Analysis of human and *in vivo* data for hepatotoxicity modelling

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Development of the hepatotoxicity knowledgebase

- Currently 84 alerts (22 rapid prototypes)
- Performance against repeat dose dataset

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Sens %</th>
<th>Spec %</th>
<th>Ppv %</th>
<th>Npv %</th>
<th>Concordance %</th>
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<tbody>
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<td>45</td>
<td>75</td>
<td>52</td>
<td>70</td>
<td>64</td>
</tr>
</tbody>
</table>

- Derek Nexus v3.0.1 KB 2014_1.0.

- Alerts use a variety of supporting data
  - Mostly human

- Issues with existing *in vivo* and human data
  - lack of definitive biomarkers
  - Mechanisms intrinsic or idiosyncratic?
  - Unbalanced datasets
  - Lack of data
eTOX data

- Repeat dose studies
  - Rat
Analysis of animal or human-based terms per alert

Hepatotoxicity terms

<table>
<thead>
<tr>
<th>Alerts</th>
<th>MOA</th>
<th>Human hepatotox terms</th>
<th>Animal hepatotox terms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

Occurrences
First look at the eTOX dataset

- Real data isn’t clean or easy to model
- Many data gaps
- Lacking in histopathology
- Clustering by chemical class doesn’t reveal clear biomarkers
Conclusions

- Performance varies by dataset

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Sens %</th>
<th>Spec %</th>
<th>Ppv %</th>
<th>Npv %</th>
<th>Balanced acc %</th>
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<td>eTox622</td>
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</tr>
</tbody>
</table>

- Derek Nexus v3.0.1 KB 2014_1.0.

- Most alerts are species-specific
Performance of alerts covering hypersensitivity

- These alerts show good positive predictivity vs human data
- Evidence provided within the alert supports this
- There is limited animal data to support these alerts
  - Expected since animal models don’t predict idiosyncrasy
Our Conclusions

• Derek Nexus performs better when predicting human hepatotoxicity

• Human toxicity is less well covered by Derek alerts based upon animal data
  • No simple correlation between animal histopathology and clinical chemistry biomarkers
  • Animal toxicity is not a good predictor of human toxicity
    • Higher doses in animals may not be relevant to humans
    • Toxicity pathways are species-specific

• For hepatotoxicity are *in silico* models better predictors of human toxicity than animal studies?
• Do human-based *in vitro* assays offer better predictivity?
Investigation of *in vitro* assay data

- Alternative methods
- Analysis of *in vitro* screens
- Biological fingerprints
- Search for co-occurrences of signals amongst assays
  - Are these a stronger measure than individual signals?
Bio-fingerprints – can we extract knowledge from them?

- Bio-fingerprints were constructed
  - For each compound create an array of *in vitro* assay outcomes
  - Did the *in vitro* assay give an inactive (0) or active (1) outcome?

| Compound          | Human BEP1 (HCC) | Human BEP2 (HCC) | Human BEP1 Combined | Human BEP2 Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined | HCC Combined |
|-------------------|------------------|------------------|---------------------|---------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Carbarsone        |                  |                  |                     |                     |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Mecrobacrol       |                  |                  |                     |                     |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Framycetin        |                  |                  |                     |                     |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Anthraclin        |                  |                  |                     |                     |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Captopril         |                  |                  |                     |                     |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Estradiol         |                  |                  |                     |                     |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Nalidixic acid    |                  |                  |                     |                     |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Glycine           |                  |                  |                     |                     |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Propranolol       |                  |                  |                     |                     |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Mifepristone      |                  |                  |                     |                     |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |

[Image of a table showing results of bio-fingerprints]
We used a number of data sources

• Publications
  • Morgan et al, Toxicol Sci, 2013, 136, 216-241 (634)
  • Xu et al, Toxicol Sci, 2008, 105, 97-105 (344)
  • Pedersen et al, Toxicol Sci, 2013, 136, 328-343 (250)
  • Dawson et al, Drug Metab Dispos, 2012, 40, 130-138 (85)
  • Aleo et al, Hepatology, 2014, 60, 1015-1022 (72)

• Tox21
  • Liver relevant data (7310)

• PubChem
  • Target search (245)

• ChemBL
  • Target search (660)
Data acquisition and collation workflow

• Data sets combined, conservative call generated for each unique compound (8390)

• In vivo liver toxicity call based on Human data (2029 compounds)
  
  • Zhu and Khrulak, Toxicology, 2014, 321, 62-72
Some combinations of assays predict better than individual assays?

• While there is a statistical relationship, we will look to see if that is mechanistically valid...

• It has been proven for BSEP and Mitochondrial toxicity
Conclusions

• Derek alerts written using human data are predictive for human outcomes
• This is not so clear for Derek alerts informed by animal data
• Looking at human in vitro datasets looks promising
  • But we need to move from a statistical relationship to one based upon mechanism (AOP)
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Work in progress disclaimer

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