Format of this Talk

- I’m going to walk you through some of the concepts regarding drug discovery toxicology.
- This is just a framework, so I’d like today to be an interactive process.
- I’ll ask questions and hope that you will do so too.
- Don’t worry about asking “stupid” questions. I’ve based a career around this.
Objectives to Understand

- How and Why Do Drugs Fail?
- Definition of Drug Discovery Toxicology
- How to Select the Right Target
- How to Select the Right Series
- How to Select the Lead Compound

Attrition Due to Safety Remains High

Attrition data 2005-2010
Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework.

Clinical development success rates for investigational drugs.
Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J.
Quiz #1: True or False?

- Most drugs fail in the clinic
- All drugs on the market are safe
- Only mice predict human safety
- Non rodent species are better predictors of human toxicity
- Animals predict human toxicity 100%
- We need better safety testing
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Drug Discovery Toxicology

- The primary objective of drug discovery toxicology is to apply tools and methods at each step of the drug discovery process
- “Fail early”
- Use human predictive *in vitro* models where animals do not translate well
- Select the best compound for *in vivo* animal studies
The Drug Discovery Process

1-12 months
The RIGHT Target

1-2 years, 1-5 series
Lead Compound Identification

1-3 years, 1-100 compounds
Lead Compound Optimization

1-2 years, 1-5 compounds
Lead Candidates

6-12 months, 1-5 compounds
Non-Clinical Studies

Clinical Phases

Discovery Toxicology

Quiz #2: Why Do We Need Drug Discovery Toxicology? True or False?

- We don’t because all marketed drugs are safe
- Because we keep losing drugs due to safety issues
- Late stage failure is very expensive
- Failure due to safety is detrimental to patients
- We need to develop models that translate better than animal studies
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Target Identification

- Identifying the biological origin of a disease and potential targets for intervention
- A good target needs to be efficacious, safe, meet clinical and commercial needs and above all, be “druggable”
- A “druggable” target is assessable to the putative drug molecule and upon binding elicits a biological response which may be measured in vitro or in vivo
- The “drug” can be a small or a large molecule
- It is intended that the modification of the pathway will produce a beneficial effect on a disease process

*A compound foreign to an organism*
Target Information Resources: Helping You Build Hypotheses

**What’s Known About My Target?**

Ensembl ([http://uswest.ensembl.org/index.html](http://uswest.ensembl.org/index.html))

  Association the genes with genetic disorders

JAX Lab Mouse Phenome ([http://phenome.jax.org/](http://phenome.jax.org/)) Mouse phenotype database

**Where is My Target Expressed?**

Protein:

mRNA:
  - BioGPS ([http://biogps.gnf.org/#goto=welcome](http://biogps.gnf.org/#goto=welcome)) Affymetrix chip information
  - BGEM ([http://www.gensat.org/index.html](http://www.gensat.org/index.html)) Brain staining in transgenic mice

**Can I Better Understand the Pathway?**


**Is There Relevant Compound Information?**

Pharmapendium ([https://www.pharmapendium.com/](https://www.pharmapendium.com/)) approved and withdrawn drugs against the target
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**The Drug Discovery Process**

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  - The RIGHT Target

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- **6-12 months, 1-5 compounds**
  - Non-Clinical Studies
  - Clinical Phases

**Discovery Toxicology**

**Series Selection:**

- Segregating volumes of compounds into high vs. low probability buckets for safety (generic) findings in short-term rat studies

  - Unfavorable physical-chemical property space increase the odds for adverse findings

  - Cytotoxicity assessment predicts “general” outcomes in rat studies
Using *In Vivo* Study Data to Establish Toxicity Dose Relationship

Results of an analysis of in house *in vivo* exploratory toxicity studies on >1000 compounds covering >100 targets at multiple doses

High Concentration

- Toxic Exposures
- C\text{max}\text{LowTox}
- C\text{max}\text{HiCln}
- Minimum exposure with observed toxicity (C\text{max}\text{LowTox}). Set to an arbitrarily high number if no toxic event is observed at any dose
- Maximum exposure without observed toxicity (C\text{max}\text{HiCln}). Set to zero if toxicity was observed at all doses assessed

Low Concentration

- Clean Exposures

Courtesy of Nigel Greene

Unfavorable Physiochemical Properties Increase Odds for Toxicity

<table>
<thead>
<tr>
<th>Low hydrophilicity, more lipophilic</th>
<th>ClogP &gt; 3</th>
<th>ClogP &lt; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Drug</td>
<td>2.4 (85)</td>
<td>1.08 (27)</td>
</tr>
<tr>
<td>TPSA &lt; 75</td>
<td>0.41 (38)</td>
<td>0.39 (57)</td>
</tr>
</tbody>
</table>

A compound that flags both properties is *six times* more likely to cause findings in a rodent study at Cmax<10μM than a compound that does not flag in either of these properties.
Quiz #3: True or False

- A compound’s lipophilicity is called ClogD
- A compound’s lipophilicity is called ClogP
- Compounds with CLogP>3 are the “safest” compounds
- All compounds have the same TPSA value
- Compounds with large TPSA are the “safest” compounds
- ClogP>3 and TPSA<75 increases your odds for a safety finding

Importance of Reducing Cytotoxicity

Compounds with high cytotoxicity are more likely to have significant findings in *in vivo* rat studies at lower exposures!

Cytotoxicity in HepG2 cells

| Concentration (uM) | Toxicity
|-------------------|----------
| <10               | 7.1 %    |
| 10-50             | 29.5 %   |
| 50-100            | 29.5 %   |
| >100              | 11.2 %   |

Cmax of Significant Tox
- ≤ 100nM
- 100nM - 1uM
- > 1uM
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Discovery Toxicology

#2017SOT #toxexpo
**Lead Selection**

- Segregating handful of compounds into high vs. low probability buckets of specific organ risks (e.g., liver vs. cardiac)
  - Do cells from specific organs predict specific organ toxicity
  - How important are mechanistic endpoints in detecting specific organ toxicities
  - The importance of Cmax prediction. Normalization increases predictivity.

**Do Cells From Specific Organs Predict Specific Risk?**

Inhibition of Hepatobiliary Transport as a Predictive Method for Clinical Hepatotoxicity of Nefazodone

Seva E. Kontubinsky,* Stephen C. Stones, Amit S. Kalugutkar, Shalini Kulkarni, James Atherton, Rochelle Marles, Nan Feng, Rajendra Kotha, James Hansen, Ellen Ueda, and Abdul R. Mustafa

*Department of Safety Science and Pharmacokinetics, Dynamics and Metabolism, Pfizer Global Research and Development, Ann Arbor, Michigan 48105 and Pfizer’s Toxicology, Department of Safety, Pfizer, Research Triangle Park, North Carolina 27709


However, In Vitro Assays Are Predictive of Outcome

PATIENT RELATED FACTORS

- Underlying disease
- Co-medications (herbals, APAP) and concurrent exposures (including environmental and work-related)
- Age, diet and gender
- Physical activity
- Genetic acquired variability (e.g., in CYPs, transporters, HLA)
- Innate and adaptive immune response

DRUG RELATED FACTORS

- Overt Cytotoxicity
- Metabolism-related toxicity
  - Bioactivation and covalent binding to macromolecules
  - Non-metabolism-related toxicity
  - Inhibitions of key cell functions (e.g., mitochondrial, lysosomal, biliary)
- Kinetics of the drug and its metabolites
- Tissue Exposure

Known Risk Factors for Hepatic Injury

Comparison of the Bioactivation Potential of the Antidepressant and Hepatotoxin Nefazodone with Aripiprazole, a Structural Analog and Marketed Drug

Jonathan N. Bauman, Kowsa S. Frederick, Aarti Samant, Robert L. Walsky, Loretta M. Cox, Ronald S. Obach, and Amit S. Kalugutkar

Pharmacokinetics, Dynamics, and Metabolism, Pfizer Global Research and Development, Groton, Connecticut

Received January 22, 2000; accepted March 5, 2000
Quiz #4: If I Want to Predict a Specific Organ Toxicity I Need to... True or False?

- Buy hepatocytes, cardiomyocytes, and kidney cells and measure cell death
- I need to measure organ specific mechanisms
- I need to have a set of reference compounds

Overall Vision for Drug Discovery Toxicology

- Series
  - General vs. Hazard screening
- Lead selection
  - Hazard vs. Risk screening
- Relative Risk vs. Specific Risk
  - You don’t care if your toxicity occurrence is 1 in 1 million unless you are the millionth person

Quiz #5: What Does a Drug Discovery Toxicologists Do? True or False?

- Conduct lots of rodent studies to find the best drug
- Comes in late to work and leaves early
- Engages at target selection
- Helps find the best series
- Helps to select the best lead compound

If you would like to know more...
Quiz 6: How Do I Become a Drug Discovery Toxicologist? True or False

- I work as a zoo keeper
- I need to have a chemistry degree
- I select a degree in science such as toxicology, biochemistry, pharmacology

Acknowledgements

- Sponsored by Society of Toxicology, Committee on Diversity Initiatives, Undergraduate Diversity Program 2017
- Thank you all