined our organizational processes and structure as well as been leaders in developing novel approaches to environmental hazard assessment.

• Despite the innumerable distractions of the last few years, we’ve significantly increased our efforts to innovate the way toxicology is applied in hazard identification and characterization.
  – We’ve embraced our intent to be more predictive and translational.

• All of our efforts to innovate the way we operate and execute our science are aligned to contemporary problems we’re trying to solve.

• We look forward to sharing the outcomes of these efforts as we share the progress and outcomes of our strategic and prioritized portfolio.
Thank you!

Questions?