The DrugMatrix® Database

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Disclaimer

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Outline

• Part 1: Overview of DM

• Part 2: Example Application of DM in a Short-term Toxicity Assessments
Part 1: Overview of DrugMatrix

- Gene Expression Profiles
  - CodeLink RU1 10K rat array
  - Affymetrix Whole Genome Arrays

- Pharmacology Profiles
  - Binding, Enzyme, ADME

- Pathology Profiles
  - Histopathology
  - Clinical chemistry
  - Hematology
  - Body and organ weights

- Literature Profiles
  - Pharmacology
  - Toxicology
  - Structure
  - Pathways

Benchmark Drugs and Compounds

Pathology Assays

Pharmacology Assays
DrugMatrix

- DrugMatrix
  - Large-scale Rat Toxicogenomics Database and Analysis Tool

- Originally owned by Iconix Pharmaceuticals and Entelos, Inc.
  - No data for these resources were generated by NTP

- Acquired by NTP in late 2010
Goals of Acquisition

• Make the computational and data resources open to the public (no fee)

• Facilitate the integration of toxicogenomics into hazard characterization

• Build a bridge between traditional toxicology and Tox21
DrugMatrix Database Content

~ 700 Short-term toxicity studies (0.25 to 5 days) in male SD rats
~ 637 compounds studied at multiple doses, time points and tissues
~ 5600 drug-treatment transcript profiles
~ 13,000 Codelink RU1 Microarrays
~ 5,000 Affymetrix RG230-2 Arrays
~ 127,000 histopathology measurements
~ 150 histopathology diagnoses over 7 tissues
~ 100,000 hematology and chemistry measurements
~ 138 hand annotated pathways
~ 290 scorable genomic signatures
~ 2500 pathway-based scorable signatures
~ 130 in vitro assays
~ 900 chemicals with detailed literature curation
~ 8000 chemical structures
~ 60,000 literature facts
~ 123,000 frozen samples
DrugMatrix Chemical Diversity

- 637 Compounds
- US FDA approved drugs, 433, 68%
- Standard biochemical, 15, 2%
- Approved outside of US, 63, 10%
- Standard toxicant, 72, 11%
- Withdrawn or discontinued drug, 54, 9%
DrugMatrix Data

- ftp://anonftp.niehs.nih.gov/drugmatrix
- Unprocessed microarray data
- Microarray data normalized by organ
- Individual animal toxicology data
- In vitro screening data
- Chemical Annotations
DrugMatrix Functionality and Analysis Tools

• Upload your own data for analysis or mine the DrugMatrix data
  – Data you upload is private – not shared with the government or other users

• Contextualize your data relative to over 4000 expression profiles elicited by >600 well characterized, phenotypically anchored prototype agents

• Find similar expression profiles

• Determine significantly up and down regulated genes

• Perform gene ontology analysis of perturbed genes

• Visualize expression profiles on pathways

• Score expression profiles for >50 phenotypes with genomic signatures

• Construct expression patterns for putative biomarker sets

• Test the performance of biomarker sets for detecting phenotypes

• Find consistently changed genes

• Identify enriched literature annotations in groups of expression profiles

• Mine the literature
Part 2: Example Application of DrugMatrix

Toxicogenomic Assessment of DE-71
(Study Scientist: Dr. June Dunnick)
DE-71: A mixture of polybrominated diphenyl ethers

- PBDEs are flame retardant components that bioaccumulate; persistent organic pollutants
- Widespread human exposure
Gene Expression Study design

- Dose level: 0 or 50 mg/kg/day
- Route: Oral Gavage (corn oil)
- Model: Male Wistar Han rats
- Exposure period: gestational day (GD) 6 to postnatal day (PND) 21
- Euthanized: PND 22
- Tissue evaluated: Liver
- Question: What are the potential toxicological effects of DE-71 that can be identified by toxicogenomics?
- DE-71 expression studies are not included in DrugMatrix Database
### DrugMatrix Analysis of DE-71- Top DEGs (Liver)

**Induced**
- Cyp1a1, Cyp2b, Cyp2c

**Repressed**
- Fgf21, Cyp17a1, Abcg8
DrugMatrix Analysis of DE-71- Signature Scoring

### Table: DE71_21.0D_50.OMG/KG_LIVER

<table>
<thead>
<tr>
<th>Signature Name</th>
<th>SP Score</th>
<th>Posterior</th>
<th>Logit</th>
<th>Derivation</th>
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<tr>
<td>Hepatic hypertrophy, centrilocular LIVER RG230-2 ASPLP ToxFX,1.2.4</td>
<td>2.668</td>
<td>0.999835654...</td>
<td>6.9067547...</td>
<td>RG230-2</td>
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<td>Hepatic lipid accumulation, centrilocular LIVER RG230-2 SPLP ToxFX,1.2.4</td>
<td>0.93</td>
<td>0.902890876...</td>
<td>2.2297663...</td>
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<td>Hepatic lipid accumulation, macrovesicular LIVER RG230-2 ASPLP ToxFX,1.2.4</td>
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<td>1.9347802...</td>
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<td>Hepatic lipid accumulation, periportal LIVER RG230-2 SPLP ToxFX,1.2.4</td>
<td>0.192</td>
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<td>1.2432892...</td>
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<td>Hepatomegaly LIVER RG230-2 ASPLP ToxFX,1.2.4</td>
<td>0.292</td>
<td>0.775934833...</td>
<td>1.2421316...</td>
<td>RG230-2</td>
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### Images:

Rat Liver - Oil Red O

DrugMatrix Analysis of DE-71- Chemical Enrichment Analysis

- Chemical ontology enrichment analysis of the top 25 most similar expression studies (Hypergeometric Analysis)

<table>
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<tr>
<th>CATEGORY</th>
<th>TERM</th>
<th>PVALUE</th>
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<tbody>
<tr>
<td>MECH_LEVEL_3</td>
<td>aromatase *</td>
<td>4.17E-06</td>
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<tr>
<td>MECH_LEVEL_2</td>
<td>Inhibit estrogen biosynthesis *</td>
<td>4.44E-06</td>
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<tr>
<td>SOLVENT</td>
<td>CMC .5 %</td>
<td>8.35E-06</td>
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<tr>
<td>ADVERSE_EFFECT</td>
<td>BBM_2_Bone Marrow Toxicity</td>
<td>1.07E-06</td>
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<tr>
<td>ADVERSE_EFFECT</td>
<td>NEU_1_Ataxia</td>
<td>3.35E-06</td>
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<tr>
<td>ADVERSE_EFFECT</td>
<td>END_2_Acute Intermittent Porphyria</td>
<td>1.07E-06</td>
</tr>
<tr>
<td>ADVERSE_EFFECT</td>
<td>KID_3_Acute Tubular Necrosis</td>
<td>1.07E-06</td>
</tr>
<tr>
<td>STRUCTURE_ACTIVITY</td>
<td>NSAID, COX-3, antipyrine like</td>
<td>1.07E-06</td>
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<tr>
<td>STRUCTURE_ACTIVITY</td>
<td>Estrogen antagonist, aromatase inhibitor *</td>
<td>6.99E-07</td>
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* DE-71 has been shown to alter aromatase activity in number of studies
DrugMatrix Analysis of DE-71- Pathway Analysis

<table>
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<th>Pathway</th>
<th>% Gene Changed in Pathway</th>
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<tr>
<td>Cholesterol Biosynthesis</td>
<td>75</td>
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<tr>
<td>Xenobiotic Metabolism</td>
<td>52</td>
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<tr>
<td>Bile Acid Synthesis</td>
<td>50</td>
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*Multiple subchronic studies have observed increases in serum cholesterol following DE71 exposure*
Part 2: Conclusions

• Identified 3 hepatic/non-hepatic toxicological effects of DE-71
  – Steatosis
  – Repro-related endocrine perturbations
  – Alterations in lipid homeostasis
  – Overall profile suggests DE-71 may exacerbate metabolic syndrome

• Suggestion of an AhR, CAR/PXR related MOA

• Helps focus future toxicological assessments
## Acknowledgments – Iconix and Entelos

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