A Consortium Approach to Predicting Toxicity

A Step Towards Building a Larger Consortium Among Competitors

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### ADRs are a Major Cause of Death

<table>
<thead>
<tr>
<th>Deaths Per Year</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>710,000</td>
<td>Heart Disease</td>
</tr>
<tr>
<td>550,000</td>
<td>Cancer</td>
</tr>
<tr>
<td>170,000</td>
<td>Stroke</td>
</tr>
<tr>
<td>120,000</td>
<td>Pulmonary</td>
</tr>
<tr>
<td><strong>100,000</strong></td>
<td><strong>Adverse Drug Reactions</strong></td>
</tr>
<tr>
<td>98,000</td>
<td>Accidents</td>
</tr>
<tr>
<td>69,000</td>
<td>Diabetes</td>
</tr>
<tr>
<td>65,000</td>
<td>Pneumonia/Flu</td>
</tr>
<tr>
<td>50,000</td>
<td>Alzheimers</td>
</tr>
<tr>
<td>37,000</td>
<td>Nephritis</td>
</tr>
<tr>
<td>31,000</td>
<td>Septicemia</td>
</tr>
</tbody>
</table>

Refs: CDC Fastats estimated 2000 causes of death(http://www.cdc.gov/nchs/fastats/lcod.htm);
To Err Human, National Institute of Medicine, 1999; Bates et al., Incidence of adverse drug events and potential adverse drug events. JAMA 274:29, 1995;

Profitability Among Pharmaceutical Manufacturers Compared to Other Industries, 1994–2000

**Note:** Percent shown is the median percent net profit after taxes as a percent of firm revenues for all firms in the industry. The second ranked industry each year was commercial banks.

**Source:** Fortune 500 Industry Rankings, *Fortune*, April issues, various years.
Fifteen Years From Now, Elderly Population Growth Will Explode

Average annual growth rate (in percent) of the elderly population: 1910-30 to 2030-50

<table>
<thead>
<tr>
<th>Period</th>
<th>Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1910-30</td>
<td>2.6</td>
</tr>
<tr>
<td>1930-50</td>
<td>3.1</td>
</tr>
<tr>
<td>1950-70</td>
<td>2.4</td>
</tr>
<tr>
<td>1970-90</td>
<td>2.2</td>
</tr>
<tr>
<td>1990-2010</td>
<td>1.3</td>
</tr>
<tr>
<td>2010-30</td>
<td>2.8</td>
</tr>
<tr>
<td>2030-50</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Not a Pretty Picture

“It is not from the benevolence of the butcher, the brewer or the baker that we expect our dinner, but from their regard to their own self interest.... [Every individual] intends only his own security, only his own gain. And he is in this led by an invisible hand to promote an end which was no part of his intention. By pursuing his own interest, he frequently promotes that of society more effectually than when he really intends to promote it.” -Adam Smith, 1776
“Picture a pasture open to all. It is expected that each herdsman will try to keep as many cattle as possible on this commons. ... Therein is the tragedy. Each man is locked into a system that compels him to increase his herd without limit, in a world that is limited. Ruin is the destination toward which all men rush, each pursuing his own best interest in a society that believes in the freedom of the commons.”  -Garrett Harding
A “Beautiful” Concept – Nash Equilibrium

DEFINITION: If there is a set of strategies with the property that no player can benefit by changing her strategy while the other players keep their strategies unchanged, then that set of strategies and the corresponding payoffs constitute the Nash Equilibrium.

A Nash Equilibrium* will be reached when each agent's actions begets a reaction by all the other agents which, in turn, begets the same initial action. In other words, the best responses of all players are in accordance with each other.

Can pharmaceutical players reach a Nash Equilibrium?!
Pharma is Living the Tragedy of the Commons

- Pharma is not more efficient despite increased R&D spending
- Mergers don’t seem to help (Is in-licensing a form of denial?)

Can a business maintain *viability* when it needs to spend >$800M over 12 years* to develop a product?

Ref: Outlook 2002. Tufts Center for the Study of Drug Development
While it might benefit all if Pharma conducts research “in accordance” with one another, many barriers remain.

Sharing toxicity Information can be a giant a “baby step”

Some precedence – The International Toxicology Information Center (ITIC) consortium (International Uniform Chemical Information Database (IUCLID))
Toxicity Prediction Software Packages are Available

- TOPKAT (http://www.accelrys.com/products/topkat/)
- CSGenoTox (http://www.chemsilico.com/)
- TOXSYS (http://www.scivision.com/ToxSys.html)
- HazardExpert/ToxAlert (http://www.compudrug.com/)
- OncoLogic – (http://www.logichem.com/)
A Simple Toxicity Assessment Strategy

- **Premise**: A compound's toxicity (e.g. pLD50) can be gauged based on the toxicities of other structurally similar compounds.

  \[ \texttt{refsim} \text{ ref.tdt} \{p\}_\text{ref-propfield} \text{ ref-namefield} \text{ sim-cutoff} \#\text{members} \{\text{LOO}\} \{\text{numref}\} < \text{qry.tdt} \]

- **Algorithm**:  
  - For each qry-mol in “qry.tdt,” identify ref-mol(s) in “ref.tdt” within “sim-cutoff” tanimoto similarity.  
  - Calculate average (“ARP”) of “ref-propfield” for ref-mol(s).  
  - Assign “ARP” to qry.mol, provided at least “#member” consortium members were used in calculation.

- **Requirement**: reasonably large, descriptive reference set

  Can we come together to build a predictive reference set?  
  {What if only fingerprints/toxprops were “shared?” – J.Delaney.}
A Starter Reference Set – “RefSet”

- **Starter Source**: RTECS – over 133K compounds
- **Subset** - 13645 examples
  - Route: Oral  Species: Rat  EndPoint: LD50
- **MWT**: Avg: 304.09 Std: 183.78
- **ClogP**: Avg: 2.05 Std: 2.53
- **QPlogS**: Avg: -2.95 Std: 2.37
- **TPSA**: Avg: 65.28 Std: 70.39
- **RotBonds**: Avg: 5.32 Std: 5.5
Drug Subset- “DrugSet”

- Comprehensive Medicinal Chemistry – CMC 2002.1 (MDL)
- Approx. 8500 compounds tested in/on man
- “DrugSet” subset: 1781 “RefSet” compounds found in CMC
- **MWT**: Avg: 367.4 Std: 95.5
- **ClogP**: Avg: 2.87 Std: 2.7
- **QPlogS** Avg: -3.97 Std: 2.1
- **TPSA**: Avg: 72.24 Std: 48.3
- **RotBonds**:Avg: 5.96 Std: 4.2
Notes: LD50 data points in DrugSet which have company source data in CMC 2002.1, legacy company-source names (e.g. Novartis/Sandoz/Ciba-Geigy, ICI/Zeneca, Wyeth/Ayerst, SmithKline/Glaxo/Wellcome, etc.) notwithstanding. Other_8, Other_7 represent companies with 8, 7, etc. data points. Over 300 source-company entries have 1 compound-LD50 data-point.
Reference Set Distribution
Oral Rat log(LD50) – pLD50

Range: [-3.85, 5.27] Avg: 2.92  SDev: 0.85
### Did you know?

<table>
<thead>
<tr>
<th>Compound</th>
<th>LD50&lt;sub&gt;(oral/rat)&lt;/sub&gt;</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2O</td>
<td>&gt;90 mL/kg</td>
<td>Food Research 21,348,1956</td>
</tr>
<tr>
<td>NaCl</td>
<td>3000 mg/kg</td>
<td>Toxicology and Applied Pharmacology 20,57,1971</td>
</tr>
<tr>
<td>Sucrose</td>
<td>29700 mg/kg</td>
<td>Toxicology and Applied Pharmacology 7,609,1965</td>
</tr>
<tr>
<td>Caffeine</td>
<td>192 mg/kg</td>
<td>Journal of New Drugs 5,252,1965</td>
</tr>
</tbody>
</table>

Note: For a 170 Lb human (77.1 Kg):
LD50 Water: 6.9 L -> 234.7 fl-oz -> 29 x 8oz cups!
LD50 Caffeine: 14.8 g -> 110 strong expresso shots! A cup of coffee contains between 60-135 mg caffeine
LD50 Sucrose: 2289.9 g ->10x8oz cups of sugar!
What is the Optimal Similarity Cutoff?

Performance with Similarity Cutoff
Ref v. Ref - LOO: #members: 1

![Graph showing the relationship between Tanimoto SimCut and Proportion Predicted. The graph includes two curves: a blue curve labeled $q^2$ and a pink curve labeled Proportion Predicted. The x-axis represents Tanimoto SimCut ranging from 0 to 1, and the y-axis represents $q^2$ and Proportion Predicted ranging from 0 to 1. The graph illustrates how the proportion predicted changes with different similarity cutoffs.](image-url)
What is the Optimal Consortium Size?

Performance with consortium size
Ref v. Ref - LOO: SimCut: 0.75

![Graph showing performance with consortium size]

- q^2 vs. #members
- Proportion Predicted

- Ref v. Ref - LOO: SimCut: 0.75
Evaluating RefSim — A Leave-One-Out Simulation

Reference set against itself - "LOO" Oral Rat LD50 predictions
nRef = 13645 nPred = 7816 SimCut: 0.75 #Members: 1 q^2:0.82

Reported pLD50 vs Predicted pLD50
CMC "LOO" Oral Rat LD50 predictions

nRef = 13645  nPred = 923/1781  SimCut: 0.75  #Members: 1  q^2: 0.74
### DrugSet Prediction Errors

**Histogram**

The histogram shows the frequency distribution of the difference between predicted and observed pLD50 values. The x-axis represents the difference (predicted pLD50 - observed pLD50), while the y-axis indicates the frequency of occurrence for each difference value.

- The x-axis values range from -3 to 3.
- The y-axis values range from 0 to 200.

**Key Observations**

- The majority of errors are clustered around 0, indicating that most predictions are close to the observed values.
- There is a significant peak at the zero difference, suggesting that many predictions are accurate.
- Errors range from -3 to 3, with the majority falling within -2 to 2.

**Data Breakdown**

- Positive errors (predicted > observed) are shown in red bars.
- Negative errors (predicted < observed) are shown in green bars.

**Frequency Distribution**

- Each bar represents the frequency of errors within a specific range.
- The tallest bars indicate the most common error ranges.
<table>
<thead>
<tr>
<th>DrugSet Molecule Name</th>
<th>DrugSet Molecule (DSM)</th>
<th>DSM Observed LD50</th>
<th>DSM Reference</th>
<th>DSM Activity Class (CMC)</th>
<th>RefSet Most Similar Molecule (RSM)</th>
<th>RSM Observed LD50</th>
<th>RSM Reference</th>
<th>DSM Prediction Error: (Pred-Obs)</th>
<th>Num Ref Sim Mol</th>
<th>Tanimoto DSM&amp;RSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLUNISOLIDE</td>
<td><img src="image" alt="FLUNISOLIDE" /></td>
<td>&gt;500 ug/kg</td>
<td>Gekkan Yakuji 26,501,1984</td>
<td>Glucocorticoid</td>
<td>DrugSet DSM</td>
<td>&gt;4 gm/kg</td>
<td>Drugs in Japan (Ethical Drugs) 6,694,1982</td>
<td>3.19</td>
<td>4</td>
<td>0.94</td>
</tr>
<tr>
<td>GLYPINAMIDE</td>
<td><img src="image" alt="GLYPINAMIDE" /></td>
<td>&gt;5 mg/kg</td>
<td>Patent, French Medicament Document #1087M</td>
<td>Antidiabetic</td>
<td>DrugSet DSM</td>
<td>&gt;5 gm/kg</td>
<td>Drugs in Japan (Ethical Drugs) 6,511,1982</td>
<td>2.96</td>
<td>2</td>
<td>0.87</td>
</tr>
<tr>
<td>BENZQUINAMIDE</td>
<td><img src="image" alt="BENZQUINAMIDE" /></td>
<td>1050 mg/kg</td>
<td>Psychotropic Drugs and Related Compounds - 208,1972</td>
<td>Antiemetic</td>
<td>DrugSet DSM</td>
<td>990 mg/kg</td>
<td>Toxicology and Applied Pharmacology 18,185,1971</td>
<td>-2.48</td>
<td>2</td>
<td>0.99</td>
</tr>
<tr>
<td>FLOCACITRIOL</td>
<td><img src="image" alt="FLOCACITRIOL" /></td>
<td>41700 ng/kg</td>
<td>Kiso to Rinsho 30,2695,1996</td>
<td>Ca regulator</td>
<td>DrugSet DSM</td>
<td>620 ug/kg</td>
<td>Patent, Japanese Kokai Tokyo Koho #94-247858</td>
<td>2.17</td>
<td>7</td>
<td>0.86</td>
</tr>
<tr>
<td>PIFLUTIXOLE</td>
<td><img src="image" alt="PIFLUTIXOLE" /></td>
<td>1500 ug/kg</td>
<td>Patent, United States Document #4309429</td>
<td>Neuroleptic</td>
<td>DrugSet DSM</td>
<td>&gt;60 mg/kg</td>
<td>Patent, United States Document #4309429</td>
<td>2.16</td>
<td>2</td>
<td>0.81</td>
</tr>
<tr>
<td>NIXYLIC ACID</td>
<td><img src="image" alt="NIXYLIC ACID" /></td>
<td>2300 ug/kg</td>
<td>Therapie 22,157,1967</td>
<td>Antiinflammatory</td>
<td>DrugSet DSM</td>
<td>250 mg/kg</td>
<td>Journal of Medicinal Chemistry 16,780,1973</td>
<td>2.10</td>
<td>2</td>
<td>0.94</td>
</tr>
<tr>
<td>INDOMETHACIN</td>
<td><img src="image" alt="INDOMETHACIN" /></td>
<td>2420 ug/kg</td>
<td>Arzneimittel-Forschung 25,1526,1975</td>
<td>Antiinflammatory</td>
<td>DrugSet DSM</td>
<td>21 mg/kg</td>
<td>Gekkan Yakuji 37,952,1995</td>
<td>1.93</td>
<td>24</td>
<td>0.86</td>
</tr>
<tr>
<td>TRYPTOPHAN</td>
<td><img src="image" alt="TRYPTOPHAN" /></td>
<td>&gt;16 gm/kg</td>
<td>Iyakuhin Kenkyu 11,635,1980</td>
<td>Antidepressant</td>
<td>DrugSet DSM</td>
<td>22 mg/kg</td>
<td>Toxicology and Applied Pharmacology 4,547,1962</td>
<td>-1.81</td>
<td>4</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Table 2. DrugSet prediction outliers. The reported LD50’s for the query DrugSet molecules (DSMs) and for their respective maximally similar molecules in the reference set (RSMs) show significant differences despite high Tanimoto similarity between DSM and RSM. This helps explain the fairly large absolute, signed DSM prediction error: pLD50(pred)-pLD50(obs).
How to Enhance Toxicity Predictions?

CMC Oral Rat LD50 predictions with Growing Reference Set
nMaxRef = 13645 nCMC = 1781 SimCut: 0.75 #Members: 1
Summary & Conclusions

- Reasonably accurate and robust toxicity predictions can be achieved with a reference similarity approach.
- Small to moderate consortia per compound-class may suffice to build a well rounded reference set.
- An increase in reference set size is likely to improve both the quality and quantity of toxicity predictions.
- Significant opportunity exists to enhance the “Starter” reference set, which only scratches the surface…
- Prediction technique can be readily incorporated into a high-throughput in silico eScreening strategy (e.g. compound prioritization, filtration, etc.).
There Can Be Safety In Numbers...
Supplementary Slides
Global Pharmaceutical R&D Expenditure by Country

ADRs are a major cause of Death

Adverse Drug Reactions may be the fourth to sixth leading cause of death

<table>
<thead>
<tr>
<th>Deaths Per Year</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>106,000</td>
<td>Non-error, negative effects of drugs¹</td>
</tr>
<tr>
<td>80,000</td>
<td>Infections in hospitals⁴</td>
</tr>
<tr>
<td>45,000</td>
<td>Other errors in hospitals⁴</td>
</tr>
<tr>
<td>12,000</td>
<td>Unnecessary surgery²</td>
</tr>
<tr>
<td>7,000</td>
<td>Medication errors in hospitals³</td>
</tr>
<tr>
<td>250,000</td>
<td>Total deaths per year from iatrogenic* causes</td>
</tr>
</tbody>
</table>

* The term *iatrogenic* is defined as "induced in a patient by a physician’s activity, manner, or therapy. Used especially to pertain to a complication of treatment."


See: http://www.chelationtherapyonline.com/articles/p62.htm
## Attrition: The Reasons Have Been Cited…

<table>
<thead>
<tr>
<th>Reasons for Failure</th>
<th>Reasons for Slow Down</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor biopharmaceutical properties, 41%</td>
<td>Poor biopharmaceutical properties</td>
</tr>
<tr>
<td>Lack of efficacy, 31%</td>
<td>Low potency</td>
</tr>
<tr>
<td>Toxicity, 22%</td>
<td>Ambiguous toxicity finding</td>
</tr>
<tr>
<td>Market reasons, 6%</td>
<td>Inherently time-intensive target indication</td>
</tr>
<tr>
<td></td>
<td>Synthetic complexity</td>
</tr>
</tbody>
</table>

• Lipper, R.A. How can we optimize selection of drug development candidates from many compounds at the discovery stage? *Modern Drug Discovery*, 1999, 2 (1), 55-60.
Causes of attrition during drug development