Extrapolation of in vitro mutagenicity alerts to the in vivo endpoint in Derek Nexus.

Rachael Tennant¹, Steven Canipa², Alex Cayley¹, Will Drewè¹, Sebastien Guesné¹, Susanne Stalhod², Richard Williams¹, Kenichi Masumura², Takeshi Morita², Masamitsu Honma².

¹ Lhasa Limited, Granary Wharf House, 2 Canal Wharf, Leeds, LS11 5PS, United Kingdom; ² National Institute of Health Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo 158-8501, Japan.

Introduction

Derek Nexus is an expert rule-based system for the prediction of toxicity. The knowledge base embedded in this software is composed of alerts, examples and reasoning rules which each contribute to the toxicity predictions made by the system. Mutagenicity alerts within Derek Nexus are primarily based on data from in vitro assays. Given the importance of assessing chemical-induced mutagenicity in vivo, structural alerts for this endpoint are currently of value. Transgenic Rodent Mutation (TGR) assays provide reliable data from which to derive these alerts. A recent collaborative project between the National Institute of Health Sciences of Japan (NIHS) and Lhasa Limited aimed to improve Derek Nexus alerts using a data set of TGR assays (Lambert et al), provided by the NIHS, in order to modify or develop new alerts to further improve the coverage of the endpoint in vivo mutagenicity in the Derek Nexus knowledge base.

Performance of Derek Nexus against the in vivo TGR assay data set before....

TGR assay dataset - 182 compounds
- Bias = 61% positive
- Sensitivity = 10%
- Specificity = 100%

How was the data analysed?

Updating an alert

Examples of modified alerts

<table>
<thead>
<tr>
<th>Alert class</th>
<th>Quinoline</th>
<th>Vic-dihalide</th>
<th>Halogenated alkene</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGR assay +ve compounds:</td>
<td>11</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>TGR assay -ve compounds:</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Positive predictivity:</td>
<td>100%</td>
<td>75%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Alert modification:
- Based on good positive predictivity and plausible mechanistic rationale, the alert was extended to predict in vivo mutagenicity of the quinoline class of compounds, with a plausible reasoning level.
- Based on equivocal activity in the TGR assay, with some rationale for in vivo mutagenicity, the alert was extended to describe such observations with a reasoning level set to equivocal.
- Based on a plausible rationale for lack of in vivo mutagenicity, the alert description comments were updated to describe inactivity of the halogenated alkene class of compounds.

Results

- 18 in vitro alerts were extended to the in vivo mutagenicity endpoint
- 1 existing in vivo mutagenicity alert was updated with examples, comments, references
- 4 in vitro alert description comments were updated to report in vivo mutagenic activity of these classes
- 1 chromosome damage alert was also extended to predict in vivo mutagenicity

Conclusion

The current approach to developing the Derek Nexus knowledge base has successfully resulted in significant improvements to the in vivo mutagenicity endpoint, reflected by a marked improvement in performance. An increase in sensitivity (from 10% to 65%) and balanced accuracy (from 66% to 77%), with only a minor concomitant reduction in specificity (100% to 89%) was achieved. There is, however, still potential for improvement in the predictions against this endpoint. The endpoint will be continually updated using newly published data and future collaborative projects.

Reference: