Addressing Toxicity Risk when Designing and Selecting Compounds in Early Drug Discovery

Lhasa Limited v ICGM, 18th June 2014

• Scott McDonald – Lhasa Limited
• Matthew Segall – Optibrium
Overview

• Lhasa and Derek
• Optibrium and StarDrop
• Derek Nexus and StarDrop
Who are Lhasa Limited

- Not-for-profit organisation
- Registered educational charity
- Controlled by our members
- Expertise in developing *in silico* prediction and database systems
Derek Nexus

- Knowledge based expert system
- Enables the evaluation of the potential toxicity of chemicals
- Decision support tool
  - Accuracy
  - Transparency
  - Supporting data
- Covers a broad range of toxicity endpoints
Alert 754 – Mutagenicity in vitro

Bacterium - PROBABLE

• Knowledge base search for matching structural alerts
• Application of rules – level of likelihood
• Supporting information provided
Levels of Likelihood

• Certain
  • There is proof that the proposition is true

• Probable
  • At least one strong argument that the proposition is true and no arguments against it

• Plausible
  • The weight of evidence supports the proposition

• Equivocal
  • An equal weight of evidence for and against the proposition

• Doubted, Improbable, Impossible, Open, Contradicted
754. Phenanthrene derivative or hetero-analogue

> Alert matches

- Description Image
- Comments

**Mutagenicity alert: Ames test**

This alert describes the mutagenicity of substituted phenanthrenes (I), methylene or carbonyl bridged phenanthrenes (II) and their hetero-analogues that are active in the Ames test. Examples include 1-methylphenanthrene [NTP 1989, LaVoie et al. 1986], 3H-cyclopenta[i]phenanthrene [Marusich et al.], 2,3-dimethylphenanthrene [LaVoie et al. 1981], 9-fluorophenanthrene [LaVoie et al. 1981] and 1-methyl-4H-cyclopenta[def]phenanthrene [Rice et al.]. These examples have all been reported to be mutagenic in Salmonella typhimurium TA98 in the presence of metabolic activation. It appears that molecules in these classes must contain activating features in order to be mutagenic. Phenanthrene is negative [LaVoie et al. 1982] and 4H-cyclopenta[def]phenanthrene is only positive with strong metabolic activation [NTP 1987].

The mutagenic activity of phenanthrenes and methyl bridged phenanthrene derivatives is likely to be mediated by electrophilic metabolites. It has been proposed that 7,8-dihydrodiol-1,6-epoxide is the ultimate mutagen. The corresponding proximate mutagen, 7,8-dihydronaphtho[1,2-b]pyrene, has been observed in vitro for 1,4- and 1,6-dimethylphenanthrene [LaVoie et al. 1982] and 15,16-dihydroneurodecahydronaphthalene [LaVoie et al. 1982]. Furthermore, DNA adducts from the 7,8-dihydrodiol metabolite of 15,16-dihydroneurodecahydronaphthalene have been observed in vitro [Coombs et al. 1979]. Alternative routes of metabolic activation have been observed for some phenanthrenes, particularly those that are unsubstituted at the 4-position including formation of non-bay-region dihydrodiols. The proximate mutagenic metabolites of 1-methylphenanthrene and 9-methylphenanthrene have been identified as either the 3,4- or 4,5-dihydrodiols [LaVoie et al. 1981]. DNA adducts from the former in HepG2 cells have been reported, albeit at a very low level compared with the more potent mutagens dibenz[a]pyrene or dibenz[a]anthracene [Koh et al.]. Metabolization of the 4-region and occasionally allyl substituents can reduce the mutagenicity of molecules, e.g. 2-methylphenanthrene [LaVoie et al. 1981].

The scope of this alert has been defined by the common structural features of the active compounds in this class and mechanistic considerations. Because the bay-region diol epoxides are potential ultimate mutagens, the 7,8-dihydrodiol proximate mutagenes have been included. Substituted benczenalkanes are also included because it is possible for them to be metabolized to bay-region diol epoxides [LaVoie et al.]. There are three features that:  

- **Skin sensitization**
- **Bacterial growth: PROBABLE**
- **Alert: 4846 Bay-region polycyclic aromatic hydrocarbon**

> Validation Comments

> Endpoints

> References

<table>
<thead>
<tr>
<th>ID</th>
<th>Title</th>
<th>Author</th>
<th>Source</th>
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<td>48464</td>
<td>Mutagenicity of a</td>
<td>LaVoie El, T</td>
<td>Mutation R</td>
<td>1983</td>
<td>DOI: 10.1061/065-128:833(00300-3)</td>
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<td>7835</td>
<td>Identification of a</td>
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<td>Cancer Res</td>
<td>1979</td>
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<td>74841</td>
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<td>LaVoie El, T</td>
<td>Cancer Res</td>
<td>1982</td>
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<td>74075</td>
<td>Metabolism of a</td>
<td>Armin S, L</td>
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<td>74410</td>
<td>Salmonella study</td>
<td>National Ts</td>
<td>National Ts</td>
<td>1989</td>
<td>More available at <a href="http://nps-server.n">http://nps-server.n</a></td>
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<td>74034</td>
<td>Synthesis and a</td>
<td>Marusevic</td>
<td>Carcinogen</td>
<td>1998</td>
<td>DOI: 10.1039/cancer:17.3:000, PMID: 1</td>
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Drug Discovery

Target Selection → Compound Discovery → Preclinical → Clinical → Market

Safety Assessment
Lhasa and Optibrium

- Collaboration commenced in 2013
- Development of the Derek Nexus Module for StarDrop
- Available as an optional module
- Facilitates the design of safe drugs in hit-to-lead and lead optimisation
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Matthew Segall, Chris Barber
Overview

• Impact of toxicity in pharma. R&D
• Application of knowledge based prediction of toxicity
• Guiding compound selection and design
  – Multi-parameter optimisation
  – Glowing Molecule
• Example
  – Exploring a COX2 screening library
• Short overview of StarDrop and the Derek Nexus module
• Conclusions
Impact of Toxicity in Pharma R&D

54% of pre-clinical failures due to tox/safety (18% of all candidates)

22% of all clinical candidates failed due to tox/safety

10.2% of approved drugs acquired black box warning, 2.9% withdrawn*
Application of Knowledge Based Prediction of Toxicity
Relating confidence and accuracy

• Derek Nexus provides a level of confidence (likelihood) for each prediction
  – This correlates well with accuracy

CFSAN

Hansen

NTP

Judson et. al. Toxicology Research, 2013, 2, 70
How Well do Expert Systems Perform?

- CDER approved drugs 2012 (n=27)

<table>
<thead>
<tr>
<th>drug</th>
<th>indication</th>
<th>prediction</th>
<th>dosing</th>
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<tr>
<td>Ingenol</td>
<td>actinic keratoses</td>
<td>chromosomal damage</td>
<td>topical treatment (cytotoxic mechanism)</td>
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<tr>
<td>Aclidinium</td>
<td>COPD</td>
<td>hepatotoxic</td>
<td>inhaled (0.4mg dose)</td>
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<tr>
<td>Linaclotide</td>
<td>IBS</td>
<td>hepatotoxic</td>
<td>metabolised in GI tract</td>
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Important Caveats/Questions

• Predict toxicity hazard
  – Risk ≈ hazard + exposure
  – Risk also depends on dose, route of administration, therapeutic index...

• Knowledge-based prediction of toxicity widely used in preclinical development
  – Assessment of risk for regulatory submission
  – Design of experiments to support submissions

• Question: How can these predictions be applied effectively in early drug discovery?
  – We don’t want to ‘kill’ potentially good compounds at an early stage due to uncertain predictions
Guiding Compound Design and Selection
The Objectives
Multi-parameter optimisation

• Identify chemistries with an optimal **balance** of properties

• Quickly identify situations when such a balance is not possible
  – Fail fast, fail cheap
  – Only when **confident**

The Challenge

200 compounds through 8 experimental assays is 1600 data points

Q. How do you use this data to make decisions?
Approaches for MPO Filtering?

- Potency
- Absorption
- Toxicity alert
Approaches for MPO
Desirability Functions*

- Relate property values to how ‘desirable’ the outcome

[Graph showing desirability function with a simple filter: >5]

* Harrington EC. (1965) Ind. Qual. Control. 21 p. 494
Approaches for MPO
Desirability Functions*

• Relate property values to how ‘desirable’ the outcome

Desired value: >5

* Harrington EC. (1965) Ind. Qual. Control. 21 p. 494
• Relate property values to how ‘desirable’ the outcome

![Desirability Functions Graph]

Rang: 4-6

* Harrington EC. (1965) Ind. Qual. Control. 21 p. 494
Approaches for MPO
Desirability Functions*

- Relate property values to how ‘desirable’ the outcome

![Graph showing desirability function with trend >8](image)

* Harrington EC. (1965) Ind. Qual. Control. 21 p. 494
Approaches for MPO
Desirability Functions*

• Relate property values to how ‘desirable’ the outcome

Ideal value: 5

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Approaches for MPO
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• Relate property values to how ‘desirable’ the outcome

\[\text{Desirability} = \begin{cases} 
\frac{x}{x_0} & \text{for} \quad 0 < x < x_0 \\
\frac{x_0}{x} & \text{for} \quad x > x_0 
\end{cases} \]

Non-linear, ideal value: 5
(Derringer Function)

• Combine multiple properties into ‘desirability index’
  - Additive:
  - Multiplicative:

• Very flexible approach allowing parameters to be weighted

• But, does not explicitly consider uncertainty

* Harrington EC. (1965) Ind. Qual. Control. 21 p. 494
Approaches for MPO
Probabilistic Scoring*

<table>
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<tr>
<th>Profile</th>
<th>Desired Value</th>
<th>Importance</th>
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<td>logS</td>
<td>&gt; 1</td>
<td></td>
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<tr>
<td>HIA category</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>logP</td>
<td>0 -&gt; 3.5</td>
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<tr>
<td>BBB log([brain]:[blood])</td>
<td>-0.2 -&gt; 1</td>
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<tr>
<td>P-gp category</td>
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<tr>
<td>PPB90 category</td>
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Approaches for MPO
Probabilistic Scoring*

- Property data
  - Experimental or predicted

- Criteria for success
  - Relative importance

- Uncertainties in data
  - Experimental or statistical

- Score (Likelihood of Success)
- Confidence in score

Error bars show confidence in overall score
Bottom 50% may be rejected with confidence

Data do not separate these as error bars overlap

Application to Toxicity Alerts
E.g. Mutagenicity

- Determine desirability function by reference to validation results:

- Also need to take into account:
  - Impact of toxicity on objective of project
  - Stage of the project, e.g. opportunity to redesign to reduce risk
Guiding Interactive Redesign

Data → Prioritise → Selection

Redesign
Interpretation of a Model
The ‘Glowing Molecule’

• Provides visual interpretation of structural influences on predicted properties
  – “Why is a property value predicted?”
  – “Where can I change this property?”
  – Interpret SAR
  – Guide efficient redesign of molecules

• Avoid Black Boxes

Example Application
Exploring a COX2 screening library
COX2 library
Chemical space
COX2 library
Scored excluding toxicity endpoints

Celecoxib

<table>
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<th>Profile</th>
<th>Desired Value</th>
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<td>pKi</td>
<td>8 -&gt; inf</td>
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<td>logP</td>
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<td>hERG pIC50</td>
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<td>2D6 affinity category</td>
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<td>PPB90 category</td>
<td>low</td>
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<tr>
<td>BBB log([brain]/[blood])</td>
<td>≤ -0.5</td>
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<tr>
<td>BBB category</td>
<td>-</td>
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COX2 library
Predicted hepatotoxicity

Lumiracoxib
COX2 library
Scored including toxicity endpoints
But wait...  
Wouldn’t we miss Celecoxib?!

- Celecoxib and Lumiracoxib would not be rejected outright
  - Highlighted hazard, confirm experimentally and consider context
- Celecoxib does exhibit signs of hepatotoxicity, but is ‘saved’ by its low dose and high therapeutic index*  

Consider Redesign Strategies

Lumiracoxib

- Glowing molecule highlights 2-Arylacetic acid alert
- Interactively explore strategies for reducing risk
  - Monitor changes in multiple properties simultaneously
Consider Redesign Strategies

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Introduction to StarDrop and the Derek Nexus module
StarDrop Helps to Guide Decisions
From selection... to design

• Probabilistic Scoring*
  – User-defined profile and weights
  – Use data from any source
  – Allow for uncertainty
  – Score for likelihood of success

• Chemical Space and Selection
  – View property distributions across chemical diversity
  – Balance quality and diversity

• Glowing Molecule
  – Interactively explore new ideas
  – Link compounds structure with properties

• Interactive Visualisation
  – R-group analysis
  – Matched Molecular Pair analysis

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*M.D. Segall et al. (2006) Expert Opin. Drug. Metab. Tox. 2(2) pp. 325-337*
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StarDrop Plug-in Modules and Integration
Extend Core Capabilities

ADME QSAR
High quality predictive models of key ADME properties

Auto-Modeller
Build and validate robust models tailored to your chemistry

Nova
Generate and prioritise new, relevant compound ideas

BIOSTER™
Explore >20k precedented transformations with the Nova module

P450
QM simulations identify sites of metabolism and lability for major P450s

torch3D™
Understand and apply 3D SAR to identify and optimise novel actives

Derek Nexus™
Knowledge-based prediction of >40 toxicity endpoints

MPO Explorer™
Develop multi-parameter optimisation strategies
Derek Nexus™ Module for StarDrop
Differences with full Derek Nexus

• Derek Nexus for StarDrop provides unique features for medicinal chemists and drug discovery projects, e.g.
  – Visualisation to explore toxicity risk of different chemistries
  – Probabilistic scoring to balance toxicity risk against other factors
  – Interactive design with Glowing Molecule to guide redesign and reduce risk of toxicity

• The full Derek Nexus platform from Lhasa Limited provides access to full Derek knowledge base for expert toxicologists
  – Information on mechanism of action, biological data and references
  – Detailed annotation of structural alerts
  – Helps to design toxicology experiments

• Reporting feature in StarDrop helps collaboration between drug discovery projects and preclinical toxicology
Conclusion

• Addressing toxicity early in the drug discovery process is key to improving success rate and productivity

• Knowledge based predictions provide a reliable way to identify toxicity hazards (potential risk)

• Results need to be used in context of other requirements of a successful drug

• Need to take confidence into account
  – Avoid rejecting good compounds due to uncertain data

• Reference:
  – Download (p)reprint from www.optibrium.com/community/publications