"DNT4 - Toward Adverse Outcome Pathways and Fit-for-Purpose Assays for DNT"

Monday, May 12th 2014

9:00-10:00 Breakfast

10:00-10:20 Welcome
Helena Hogberg and Alan Goldberg, CAAT, Johns Hopkins University

10:20-10:40 Keynote lecture: The critical importance of the adverse outcome framework in linking DNT research to regulatory needs
Kevin Crofton, USEPA

10:20-10:40 Discussion

Session 1: New concepts and test strategies
Chairs: Helena Hogberg and Alan Goldberg

This session will expand on the OECD concept of AOP and present AOPs for DNT based on a workshop held by the European Commission. Mechanisms of DNT and how to apply mechanistic data to identify DNT will be presented.

10:50-11:10 The concept of the adverse outcome pathway (AOP) applied to developmental neurotoxicity evaluation
Anna Price, European Commission, Joint Research Centre

11:10-11:20 Discussion

11:20-11:40 Refreshment Break

11:40-12:00 Molecular mechanisms triggering Developmental Neurotoxicity (DNT)
Ellen Fritsche, IUF - Leibniz Research Institute of Environmental Medicine

12:00-12:10 Discussion

12:10-12:30 Strategy for applying mechanistic data to identify gene-environment interactions of relevance to DNT
Pamela Lein, University of California - Davis

12:30-12:40 Discussion

12:40-1:30 Lunch

Session 2: Mechanistic and omics tools, as well as functional endpoints, to increase assay information content
Chairs: Marcel Leist and Andrea Seiler

This session will explore the use of different approaches for DNT testing. Breakout groups will discuss the most important research gaps, identify convergent mechanisms of DNT, and discuss how 'omics' and other mechanistic approaches can be used to provide maximum information.

1:30-1:50 **Using the zebrafish model system and –omic tools in DNT studies**
Jennifer Freeman, Purdue University

1:50-2:00 **Discussion**

2:00-2:20 **The European Commission funded project DENAMIC: Developmental neurotoxicity assessment of mixtures in children**
Milou Dingemans, Utrecht University

2:20-2:30 **Discussion**

2:30-2:50 **DNTox-21c 3D brain models and omics toward POT identification.**
Lena Smirnova, CAAT, Johns Hopkins University

2:50-3:00 **Discussion**

3:00-3:20 **Refreshment Break**

3:20-4:50 **Breakout groups**
- Identify the most important research gaps to understand DNT
- Identify convergent mechanisms of DNT
- What are the advantages and disadvantages of 'omics' vs. traditional cell assays?
- How can we identify AOPs?

4:50-5:10 **Refreshment Break**

5:10-6:10 **Report from breakout groups**

6:10-8:00 **Reception and Poster Session**

Tuesday, May 13th 2014

8:00-8:30 Breakfast

8:30-8:50 Keynote lecture: Use of transcriptomics approaches in human cell-based DNT testing
Marcel Leist, University of Konstanz

8:50-9:00 Discussion

Session 3: How to accelerate testing for DNT
Chairs: Thomas Hartung and Ellen Fritsche

This session will discuss the need for testing large numbers of chemicals and how to accomplish it. Which assays can be used in a multi-lab-style assessment and what are the quality criteria for an assay for qualification? How do we attract sponsors to fund assay evaluation by testing an extended set of reference of chemicals? What would be the structure and what should be included in a publicly available database of existing DNT data?

9:00-9:20 Screening and prioritization for developmental neurotoxicity testing using *in vitro* and alternative animal models
Mamta Behl, NTP, NIEHS

9:20-9:30 Discussion

9:30-9:50 Testing chemicals for developmental neurotoxicity at the USEPA
William Mundy, USEPA

9:50-10:00 Discussion

10:00-10:20 Assessment of Chemical Effects on Neuronal Network Function Using Microelectrode
Timothy Shafer, USEPA

10:20-10:30 Discussion

10:30-10:50 Refreshment Break

10:50-12:20 Breakout groups

- How to define reference chemicals
- Potential sources for funding (could also be part of general discussion)
- Which criteria for assays to enter the test battery?
- How can test battery results be used for better information on assays?
- How can test battery results be used for better information about chemicals?
- Development of a database with DNT data - what will be the structure and what should be included?

12:20-1:10 Lunch

1:20-2:20 Report from breakout groups

2:20-2:40 Keynote Lecture: How does FDA use mechanistic data for regulatory decision making?
William Slikker, FDA, NCTR

2:40-2:50 Discussion

Session 4: The use of AOPs and alternative assays for safety assessment
Chairs: Anna Price and William Mundy

This session will discuss how AOPs and alternative assays can be used for safety assessment. What are the regulatory needs and how do our approaches meet the regulatory requirements?

2:50-3:10 Using alternative assays in risk assessment: DNT considerations
Anna Lowit, Health Effects Division, USEPA

3:10-3:20 Discussion

3:20-3:40 Integrated Testing Strategies (ITS)
Thomas Hartung, CAAT, Johns Hopkins University

3:40-3:50 Discussion

3:50-4:10 Refreshment Break

4:10-5:40 Breakout groups
- How can AOPs and alternative assays change regulation?
- How do our approaches meet the regulatory requirements?
- What are the gaps?

5:40-6:40 Report from breakout groups

Wednesday, May 14th 2014

8:00-8:30 Breakfast

8:30-8:50 Keynote Lecture: Towards predictive *in vitro* testing strategies for chemical-mediated developmental neurotoxicity (DNT): A complex toxicological endpoint tackled by the German BMBF joint project
Andrea Seiler, Federal Institute for Risk Assessment

8:50-9:00 Discussion

Session 5: Frontiers in DNT testing
Chairs: Timothy Shafer and Mamta Behl
What are the new cutting-edge technologies for DNT?

9:00-9:20 Revolutionizing toxicity testing for predicting developmental outcomes
Nisha Sipes, ORISE Fellow at USEPA

9:20-9:30 Discussion

9:30-9:50 Characterization of a Brain Microphysiological System for Studying Gene/Environment Interactions
David Pamies, CAAT, Johns Hopkins University

9:50-10:00 Discussion

10:00-10:20 Refreshment Break

10:20-10:40 3D neural tissues derived from human embryonic stem cells and IPSC as in vitro models for developmental neurotoxicity studies
Luc Stoppini, Hepia, University of Applied Sciences Geneva

10:40-10:50 Discussion

10:50-11:10 A tomographic tool for pancellular assessment of tissue architecture
Keith Cheng, Penn State College of Medicine

11:10-11:20 Discussion

11:20-12:40 Panel and Plenary discussion "Where are we at DNT4?"
Panel: Steering Committee
Moderator: Alan Goldberg, CAAT, Johns Hopkins University

What has changed since DNT3? Make a gap analysis, a test battery definition, structure of a report.

12:40-1:00 Toward DNT5
Helena Hogberg, CAAT, Johns Hopkins University

1:00-2:00 Lunch

2:00-4:00 Steering group meeting – closed