NTP’s Proposed Approach to Study Design for Genomic Dose-Response Modeling

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• Traditional toxicity assessments are designed/powered for pairwise statistical analysis with the goal of identifying No Observed Effect Levels
  – Example design: 3 dose levels and control, 10 biological replicates/dose group

• This approach is often not conducive to applying a Dose-Response modeling approach such as Benchmark Dose
  – Not enough dose levels to estimate an acceptable curve fit, particularly when there is little prior knowledge of the dose-response relationship

• For GDRS studies NTP proposes to use a BMD focused study design
  – More dose levels fewer biological replicates
  – Example design: 10-12 dose levels, 3 biological replicates/dose group
  – Will allow for better coverage of the numerous dose-response relationships in each study, more confident fits of the data and greater certainty in the BMD estimates for the features
**Sex/Strain/Species:** Male Sprague Dawley Rat

- Historical precedent, Legacy data that will help with interpretation

**Duration:** 5 Days (5 doses, 1 per day, Euthanize 24 hours after last dose)

- Thomas *et. al*, 2013, showed transcriptional POD from 5 days approximated PODs from apical endpoints including cancer

**Target Organ Selection:** Liver and expert selected targets

- Most studies will be done by the oral route
- Liver is common target organ and often responds to effects in other organs/tissues
- Other organs selected based on expert review of available data

**Top dose selection:** 5 day Maximum Tolerated Dose

- To ensure clear response at the top dose level and ensure the identification of responsive features and improved model fitting
In Vitro Study Design Parameters

- **Species**: Human
  - Tox21 is focused on modeling human responses
- **Sex**: Determined by availability
- **Duration**: Expert determination
  - Goal: Employ timepoint that maximizes response to test article
- **Cell Type(s)**: Organotypic, Commonly Used, Broad Query Biological Space
  - Better modeling of target tissue responses, link/leverage existing data, diversity of response
- **Top dose selection**: LC20 (where feasible)
  - Allows more effective identification of responsive features which can then be modeled more accurately in the lower dose range
• BMD-centric design

• In vivo parameters
  – Male rats, 6-8 weeks of age
  – 5 day repeat dose
  – Liver and other expert selected organs
  – Use of a 5 day maximum tolerated dose

• In vitro parameters
  – Organotypic culture
  – Top dose selection: LC20

• Other variables to consider
  – More time points?
  – Identifying response maximum?
  – Link cause and effect?
  – Phenotypic anchoring?