IVIVE for High-Throughput Prioritization and Decision Making

Day 1 Wrap-Up

Barbara A. Wetmore, Ph.D.
ScitoVation

February 17, 2016

In Vitro-to-*In Vivo* Extrapolation for High-Throughput Prioritization and Decision-Making

- Webinars: First Wednesdays, 11:00AM E.D.T.
  - October 7 – Barbara Wetmore: Setting the Stage
  - November 4 – John Wambaugh: Model Development
  - December 2 – Lisa Sweeney: Model Evaluation
  - January 6, 2016 – Corey Ellison: Internal TTC

- In-person Meeting: February 17-18, 2016
  - US EPA, Research Triangle Park, NC

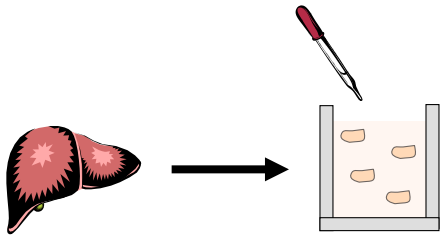
In Vitro - *In Vivo* Extrapolation

Definition: Utilization of *in vitro* experimental data to predict phenomena *in vivo*

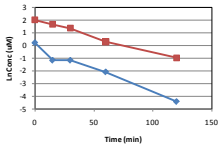
- **IVIVE-PK/TK (Pharmacokinetics/Toxicokinetics):**

  Fate of molecules/chemicals in body
  - Considers ADME; uses PK / PBPK modeling
- **IVIVE-PD/TD (Pharmacodynamics/Toxicodynamics):**
  Effect of molecules/chemicals at biological target *in vivo*
  - Assay design/selection important; perturbation as adverse/therapeutic effect, reversible/ irreversible
- **Both contribute to predict *in vivo* effects**

Population-based *In Vitro-In Vivo* Extrapolation

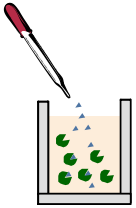


Primary Hepatocytes

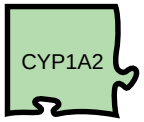


Hepatic Clearance
$Cl_{in\ vitro}$

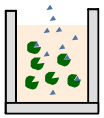
Plasma C_{ss}
General Population
Plasma C_{ss} for:



rCYP1A2

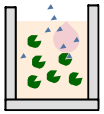


$Cl_{rCYP1A2}$



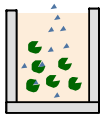
rCYP3A4

$Cl_{rCYP3A4}$



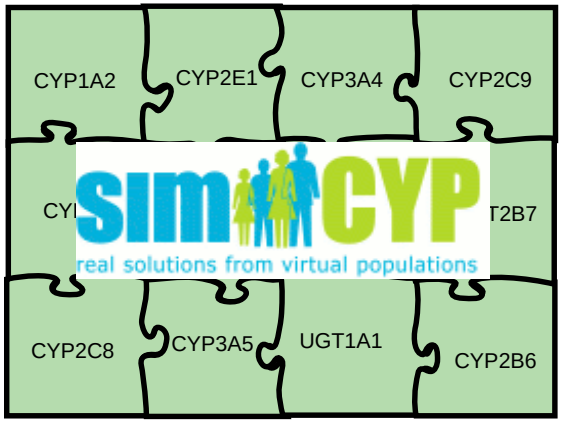
rCYP…

$Cl_{rCYP…}$



rUGT …

$Cl_{rUGT…}$



Intrinsic Clearance Rates

Neonates

Asians

Northern Europeans

Children

And so on…

In Vitro Assays - Considerations Relevant for IVIVE to Predict Chemical PD/TD

- Span from cell-free to immortalized lines to physiologically relevant systems
- Consideration of relevant mass balance / uptake issues
- Coverage of biological space?
  - Suite of relevant assays
  - Genomics/transcriptomics
  - Sufficient coverage across potential adverse outcomes?
- Ability to discriminate reversible perturbation from irreversible effect, potential adverse outcome
- Temporality – relating in vitro to in vivo

Day 1 Take-Home

- Terminology
- Fit for (what) purpose?
- Domain of applicability
- Multidisciplinary efforts and collaboration key
- Education and Re-education
- Tackling Variability…
- Solely in vitro? We are not there yet…
- Value in parallelogram; tiered approaches; frameworks
- Although many gaps and considerations exist in applying IVIVE to inform TK and TD issues in prioritization and decision-making, many of these can – and are – being addressed.

Day 2: Breakout Sessions

- **90 minutes** each, a projector and note taker will be available in each room
- Participants will be allowed to choose which session they want to attend and may change rooms
- Breakout group leaders will be asked to summarize the breakout group discussion in preparing a section for the workshop report

Guiding questions:

- Moderators are asked to focus conversations around the questions below.
- During the discussion, participants are asked to keep in mind:
- What are the effects/implications when considering human vs rat values, non-animal vs in silico
- How are we defining the purpose in fit for purpose and what are the implications for using the approach or assumption in each application (prioritization/screening/risk assessment)

-- Day 2 Breakout Sessions --

Session		A: TK model considerations	B: In silico and non-animal methods for obtaining TK parameters	C: Application to prioritization /screening/ risk assessment
		Annie Jarabek, EPA Alicia Paini, EURL ECVAM	John Wambaugh, EPA Nisha Sipes, NIEHS	Scott Lynn, EPA Nicole Kleinstreuer, NICEATM
AM1	1	What needs to be done to determine the state of the science (including current toolbox)? How well are these tools working for understood chemicals / kinetic processes?	What experiments/methods are needed for determining oral bioavailability? What about methods for other routes of exposure?	Who are the stakeholders? What are their needs? How do their needs vary?
AM1	2	What are the pros and cons of a simple (1 compartment) model? How do we assess when models are good enough?	What is best practice for rapidly parameterizing a model? How should confidence in these parameters be evaluated and reported?	How do we increase buy-in and what are the training needs? On regulatory and industry side? How do we build capacity and what resources are needed?
Break				
AM2	3	How can the in vitro output be related to the in vivo toxicity/adverse outcome?	How do we define the domain of applicability for the in silico models? How should this be evaluated and reported?	Can IVIVE refine how default uncertainty factors are applied? Can it be used to develop data-driven uncertainty factors (interspecies and inter-individual)?
AM2	4	How do we validate methods and approaches (context, limitations, scope)?	How do we store/share models and information/data? What reporting requirements are needed? Do existing reporting formats currently exist, or can existing formats be changed to meet our needs?	What are the requirements or implications for use in prioritization/regulation? What areas are ready to incorporate IVIVE in the short-term? Long-term?