NTP
National Toxicology Program

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

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Expert Panel Meeting on the Peer Review of Draft NTP Approach to Genomic Dose-Response Modeling
October 25, 2017

Study Design

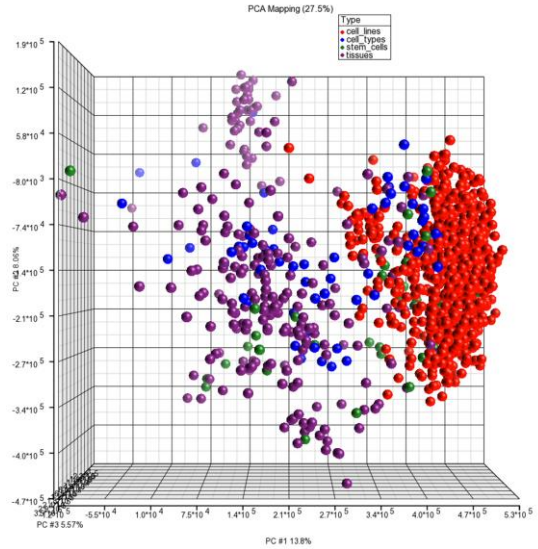
- Traditional toxicity assessments are designed/powered for pairwise statistical analysis with the goal of identifying No Observed Effect Levels
  - Example design: 3 dose levels and control, 10 biological replicates/dose group
- This approach is often not conducive to applying a Dose-Response modeling 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

In Vivo Study Design Parameters

- **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

Points to Consider

- 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?