Reducing Attrition Risk: Evolution of an \textit{in silico} “Compound Safety Evaluator”

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Designing Safer Medicines in Discovery.

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Introduction

• Safety is a major cause of attrition
  – Low therapeutic index (not potent enough, poor PK, high peak:trough, promiscuous).......
  – High Dose (idiosyncratic tox, active & reactive metabolites & metabolic burden...)
  – Manipulating target/pathway is unsafe (out of scope for today)

• Need to ‘flag’ earlier those compounds/series at greater risk of safety attrition.
  – Focus resource on leads/series/targets with better chemical equity
  – Save $$ and animals
Outline of Presentation

• Introduction to Compound Safety Prediction Group
• Compound Safety Evaluator v1.0
  – Criteria used & basis for scoring
  – Retrospective analysis of pre-clinical tox studies
  – Retrospective analysis of some Pfizer candidates
• Drugs on the Market
  – Impact of CSE Score and Dose size
• Compound Safety Evaluator v2.0
  – Improving predictions
• CSE vs Dose: getting better dose predictions.
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Compound Safety Prediction Group

- Compound Safety Prediction Group at Pfizer
  - Based in Groton, USA & led by Bill Pennie
- Building a research program to characterize underlying mechanisms of toxicity.
- Building predictive assays (in silico or in vitro) for these mechanisms.
- Assembling these assays into a validated, predictive panel for compound testing.
- Reporting results to project teams to help define “safer” chemical space and assist teams in series & candidate selection decisions.
- Developed Compound Safety Evaluator (CSEv1.0) to generate a ‘Safety Score’ for compounds
Compound Safety Evaluator: CSEv1.0

- Goal is to help project team define safer chemical space by providing an integrated report of the safety ‘profiling’ of a compound or series.

- Decisions will always lie within project teams.
  - e.g. an acceptable risk in oncology is different to pain management.
Compound Safety Evaluator: CSEv1.0

**Objective:** To derive a single score to allow easy comparison of compounds across a panel of assays and properties.

- Makes use of Multi-Parameter Optimization
  - the Score is on a 0 to 1 scale with 1 = ☺ and 0 = ☹
- Used assays already available to Project teams
  - Cerep binding assays (%inhib @ 10μM)
    - Subset of 15 assays used to assess promiscuity
  - THLE cytotoxicity*
  - Genetic Tox assays (BiolumAmes & IVMN)
  - Dofetilide binding and hERG
- Incorporates knowledge from Beyond Structural Alerts work (Bio. Med. Chem. Lett. (2008), 18, 4872-4875)
  - cLogP and TPSA (3/75 guideline)
  - Basic pKa

* THLE = transformed human liver epithelial
Compound Safety Evaluator: CSEv1.0

- **MPO Scoring Methodology:**
  - CSE Score = \( \left( y_1 w \cdot y_2 w \cdot y_3 w \cdot y_4 w \cdot \ldots \right)^{1/(w_1 + w_2 + w_3 + w_4 + \ldots)} \)
  - For each assay: \( y, X_1 \) and \( X_2 \) and relative weight \( w \) were defined e.g.

\[
\begin{align*}
\text{y} &= 1.0 & \text{Monotonic Increasing e.g. THLE IC}_{50} \\
\text{y} &= 0.5 & \text{Decreasing e.g cLogP} \\
\text{y} &= 0.1 & \text{Mixed}\n\end{align*}
\]

I cannot disclose all the proprietary assay thresholds, weighting and scoring MPO at this time.
Compound Safety Evaluator: CSEv1.0

- Why only 15 CEREP assays?
- 15 targets selected due to known risks/issues - The ‘Promiscuity Panel’
- Covering GPCRs, ion-channels, transporters, PDE
- Provides a lower cost, ‘quick look’ at promiscuity
- High average inhibition of the 15 targets generally correlates with wider promiscuity
Sorted by Average %I across the 15 ‘Promiscuity Panel’ Targets. Each row is a compound.

The most promiscuous compounds across 15 targets carry on hitting multiple targets in the rest of the Full panel.

In contrast, the compounds with low average %I in the P-Panel are generally cleaner across the rest of the CERE Panel full panel.
Compound Safety Evaluator: CSEv1.0

- Representative CSEv1.0 display

- Genetic tox. risks
- THLE: Indicators of cell toxicity
- CEREP Promiscuity panel
- PhysChem properties
- Toxicophore alerts
- Potential CV safety

e.g. Paroxetine
Compound Safety Evaluator: CSEv1.0

- Retrospective Scoring of compounds that underwent *in vivo* toxicology assessment

- Analysis and ‘CSE Scoring’ of 256 compounds that were profiled in exploratory toxicology studies (primarily in rat).

- Compounds were flagged as either:
  - Clean = No ‘adverse toxicity findings’ were observed at a Cmax at or above 10μM total drug
  - Toxic = ‘Adverse toxicity findings’ were observed at a Cmax below 10μM total drug
**Compound Safety Evaluator: CSEv1.0**

- **Data set**: 256 compounds with *in vivo* toxicology outcomes (‘clean’ vs ‘adverse toxicity findings’ at 10μM total drug)

Some of these may be manipulating ‘unsafe’ targets/pathways or have unknown tox reasons.

CSE Score <0.75 correlates with greater risk of adverse findings at 10μM.

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**Legend**

- Clean@>10μM
- Findings@<10μM

<table>
<thead>
<tr>
<th>Clean@&gt;10μM</th>
<th>Findings@&lt;10μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>54</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
</tr>
</tbody>
</table>

**Scores**

- CSE Score 0.85
- CSE Score 0.75
What About the Dose?

• High dose risks:
  – Metabolic burden (esp. liver & kidney)
  – Reactive metabolites $\rightarrow$ covalent binding $\rightarrow$ idiosyncratic tox?
  – DDIs

• What defines the Dose?
What Defines the Dose?

For a diverse set of compounds/target mechanisms - it is simpler to track HLM as a component of Dose

Major advances in predicting and improving HLM over last decade

Oxidative metabolism (HLM)
- Other metabolism (e.g. AO)
- Transporter clearance
- Renal clearance

Potency
- Biochemical efficiency

Dose
- C_{eff}
- Fa
- Unbound Clearance

Solubility
Permeability
307 Pfizer Candidates with CSEv1.0 & HLM

All these Launched Drugs have CSEv1.0 >0.75 & HLM Clint <100

These are inhaled or oncology candidates

HLM Clint is one component of Dose

Could some these failures have been avoided?
**Pie Chart**

586 Stopped Pfizer Candidates

- **0.85 < x**
  - Safety: 40%
  - ADME: 12%
  - Other: 48%

- **0.75 < x ≤ 0.85**
  - Safety: 48%
  - ADME: 12%
  - Other: 40%

- **x ≤ 0.75**
  - Safety: 65%
  - ADME: 2%
  - Other: 33%

Other reasons includes:
- Pharmacology
- Chemistry
- Biopharmaceutics
- Strategic

When CSE <0.75: Safety is given as reason for Stopping for 65% of candidates.
Total of 244 stopped due to Safety concerns – what type of Safety?
Reasons for Safety Attrition: 244 Pfizer Candidates

When CSE < 0.75:
Pre-clinical non-hepatic animal tox is clearly the main reason for attrition
When CSE >0.85:
Since 2007 fewer cpds are stopping due to safety reasons

Other reasons includes:
- Pharmacology
- Chemistry
- Biopharmaceutics
- Strategic
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Drugs on the Market

- What would the CSE Score of Launched Drugs look like?
- Safety is more stringent now compared to 1990 or even 2000
- Impact of Dose – we know the dose ranges that are approved
Drugs on the Market

- Data set analysed:
  - Identified all Oral Drugs launched since 1990
  - Filtered to MW <600 to remove large biologics etc.
  - Must be present in the Pfizer File
  - Must already have CEREP data generated in Pfizer database
  - Gave 157 launched Drugs for analysis (a snapshot – not comprehensive)

With this data set:
17/18 Drugs with dose >500mgs have CSE Score >0.85
(exception being Gleevec; CSE Score 0.81; Typical oncology dose 400-800mg)

Low dose (<50mg) more forgiving of potential Safety Risks (high potency → high TI)
Caveat – this is only a subset of all launched drugs
Drugs on the Market

- Focussing on the higher dose Drugs:
  - Plot lowest approved dose vs CSEv1.0 Score

With this data set:
Trend for high CSE Score required if dose has to rise.
Drugs on the Market

With this data set:
The majority of ‘high’ dose compounds are MW <450, cLogP <3, TPSA >75
Drugs on the Market

With this data set:
High cLogP and low TPSA can (historically) be successful if the dose is low
But, many of these drugs carry safety warnings – would they be approved in today’s ‘climate’?
Drugs on the Market

Higher risk CSEv1.0 Score:
e.g. Paroxetine
Initially 20mg daily
rising to max of 50mg

Lower Risk CSEv1.0 Score
e.g. Lamotrigine
Daily maintainence dose of 100-
500mg
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Compound Safety Evaluator: CSEv2.0

• CSEv1.0 was refined....

• The results of the 15 CEREP assays (v1.0) are summarized in a GINI coefficient, which provides a measure of compound promiscuity

• Additional proprietary cell based mechanistic assays have been included in the CSE panel of assays: e.g. mitochondrial function and apoptosis

• A Random Forest method was used to identify the assays that provide the greatest predictive value.

• CSE v2.0 uses 12 chemical and biological endpoints to generate an MPO score

I cannot disclose the assay threshold, weighting and scoring MPO at this time.
Compound Safety Evaluator: CSEv2.0

- **Data set**: Same 236 compounds with *in vivo* toxicology outcomes (‘clean’ vs ‘adverse toxicity findings’ at 10μM total drug)

CSEv2.0 Score <0.5 correlates with greater risk of adverse findings at 10μM
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Attrition Risk (CSE vs Dose):
Examples of Drugs on the Market

- Lamotrigine
  - CSEv2.0 = 0.88
  - Daily maintenance dose of 100-500mg

- Paroxetine
  - CSEv2.0 = 0.2
  - Initially 20mg daily rising to max of 50mg

- Attrition Risk can be mapped as a ‘value-range’ to take into account both these properties.
- Can we improve the dose prediction for hits, leads and potential drug candidates?
Improving the Oral Dose Prediction

- **Potency**
- **Biochemical efficiency**
- **C_{eff}**
- **Dose**
- **Unbound Clearance**
- **Fa**
- **Solubility**
- **Permeability**

**C_{eff}** is still hard to predict for new mechanism that have not been to patients.

**BioPfarm-X-treme** (BPX) is Pfizer’s new in-house program
- BPX-Mini for 1000s cpds to help with series selection etc
- BPX- Maxi for refined Fa and Dose prediction on selected leads

**Unbound Clearance** prediction is good if mainly HLM mediated, and improving with advancing knowledge of other clearance mechanisms.

**Fa** module is well validated (Sugano; *Expert Opin. Drug Metab. Toxicol.* (2009) 5 (3):259-293)

**C_{eff}** can be hard to determine without validated models or clinical data
Attrition Risk (CSE vs Dose):
Examples of Series in a Project

- Attrition Risk Grid can be used to visualise Series risks e.g.

  ★ Series 1

  ● Series 2 (Higher Dose Risk)

  □ Series 3 (Higher Safety Risk)
Summary

- Compound Safety Evaluator (CSE) is established as a tool to alert Projects to some potential safety risks of their Leads and Series.
- The impact of Dose and TI must be taken into consideration, in view of the acceptable level of risk for the given therapeutic indication.
- A proprietary *in silico* dose prediction method (BioPf arm-X-treme; BPX-Dose) has been developed, using ADME and Pharmaceutical properties. But $C_{eff}$ is still an issue for many Projects.
- The combination of CSE Score and Dose Prediction for leads & series in a Projects (and Projects within a Portfolio) can be mapped on an Attrition Risk Grid.
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  – Tony Wood, Alan Stobie, Andy Bell, Dave Price, Mark Gardner

• BioPfarm-X-treme
  – Stefan Steyn, Kiyohiko Sugano
The Legacy of the Pfizer R&D in Sandwich UK

**Amlodipine** (Norvasc™)  
5-10 mg  
Hypertension

**Fluconazole** (Diflucan™)  
100-400 mg  
Antifungal

**Sildenafil** (Viagra™)  
25-100 mg prn  
Impotence

**Sildenafil** (Revatio™)  
20 mg tid  
PAH

**Doxazosin** (Cardura™)  
4-8 mg  
Hypertension & BPH

**Dofetilide** (Tikosyn™)  
<1 mg  
Antiarrhythmia

**Voriconazole** (Vfend™)  
50-200 mg  
Antifungal

**Dalcetrapib** (Trulus™)  
200 mg  
HIV

**Eletriptan** (Relpax™)  
20-40 mg  
Migraine

**Maraviroc** (Celsentri™)  
150-300 mg  
HIV

**Darifenacin** (Enablex™)  
7.5-15 mg  
Incontinence