Biomarkers To Improve Safety/Efficacy Prediction

Pediatric Medical Countermeasures

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Views expressed in this presentation are those of the presenter and not necessarily those of the U.S. Food and Drug Administration
Outline

• Improve Species Extrapolation
  – Genomics

• Aging and Drug Sensitivity
  – Genomics and Metabolomics
Hepatotoxicity

• Testing in animals identifies many toxic drugs but not a complete safety net
  – ~50% of drugs that cause human hepatotoxicity were not detected in preclinical animal testing

• ~1% of hospitalized patients develop drug-induced liver injury (DILI)

• Liver injury in humans linked to ~1000 drugs

Global Similarities in Gene Response Upon *In Vivo* Exposure

Each column = 1 gene

Prediction of Hepatotoxicity

• Genomics can classify compounds accurately with *in vitro* and *in vivo* approaches

• Very different biomarkers

Martin et al., Pharmacogenomics 7:1003-1016, 2006
Aging and Drug Sensitivity

Genomics

Metabolomics
Principal Components Analysis

Normal F344 rats

Differentially expressed genes (3,770)

= 1 animal

Male

Female

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Age Susceptibility to Gentamicin

6 days of treatment
50 mg/kg/day
Small subset of large study

<table>
<thead>
<tr>
<th>Biomarkers of Gentamicin</th>
<th>Age of Rats</th>
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<tbody>
<tr>
<td></td>
<td>25 Days</td>
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<tr>
<td>Histology</td>
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<td>Serum Creatinine</td>
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<td>BUN</td>
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Principal Components Analysis
NMR Spectra

Sprague Dawley Rats
+/- Gentamicin Treatment

Metabolomics Analysis

Age separates them more than treatment
## Biomarkers of Gentamicin

<table>
<thead>
<tr>
<th>Age of Rats</th>
<th>25 Days</th>
<th>40 Days</th>
<th>80 Days</th>
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<td>Histology</td>
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<td><strong>NMR</strong></td>
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<td>Urinary Glucose*</td>
<td>-</td>
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<td>Urinary Hippurate**</td>
<td>↓</td>
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* Potential Biomarker of Nephrotoxicity
** Potential Biomarker of Efficacy
Conclusions

• Genomic profiling (cultured rat hepatocytes, rat liver) can identify hepatotoxic compounds
  – Can improve species extrapolation
  – Biomarkers may be different between *in vitro* and *in vivo*

• Genomics and metabolomics profiling can provide insight into sex- and age-specific differences

• Urinary metabolomic analysis may identify more sensitive biomarkers of injury and efficacy than routine tests
Division of Systems Biology

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Genomics

Rick Beger
Metabolomics