How do metabolites differ from their parent molecules - How are they excreted?
NME Success Rates 2006-2010

Success rates for each phase:

- **Preclinical**: 63%
  - bioavailability
  - animal toxicity
- **Phase 1**: 47%
  - side effects
  - toxicity
  - pharmacokinetics...
- **Phase 2**: 23%
  - efficacy
  - side effects
- **Phase 3**: 59%
  - idiosyncratic tox
- **Registration**: 79%

Number of NMEs that will achieve 1 approval:

- Preclinical: 32.4
- Phase 1: 20.5
- Phase 2: 9.6
- Phase 3: 2.2
- Registration: 1.3

12/11/2012
Computational Prediction of Metabolism

**SOM**
- Identification of atom positions with metabolic liability
- Reactivity
- Data mining
- Shape
- MIths
- Docking

**Metabolite Structure**
- Prediction of the chemical structure of potential metabolites
- Expert systems
- Data mining
- Reaction modeling

**Enzyme Structure & Function**
- Fundamental insight on enzyme function and SARs
- SAR
- Molecular modeling
- QM/MM

**Enzyme Inhibition**
- Elucidation of SAR of CYP substrates/inhibitors
- QSAR & ML
- 3D-QSAR
- Pharmacophores
- Docking
- MD

**Enzyme Induction**
- Rationalization of biological activity on inducing targets: AhR, CAR, PXR
- QSAR & ML
- 3D-QSAR
- Pharmacophores
- Docking


12/11/2012
MetaPrint2D: Data Mining of Metabolism Databases

Results

Input

SMILES: CCCc1nn(C)c2(C(=O)NC(=NC12)c3cc(ccc3OCC)S(=O)(=O)N4OCN(C)C4
Model: ALL (Metabolite 2010.2)
Settings: DEFAULT

Instructions

The colour highlighting an atom indicates its normalised occurrence ratio (NOR). A high NOR indicates a more frequently reported site of metabolism in the metabolite database.

Note: The normalised occurrence ratio does not indicate how likely a molecule is to be metabolised, but rather the relative likelihood of metabolism occurring at a particular site in the molecule, assuming it is metabolised.

Results Colour Scheme

<table>
<thead>
<tr>
<th>Colour</th>
<th>NOR Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red</td>
<td>0.66 &lt;= NOR &lt;= 1.00</td>
</tr>
<tr>
<td>Orange</td>
<td>0.33 &lt;= NOR &lt; 0.66</td>
</tr>
<tr>
<td>Green</td>
<td>0.15 &lt;= NOR &lt; 0.33</td>
</tr>
<tr>
<td>White</td>
<td>0.00 &lt;= NOR &lt; 0.15</td>
</tr>
<tr>
<td>Grey</td>
<td>Little/no data</td>
</tr>
</tbody>
</table>

Move the cursor over an atom for detailed results.
MetaPrint2D’s Circular Fingerprints

N.sp³; N.sp³, C.sp², C.ar; C.sp² [x3], C.ar [x2], O.sp²

J. Kirchmair, UK-QSAR Meeting 2012, Downing College, Cambridge, UK
Atom Reactivity Library

A. Calculate Quantum Chemical Reference Energies
   Calculate transition state energies using density functional theory

B. Define SMARTS Rules
   Group calculations by fragments and calculate average energies

---

SMARTCyp

1. Assign Energies By SMARTS matching

<table>
<thead>
<tr>
<th>Atom</th>
<th>SMARTS</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><a href="=O">CX3H1</a>[#6]</td>
<td>40.2</td>
</tr>
<tr>
<td>2</td>
<td>[CX4][N]</td>
<td>39.8</td>
</tr>
<tr>
<td>3</td>
<td>[N^3][H1,H2]</td>
<td>54.1</td>
</tr>
</tbody>
</table>

2. Compute Accessibility Descriptor

\[ A_i = \frac{\text{Maxbonds}_i}{\text{Maxbonds}_{\text{all}}} \]

- \( A_1 = \frac{2}{3} = 0.67 \)
- \( A_2 = \frac{2}{3} = 0.67 \)
- \( A_3 = \frac{3}{3} = 1.00 \)

3. Compute Score and Rank Atoms

Score, \( S = E - 8A \)

- Lowest score gets rank 1

\[ \begin{align*}
   S_1 &= 40.2 - 8 \times 0.67 = 34.84 \\
   S_2 &= 39.8 - 8 \times 0.67 = 34.44 \\
   S_3 &= 54.1 - 8 \times 1.00 = 46.10 \\
\end{align*} \]

- Atom 1 - Rank 2
- Atom 2 - Rank 1
- Atom 3 - Rank 3

---

Olsen et al., 2006, doi: 10.1021/jm060551l
Rydberg et al., 2010, doi: 10.1021/ml100016x
### Prediction Accuracy on CYP3A4

<table>
<thead>
<tr>
<th>Method</th>
<th>test</th>
<th>isoforms</th>
<th>training</th>
<th>params</th>
<th>top-1</th>
<th>top-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC orig</td>
<td>Zc</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>63.1</td>
<td>79.1</td>
</tr>
<tr>
<td>MP</td>
<td>Zc</td>
<td>all</td>
<td>Zrem</td>
<td>def</td>
<td>47.1</td>
<td>68.3</td>
</tr>
<tr>
<td>MP</td>
<td>Zc</td>
<td>all</td>
<td>Zrem</td>
<td>opt</td>
<td>48.6</td>
<td>70.2</td>
</tr>
<tr>
<td>MP+SC</td>
<td>Zc</td>
<td>all</td>
<td>Zrem</td>
<td>opt</td>
<td>66.9</td>
<td>86.6</td>
</tr>
</tbody>
</table>

MP MetaPrint2D, SC SmartCyp, Zc Zaretzki calibration set, Zrem Zaretzki test data removed from training data, opt MetaPrint2D optimized parameters
MetaPrint2D-React

- reaction types identified using SMARTS patterns:
  - hydroxylation: [:1]>>[*:1]-[OH]
  - glucuronidation: [:1]>>[*:1]C1C(O)C(O)C(O)C(C(=O)O)O1

- generic reaction classes may need several smarts patterns to represent all reactions

MetaPrint2D: Current Status & Objectives

- **Method development**
  - Data fusion models
  - Visualisation of metabolic schemes
  - Tautomerism
  - Optimization of chemical descriptors/fingerprints
  - Parameter optimization

- **Model refinement**
  - Species-specific models
  - Isozyme-specific models
  - Chemical space-specific models
Physicochemical Properties – Shifts Introduced by Metabolism

Physicochemical property shifts introduced by metabolism

Physicochemical property shifts introduced by individual metabolic reactions

Excretion of metabolites: Bile, Faeces, Urine
Data Source: Metabolism Database
Datasets

- Approved drugs [~1400 mols]
- Metabolite database [~100,000 experimental observations]
- TCM molecules [~40,000 mols]
- Human metabolites [~8000 mols]
Shifts Introduced by Metabolism

Molecular weight shifts: d(red), h(green), t(blue)

logP shifts: d(red), h(green), t(blue)

hydroxylation
glucuronidation
deglucosidation

Molecular weight shift [Da]

logP shift

J. Kirchmair, UK-QSAR Meeting 2012, Downing College, Cambridge, UK
Shifts Introduced by Metabolism

molecular weight and logPo_w shifts: d : d_c
molecular weight and logPo_w shifts: d : h_c
molecular weight and logPo_w shifts: d : t_c

- drugs
- terminal metabolites
- human metabolites
- TCM
- terminal metabolites

J. Kirchmair, UK-QSAR Meeting 2012, Downing College, Cambridge, UK
What Shifts Do Phase I Reactions Induce?

Phase I molecular weight shifts: d(red), h(green), t(blue)

Phase I logP shifts: d(red), h(green), t(blue)

hydroxylation
What Shifts Do Phase II Reactions Induce?

Phase II molecular weight shifts: d(red), h(green), t(blue)

- Glc. acid
- Methylation
- Sulfation
- Glutathionation

Phase II logP shifts: d(red), h(green), t(blue)

- Glucuronidation
- Methylation
- Glutathionation

J. Kirchmair, UK-QSAR Meeting 2012, Downing College, Cambridge, UK
What Metabolites Are Found in Bile/Faeces/Urine?

MW approved drugs: bile(red), faeces(green), urine(blue)

MW human metabolites: bile(red), faeces(green), urine(blue)

MW TCM molecules: bile(red), faeces(green), urine(blue)

purines
steroids
glucosteroids

J. Kirchmair, UK-QSAR Meeting 2012, Downing College, Cambridge, UK
What Metabolites Are Found in Bile/Faeces/Urine?

- logP approved drugs: bile(red), faeces(green), urine(blue)
- logP human metabolites: bile(red), faeces(green), urine(blue)
- logP TCM molecules: bile(red), faeces(green), urine(blue)

drugs  human metabolites  TCM

bile  faeces  urine  all clustered
Outlook and Conclusions

- MetaPrint2D: allows to predict the SOM with an 70-80% success rate for the top-3 ranked atom positions

- Significant performance increase by consensus scoring

- Metabolism causes substantial shifts in physicochemical properties of small organic molecules:
  - molecular weight is mainly increased by glucuronidation, sulfation and other conjugation reactions
  - terminal metabolites of drugs and TCM molecules have ~1 log unit lower logP
  - excretion of human metabolites is prevented by avoiding the introduction of hydrophilic groups

- Differences in chemical properties between metabolites found in the various excretion systems are generally minor, although trends for extreme ranges can be identified
Thanks for Your Attention,
The UCC Metabolism Team