Overview of NICEATM Activities

Validation Strategies for Tox21

The Tox21 High Throughput Screening (HTS) program represents a new paradigm in toxicological testing. The HTS approach to toxicological testing screens ~10K chemicals for mechanistic targets active within cellular pathways considered critical to adverse health effects such as carcinogenicity, reproductive and developmental toxicity, genotoxicity, neurotoxicity, and immunotoxicity in humans. Validation approaches are currently being explored by NICEATM that would allow HTS data to be used in a regulatory context. These proposed approaches, along with relevant examples, will be discussed.

Endocrine Disruptor Screening Program (EDSP)21

The EDSP21 Work Plan describes an approach for using computational and/or *in silico* models and molecular-based *in vitro* high-throughput assays to prioritize and screen chemicals to determine their potential to interact with the estrogen, androgen or thyroid (E, A, or T) hormonal systems. The President's proposed fiscal year 2012 budget for the agency states that "In FY 2012, EPA will begin a multi-year transition from the EDSP to validate and more efficiently use computational toxicology methods and high throughput screens that will allow the agency to more quickly and cost-effectively assess potential chemical toxicity" (President's Budget FY2012). NICEATM has recently (August 2013) been asked by EPA to provide support in the validation of methods and approaches used in the EDSP21 Work Plan. Details of the collaboration are still under discussion.

Developing an Open-source R Version of a Bayesian Network Based Integrated Testing Strategy

A Bayesian network (BN) based integrated testing strategy (ITS) for skin sensitization has been presented (Jaworska et al., 2013). In this model, *in silico* sensitization predictions, bioavailability information, and results from several assays that cover mechanistic steps relevant to skin sensitization, and map to the adverse outcome pathway approved by the Organization for Economic Co-operation and Development (OECD), are structured into a probabilistic framework that facilitates complex reasoning about the hazard of a chemical given the available evidence. The original models were developed using a commercial (proprietary) software package. While the commercial software is a powerful environment for working with Bayesian networks, it is not available to a large percentage of the population interested in applying the ITS. In addition, several key calculations in the commercial software are performed via "black box" algorithms that do not allow the user access to the equations or assumptions being used for the calculations. The limited availability of software tools for developing and evaluating Bayesian networks makes it difficult for an interested user to test, verify, and build upon the stated assumptions of analysis performed by other groups. In response, NICEATM (via support from Integrated Laboratory Systems, Inc. and Social and Scientific Systems, Inc.) in collaboration with Jaworska et al., have produced a version of the Bayesian network ITS using the free and open-source statistical programming language R. This version provides complete transparency and represents a major step in making the model reproducible and accessible to others. The modular nature of the network also allows for performance based analysis of various *in silico* and *in vitro* alternative models that serve as inputs to the ITS.

Planned Workshops

- Translational Alternative Models and Biomarkers Predictive of Drug or Chemical Cardiovascular Risk (October 2013, presented by NICEATM and EPA)
- Zebrafish workshop at North Carolina State University (Spring 2014, sponsored by NIEHS, EPA, FDA, and NCSU)

Validation of Alternative Methods Through a Phase IIb Grant Mechanism

The goal of the Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) programs to develop commercializable products is often hampered by the "Valley of Death," i.e., the gap in funding between development of assays and the commercialization phase. Validation efforts are usually beyond the scope of a Phase II grant and often require additional time and effort to carry out studies needed for commercialization and acceptance by regulators and the end-user communities. NIEHS has implemented a Phase IIb mechanism that allows small businesses with Phase II grants to apply for up to 3 years of support (up to $1M/year) for developing products that require approval of a regulatory agency and for facilitating the transition of the SBIR Phase II projects to the commercialization stage. As a condition of the Phase IIb grant, test method sponsors would be required to consult with NICEATM throughout the validation process. The objective of these interactions is to maximize the likelihood that validation studies and submissions will adequately characterize the usefulness and limitations of the proposed test method and will ultimately be accepted by both industry and regulators.