Predicting Adverse Drug Reactions: What works and What Doesn’t

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Guiding Optimal Compound Design & Development
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Drugs Discovery is Time Consuming, Risky and Expensive

- Average Cost of Developing a New Medicine > $2.0B
- Average Time from Discovery to Patient = 10-15 Years
- 1 in 5,000-10,000 Compounds Approved by FDA
Fundamental Elements of Toxicity

Mechanism(s) of Action
• What does the compound do to affect cellular function?
• “Safety”

Level of Exposure
• How much of the compound needs to reach the site of action?
• “ADME”

Need to consider both elements in order to be truly predictive
Therapeutic Index is Often Uncertain

- Why risk a safety liability?
- Find *productive* chemistry space early
The Basic Question

What design features signpost risk?
Factors that Influence Safety Profiles

**Primary pharmacology**
- PDE-4 inhibitors are linked to emesis and vasculitis

**Chemical structure**
- Clozapine causes agranulocytosis and forms reactive metabolites

**Physicochemical properties**
- Lipophilic basic compounds at risk of: Phospholipidosis, QT interval prolongation

**Origins of adverse safety profile**
- D1 activity is linked to tremor

**Secondary pharmacology**
- Ariflo
- Terfenadine
- PDE-4 inhibitors are linked to emesis and vasculitis
Structural Alerts: 81 drugs withdrawn for idiosyncratic toxicity reasons

- aniline group: 25%
- quinone group: 17%
- e rich Ar group: 15%
- acyl glucuronide group: 10%
- quinolone: 5%
- hydrazide/hydrazine: 10%
- Michael: 5%
- benzodioxolane: 10%
- none group: 5%
- other STAs (singletons): 5%

Overall: 67%
Osaka, Japan, December 27, 2013 – Takeda Pharmaceutical Company Limited (Takeda) announced today that it has decided voluntarily to terminate the development activities for fasiglifam (TAK-875), an investigational treatment for type 2 diabetes, due to concerns about liver safety.
The IMPORTANT role of physiochemical properties

A compound that flags both properties is \textbf{six times} more likely to cause findings in a IVT study at Cmax<10\mu M than a compound that does not flag in either of these properties.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Total Drug & TPSA < 75 & TPSA > 75 \\
\hline
ClogP > 3 & 2.4 (85) & 0.41 (38) \\
ClogP < 3 & 1.08 (27) & 0.39 (57) \\
\hline
\end{tabular}
\end{table}

\textit{Expert Opin. Drug Metab. Toxicol.} (2009) 5(8)
Off Target promiscuity

Promiscuity defined as >50% activity in >2 Bioprint assay out of a set of 48 (selected for data coverage only)

Ratio of promiscuous to non-promiscuous compounds

<table>
<thead>
<tr>
<th>Cerep</th>
<th>TPSA &lt; 75</th>
<th>TPSA &gt; 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClogP &gt; 3</td>
<td>6.25 (29)</td>
<td>0.44 (13)</td>
</tr>
<tr>
<td>ClogP &lt; 3</td>
<td>0.80 (18)</td>
<td>0.25 (25)</td>
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Odds Ratio = 25 X
Impact of daily dose on IADRs

Drugs withdrawn due to IADRs

Drugs associated with BBW

Drugs associated with IADRs are frequently the ones with a higher daily dose.
What About Liver Injury

Majority of DILI is observed at high dose or exposure

cLogP >3 & Daily Dose >100mg is as predictive as any in vitro assay for this set!

Compounds from the FDA LTKB

Drug Discovery Today (2011), 16 (15–16), 697–703
What Have We Learned From High-Throughput Screening?

Hypothesis: ~80% of chemicals cause toxicity through non-specific interactions

Thomas et al., Tox Sci., 2013
Cell Death and In Vivo Toxicity are Correlated

- Cells die through many mechanisms
  - apoptosis (planned self-destruction)
  - necrosis (mechanism often unclear)
Properties related to LOAEL


LOAEL = Lowest Observable Adverse Effect Level

- Volume of distribution and cytotoxicity had largest impact on LOAEL in a rodent study.
  - Increase in Vd $\rightarrow$ Decrease in LOAEL
  - Increase in LC50 $\rightarrow$ Increase in LOAEL
The Problem with using LOAELs

The observed NOAEL and LOAEL are heavily reliant on where doses are set in a study. What if a compound would cause adverse effects only above an 8µM concentration?

This is real data!
Note: non-linear TK often observed in safety studies

Observed NOAEL dose = 3mg/kg
Observed LOAEL dose = 30mg/kg
Theoretical concentration where toxicity will occur
Theoretical NOAEL dose = ~23mg/kg?
A Strategy for Predicting Toxicity

• If most toxicity is driven through non-specific binding interactions…
• … and if local dose (concentration) makes the poison…
• … then target organ will depend heavily on specific tissue distribution

• Tissue level exposure is not (often) measured

• What if we simply focus on the concentration where we see any toxicity rather than where it occurs?
Toxic Cmax Approach

Graphical Representation of ETS Outcome as a Function of Exposure

- **Severity**
- **Log(Exposure) nM**

**Threshold for significant tox**

- **Low Dose**
  - (NOAEL)
- **Mid Dose**
  - (LOAEL)
- **High Dose**
  - (LOAEL)

**Toxic_Cmax**

1 2 3 4 5 6

Log(Exposure) nM
Correlations to Toxic_Cmax

- Red: $\text{Tox}_C\text{max} < 3\mu\text{M}$
- Yellow: $3\mu\text{M} < \text{Tox}_C\text{max} < 30\mu\text{M}$
- Green: $\text{Tox}_C\text{max} > 30\mu\text{M}$

**Calculated VDss**

**PSA**

**Acidic pKa$_1$**

**Basic pKa$_1$**
Comparing Assays to Toxic Cmax

- "Diverse" dataset combining of basic, neutral and acidic compounds

Cell line: HepG2

Cell line: THLE

Cell line: NRK

Tox_Cmax < 3µM
3µM < Tox_Cmax < 30µM
Tox_Cmax >30µM
The Importance of Ionization State

Acidic compounds

Basic compounds
Toxicity Profiling in Drug Discovery

Prospective Tox Profiling

Target PoC

Screen Development & High Throughput Screening

Primary HITS Screen

Hit to Lead

Parallel Med Chem

Optimal Potency/Selectivity

Candidate Seeking

Efficacy in Pivotal In Vivo Models

In Vivo Toxicity Studies

Retrospective Tox Profiling (Issue Management)

Characterization, Mechanisms, Modeling, Biomarkers & Screening for STR

\textit{In silico / in vitro} assessment

Target Safety Assessment

Lead Optimization

Compound Selection (CS)
Summary

• Predictive platform predicts the exposure at which toxicity is observed for around **80% of the compounds** in preclinical species.

• Helped guide the early chemistry efforts on >70 discovery projects
  • **Initiates safety considerations early** in projects
  • A framework for evaluating the predictivity of new assays.

• **Relies heavily on well characterized training compound sets**

• Requires engagement across multiple disciplines
  • Biologists, chemists and computational scientists

• Address the impact of dose projection, and to model severity of toxicity

• **Steering away from no hope chemistry**
  • => better survival and resource utilization
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- Rob Owen
- Kevin Dack

And many others!!
“Mr. Osborne, may I be excused? My brain is full.”