Overview of the NTP Proposed Approach to 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 23, 2017
Overview of Approach GDRS

**Study Design**
Many dose levels, limited biological replication, select target organs/cell types

**Filtering Measured Features**
Statistical and effect size filter

**Fitting Features to Dose-Response Models**
Fit multiple models, determine potency using best fit model

**Determination of Gene Set Level Potencies**
Identify “active” gene sets, report potency for active gene set

**Biological Interpretation**
Use detailed curation of gene sets to provide toxicological associations/contextualization
**NOEL/LOEL vs BMD Design**

**Benchmark Dose**
- **Goal:** Accurately determine a point of departure
- **Example:** 9 Dose Levels and Control
  - 3 Biological Replicates
- Derives power from using all of the data and a fitted model to identify a minimum effect level (point of departure)
- More effective at capturing a diversity of dose-response patterns and potencies in the same study
- **Shortcoming:** Limited ability to detect hazards

**NOEL/LOEL**
- **Goal:** Identify hazards
- **Example:** 4 Dose Levels and Control
  - 6 Biological Replicates
- Derives power from high biological replication which allows for robust pairwise comparisons (treated vs control)
- More effective at identifying low incidence hazards
- **Shortcoming:** Due to limited number of dose groups often does not support dose-response analysis and accurate estimation on minimum effect levels

**Conclusion**

Our goal with GRDS to accurately estimate the minimum biological potency, not to detect hazards. In addition, we will fit a diversity of features from a single study with an array of potencies with the hope of accurately estimating their POD. For this reason we have chosen the Benchmark Dose Approach.
Identified ~100 microarrays from vehicle treated rat liver (TG-Gates, 7 day) with no batch effect – http://toxico.nibio.go.jp/english/index.html

Randomly sample arrays to create 5 null data sets of 30 microarrays
- Dose levels 0, 0.1, 1, 10, 100, 1000
- 5 samples per dose group

Ran null sets through BMDExpress using no statistical/effect size filter
- Instead a global goodness of fit statistic (p>0.1) and BMDL/BMD ratio<20 to the dose-response model was used to remove features

<table>
<thead>
<tr>
<th>Null Set</th>
<th>ANOVA (FDR&lt;0.05) (31,000)</th>
<th>Individual Genes (n=14073)</th>
<th>GO BP (n=12355)</th>
<th>MSigDB Pathways (n=4725)</th>
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**Conclusion**
We need some sort of filter other than the global goodness of fit filter and the BMD/BMDL ratio
• Why use the US EPA models?
  – They are validated
  – They are used broadly in risk assessment to derive potencies (BMD)
    • Our target audience is comfortable with the BMD metric and the modeling process
  – Diversity of models allows for adequate fitting of variety of dose response patterns
  – Great documentation and guidance on how to use the models
Why use gene sets?

- Better coverage of biological space
  - Less blind spots in uncharacterized biological settings
- Gene sets better represent the underlying totality of the emergent properties at the cellular and tissue level
- Gene sets give a better representation of the uncertainty in biological potency
Why attempt biological interpretation?

- Facilitate uptake by the toxicology community
- A degree of consensus exists as to interpretation of subset of gene signatures and biological processes
- Start the process of building some consensus in regard ranking levels of toxicological “distress” when a gene set is altered by treatment
  - P53 vs. Xenobiotic Metabolism
- Importantly, interpretation will not be used for traditional hazard labeling at this time
• Overall Analysis Approach and Design: NOEL/LOEL approach vs. BMD
• Statistical and effect size filtering: To do it or not?
• Dose-response modeling: Type and how many?
• Potency reporting: Gene sets vs. Genes
• Biological interpretation: Do it or not?

• Variables to consider?
  – Better established define how data will inform screening level risk assessment?
  – Greater detail biological interpretation and engagement of the toxicology community?