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

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Computational Sciences CoE

Guiding Optimal Compound Design & Development

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Pfizer

WORLDWIDE RESEARCH & DEVELOPMENT

Medicinal Chemistry

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

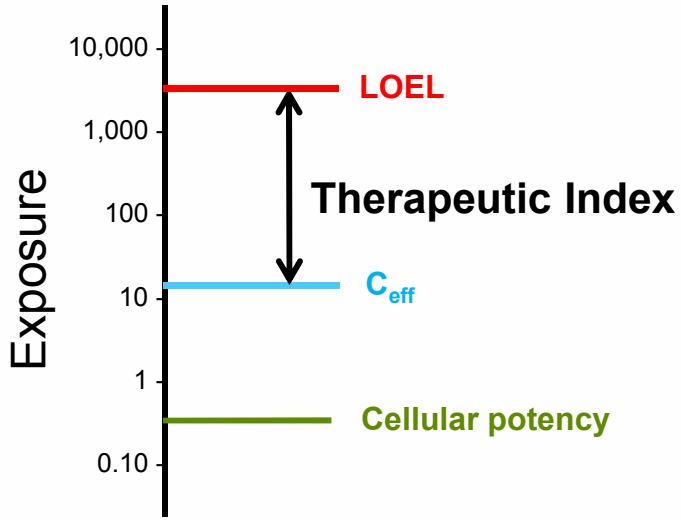
- What does the compound do to affect cellular function?
- "Safety"

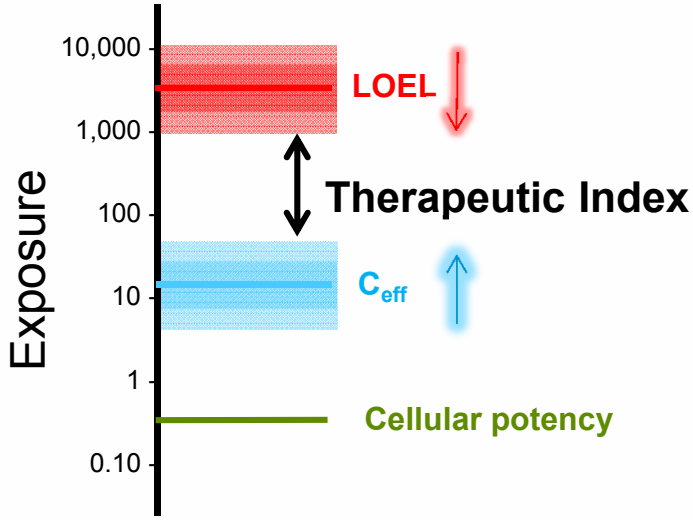
Level of Exposure

- 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





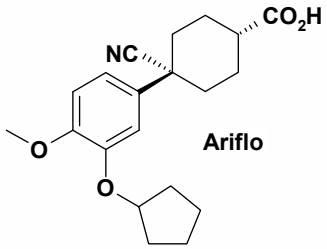
- Why risk a safety liability?
- Find *productive* chemistry space early

The Basic Question

What design features signpost risk?

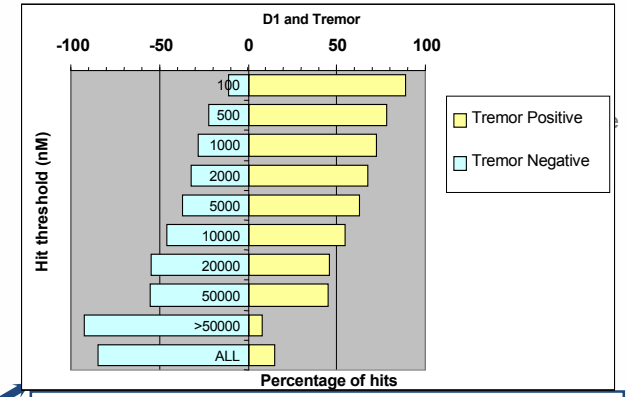
Factors that Influence Safety Profiles

PDE-4 inhibitors are linked to emesis and vasculitis



Ariflo

D1 activity is linked to tremor



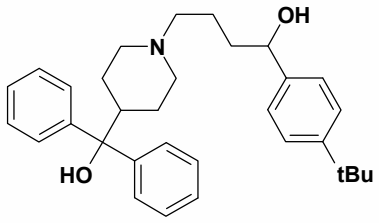
Primary pharmacology

Secondary pharmacology

Origins of adverse safety profile

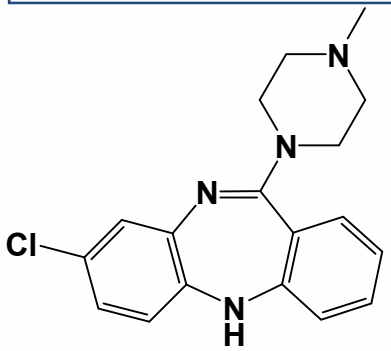
Physicochemical properties

Chemical structure



Terfenadine

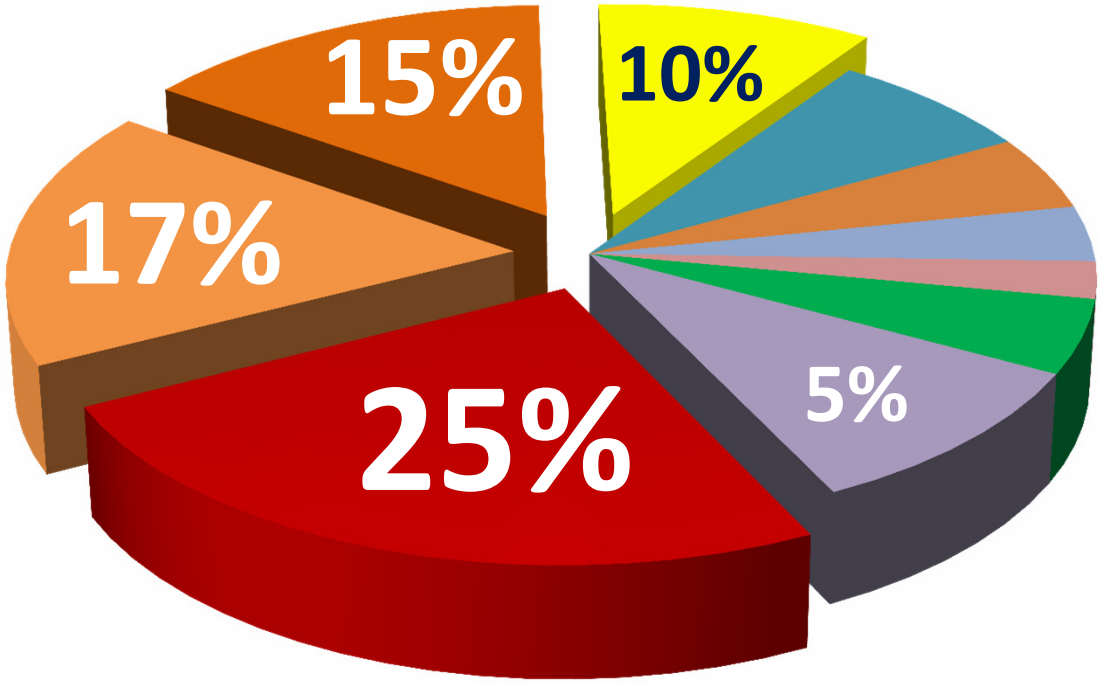
Lipophilic basic compounds at risk of:
Phospholipidosis
QT interval prolongation



Clozapine

Clozapine causes agranulocytosis and forms reactive metabolites

Structural Alerts: 81 drugs withdrawn for idiosyncratic toxicity reasons



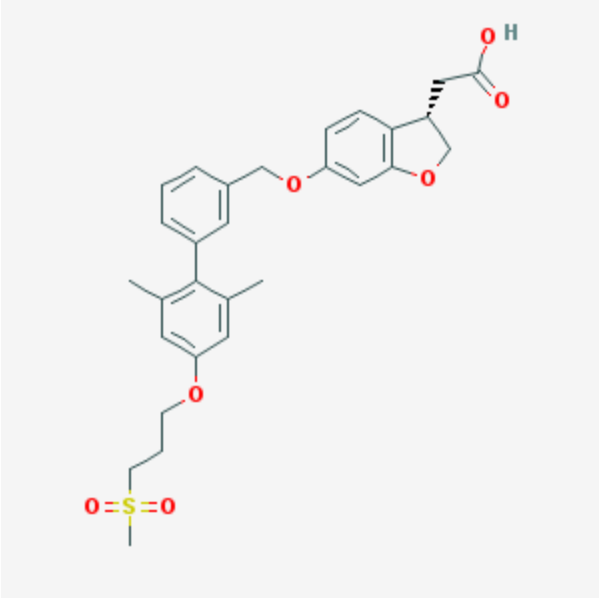
- **aniline group**
- **quinone group**
- **e rich Ar group**
- **acyl glucuronide group**

67%

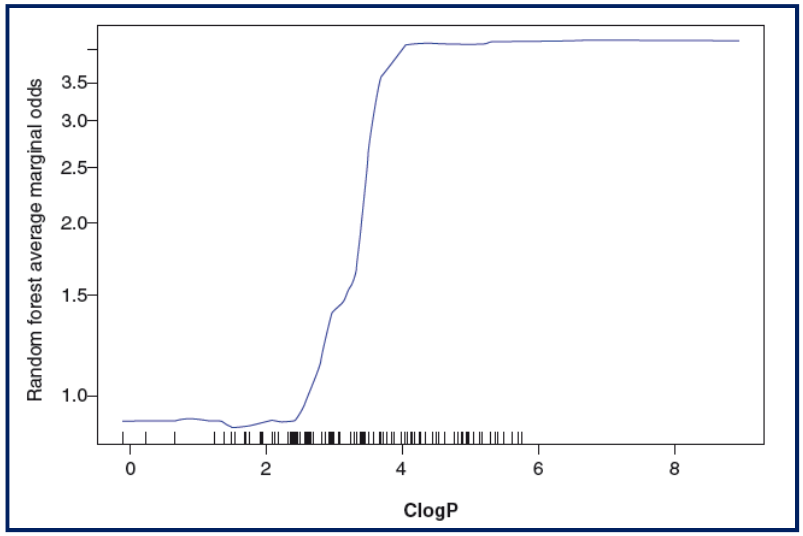
- quinolone
- hydrazide/hydrazine
- Michael
- benzodioxolane
- ***none group***
- other STAs (singletons)

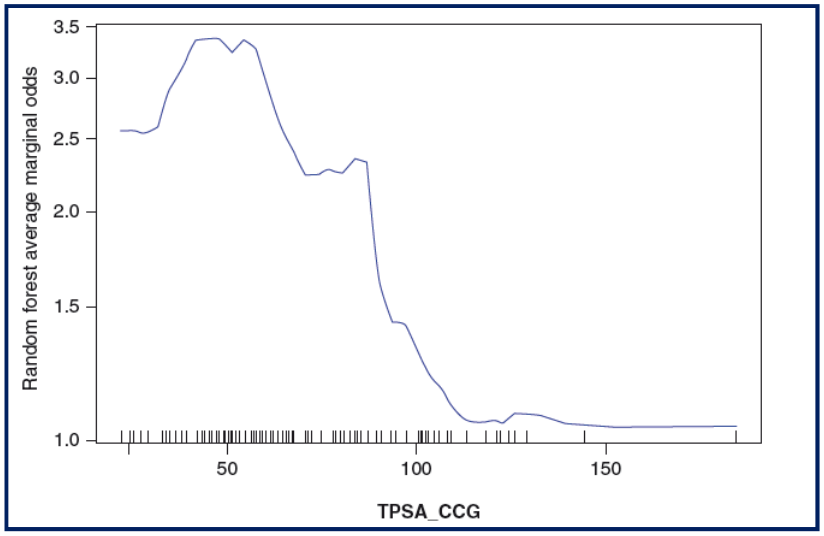
Recent Example: Fasiglifam (TAK-875)

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





Total Drug	TPSA < 75	TPSA>75
ClogP > 3	2.4 (85)	0.41 (38)
ClogP < 3	1.08 (27)	0.39 (57)

A compound that flags both properties is ~**six times** more likely to cause findings in a IVT study at Cmax<10μM than a compound that does not flag in either of these properties.

Expert Opin. Drug Metab. Toxicol. (2009) **5**(8)

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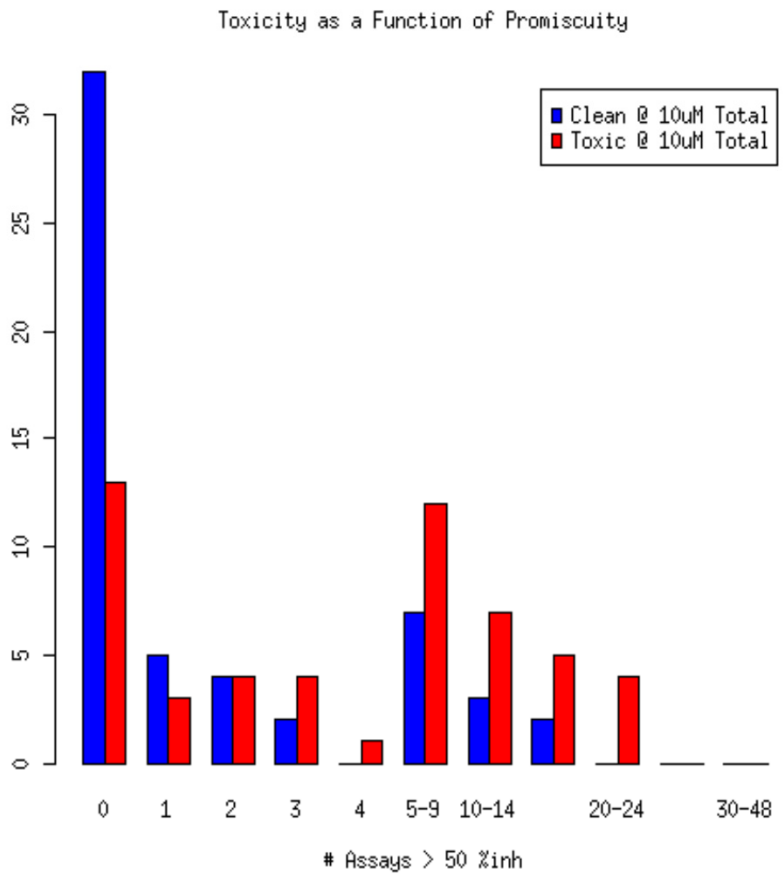
Off Target promiscuity



Ratio of promiscuous to non-promiscuous compounds

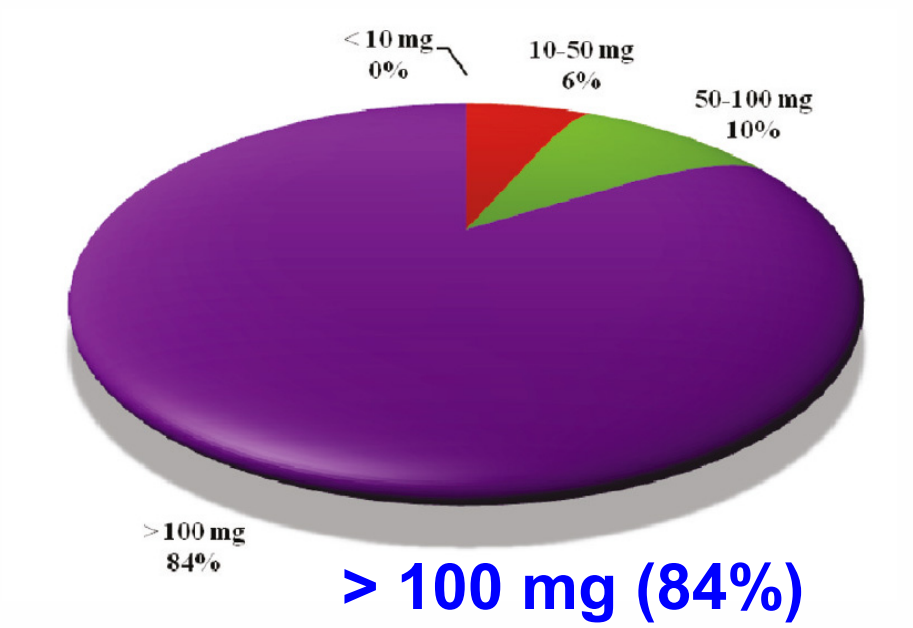
Cerep	TPSA < 75	TPSA>75
ClogP > 3	6.25 (29)	0.44 (13)
ClogP < 3	0.80 (18)	0.25 (25)

Odds Ratio = 25 X

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

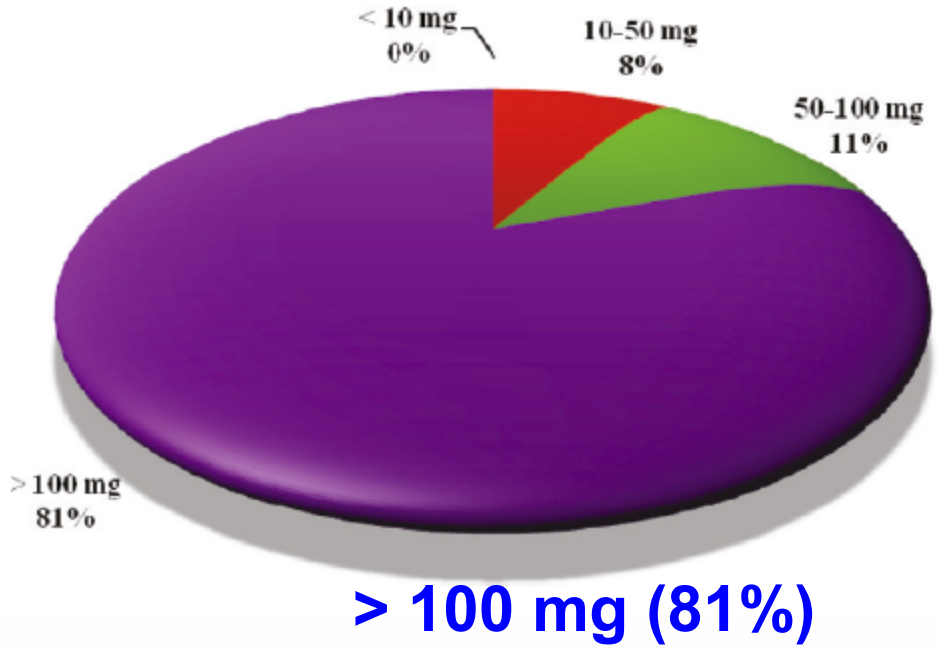
Impact of daily dose on IADRs

Drugs withdrawn due to IADRs



> 100 mg (84%)

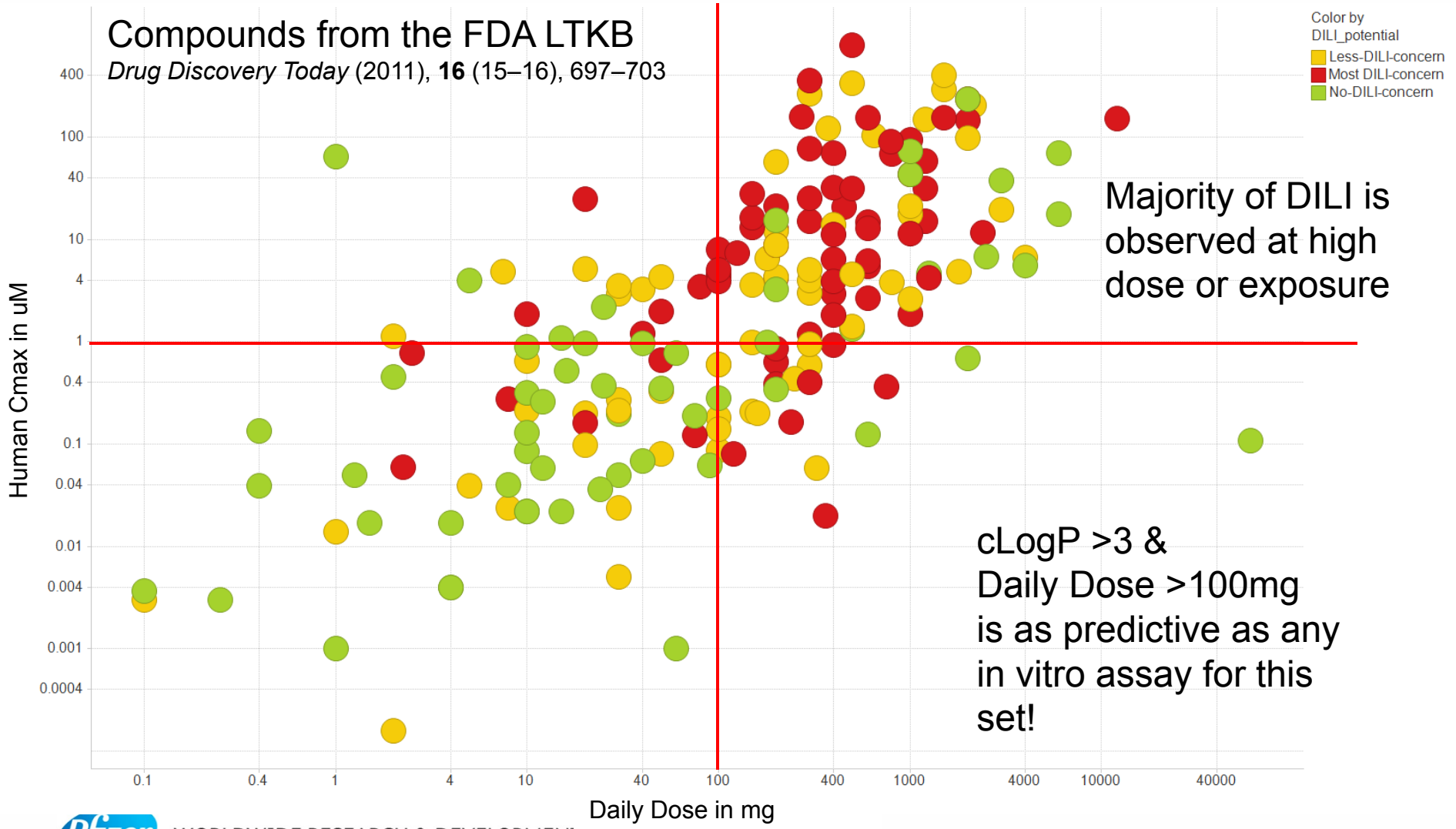
Drugs associated with BBW



> 100 mg (81%)

Drugs associated with IADRs are frequently the ones with a *higher* daily dose

What About Liver Injury



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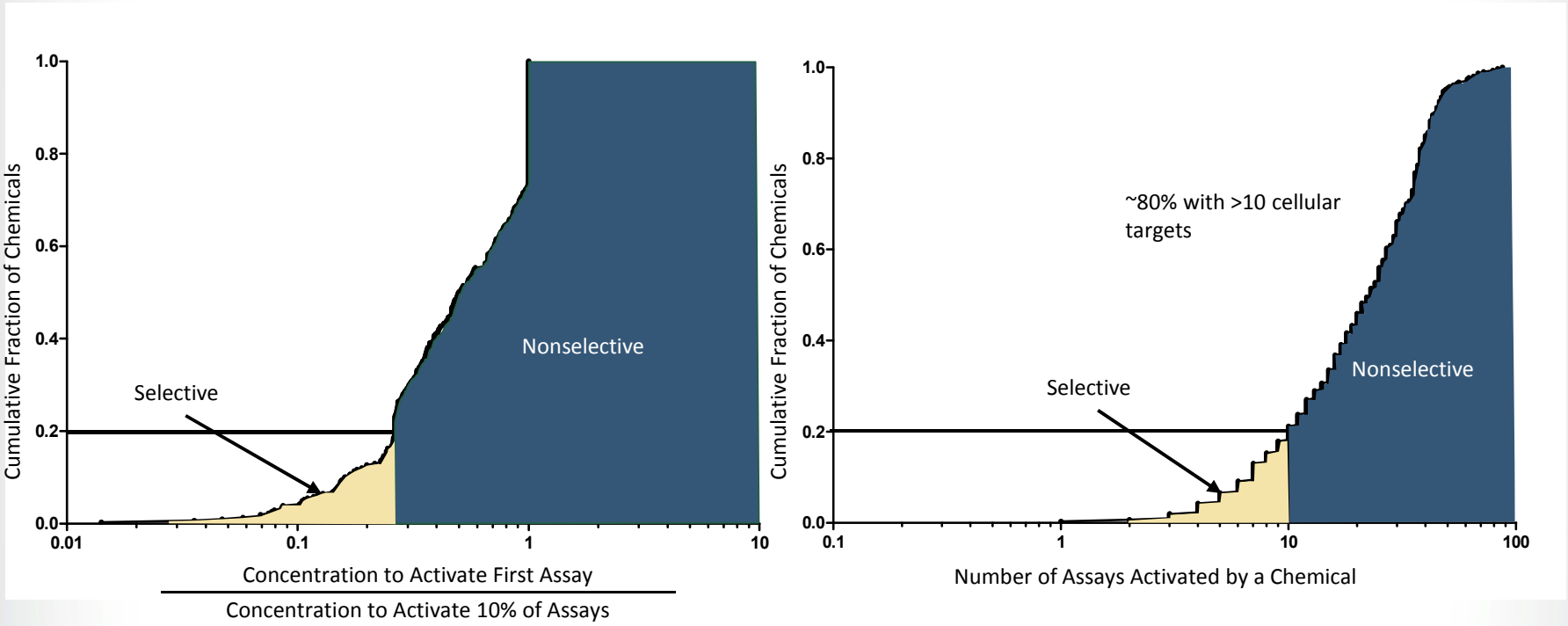
What Have We Learned From High-Throughput Screening?

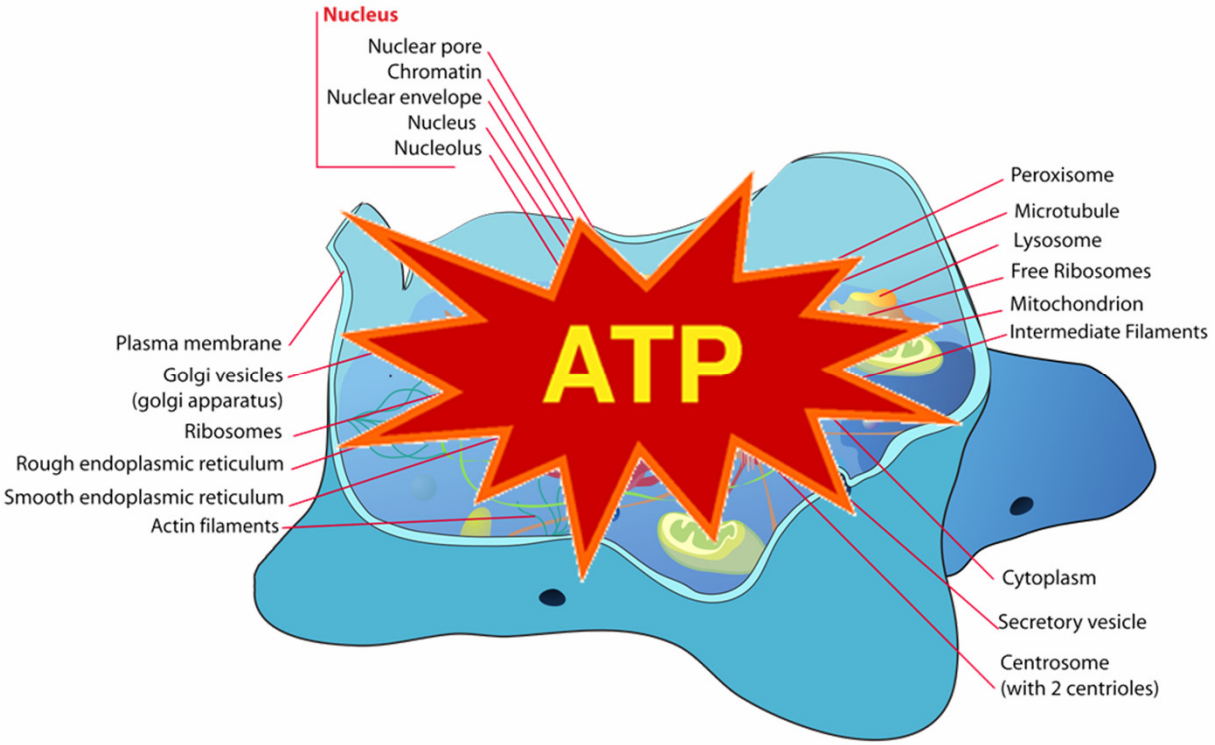


Hypothesis: ~80% of chemicals cause toxicity through non-specific interactions

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)

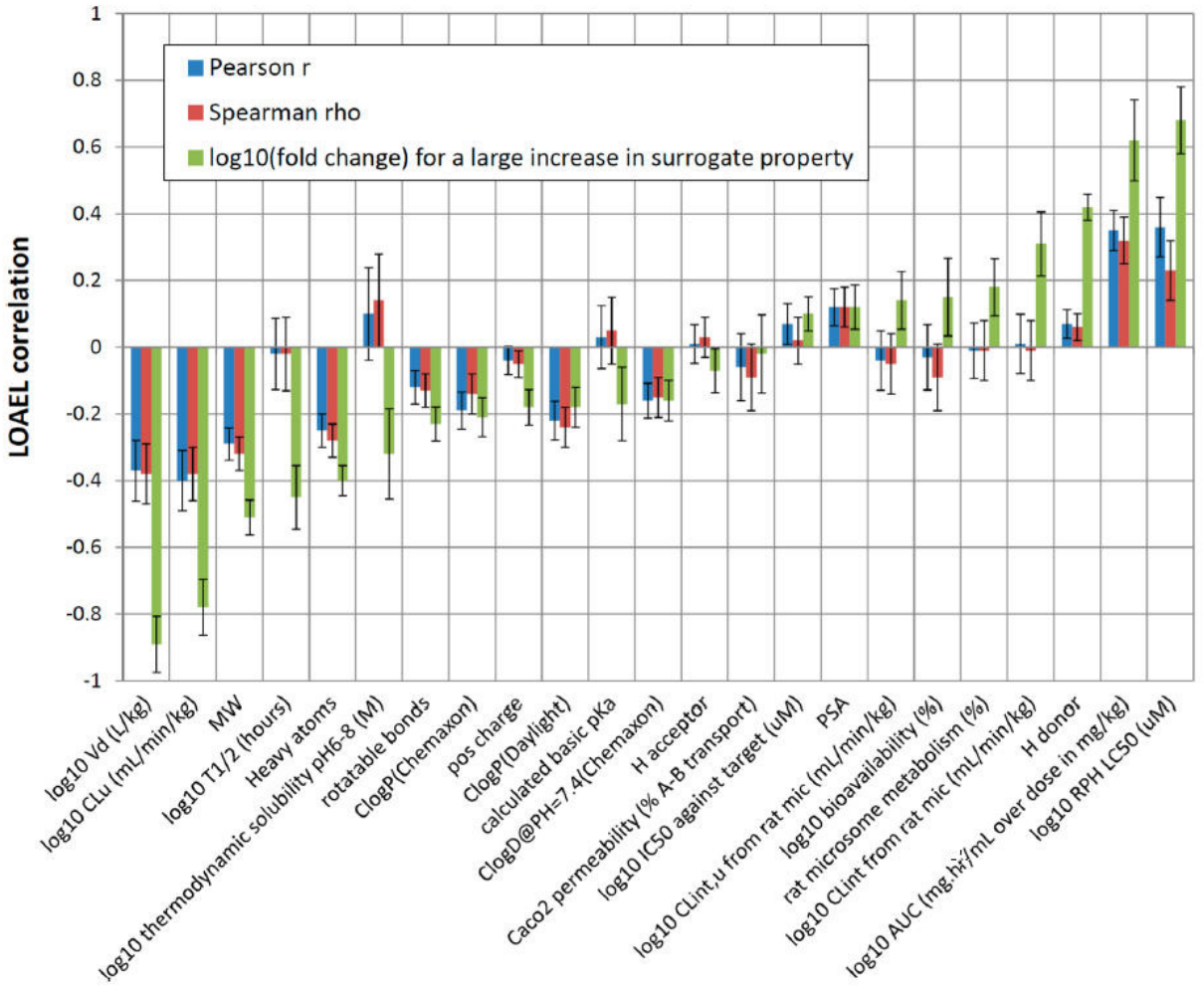


Properties related to LOAEL

Sutherland, J.J., *et al.*, J Med Chem, 2012. **55**(14): p. 6455-66.

LOAEL = Lowest Observable Adverse Effect Level

- Volume of distribution and cytotoxicity had largest impact on LOAEL in a rodent study.
  - Increase in Vd → Decrease in LOAEL
  - Increase in LC50 → Increase in LOAEL



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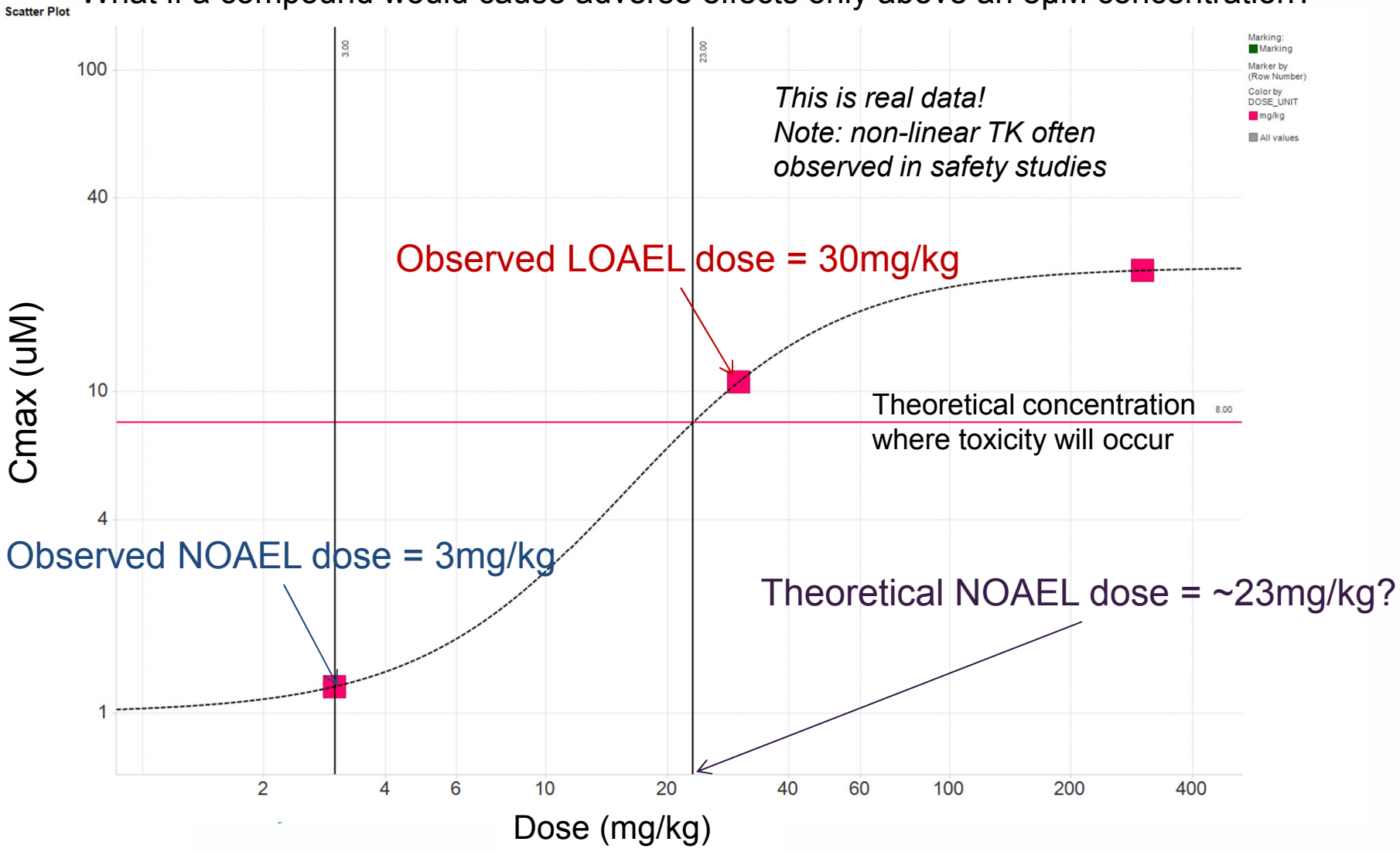
The Problem with using LOAELs

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?



A Strategy for Predicting Toxicity

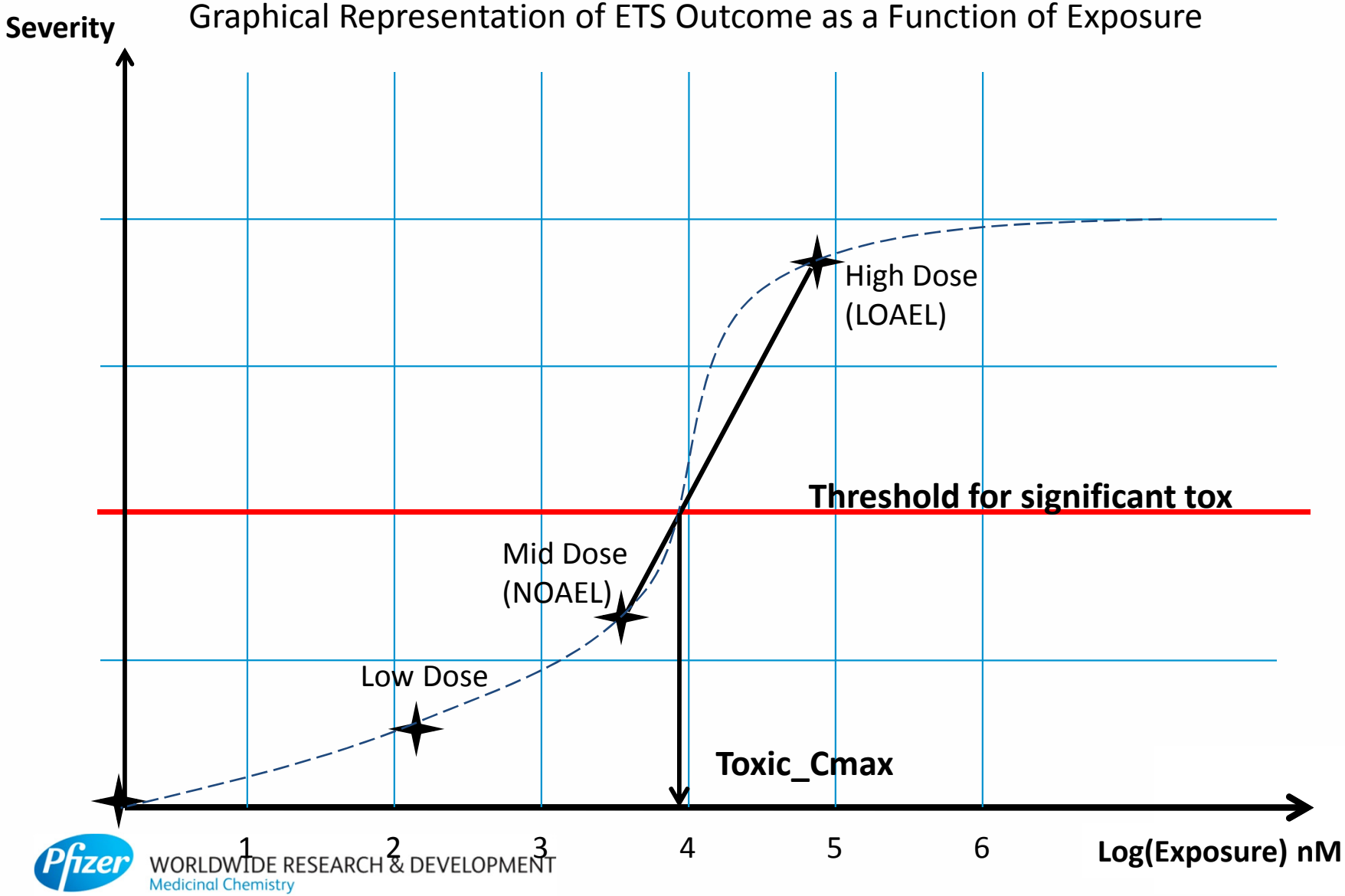
- If most toxicity is driven through non-specific binding interactions…
- … and if local dose (concentration) makes the poison…
- … then target organ will depend heavily on specific tissue distribution

- 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

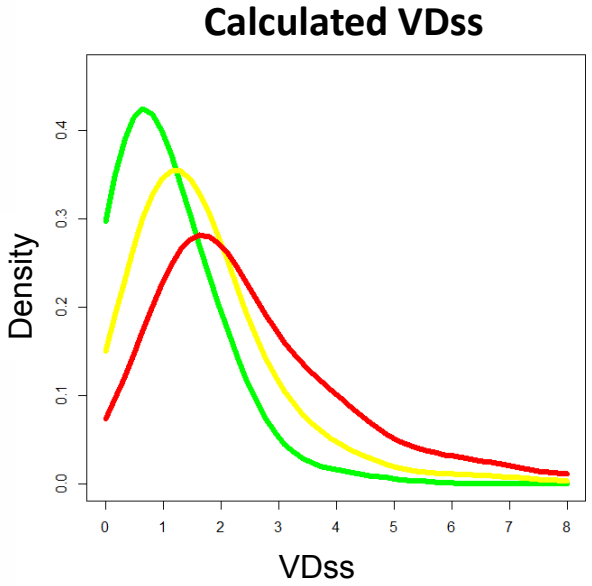


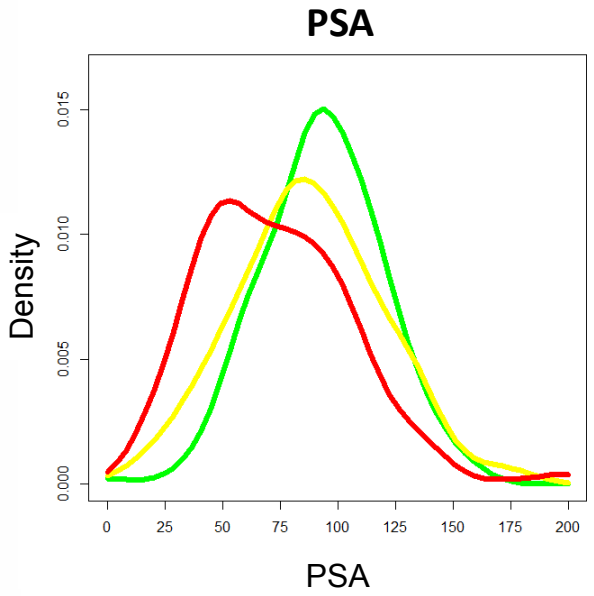
Correlations to Toxic_Cmax

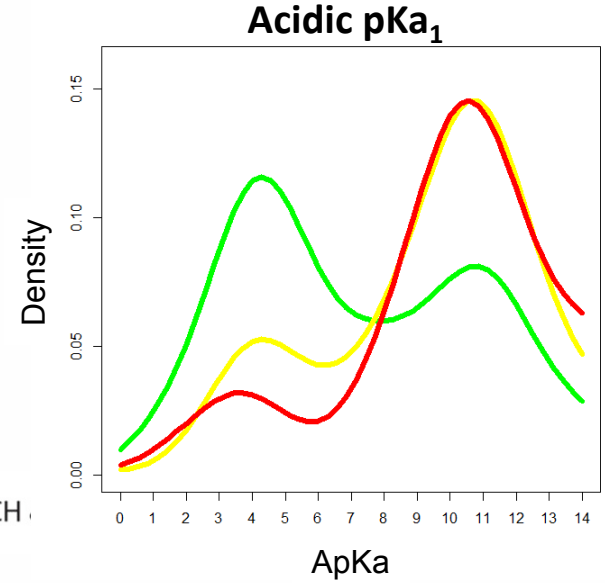
Tox_Cmax < 3μM

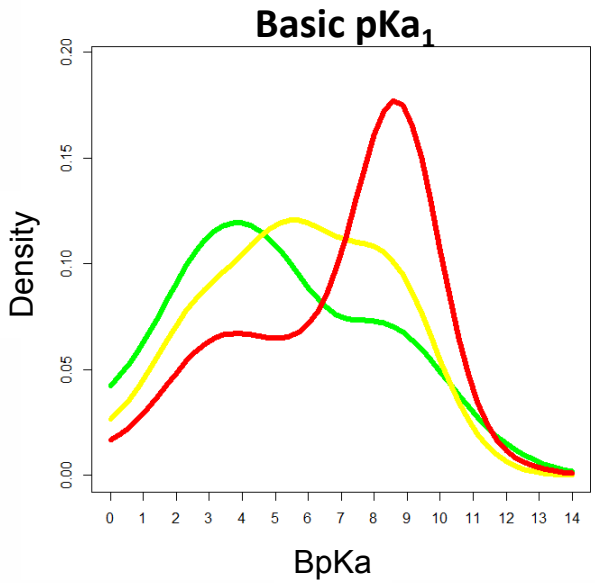
3μM < Tox_Cmax < 30μM

Tox_Cmax >30μM









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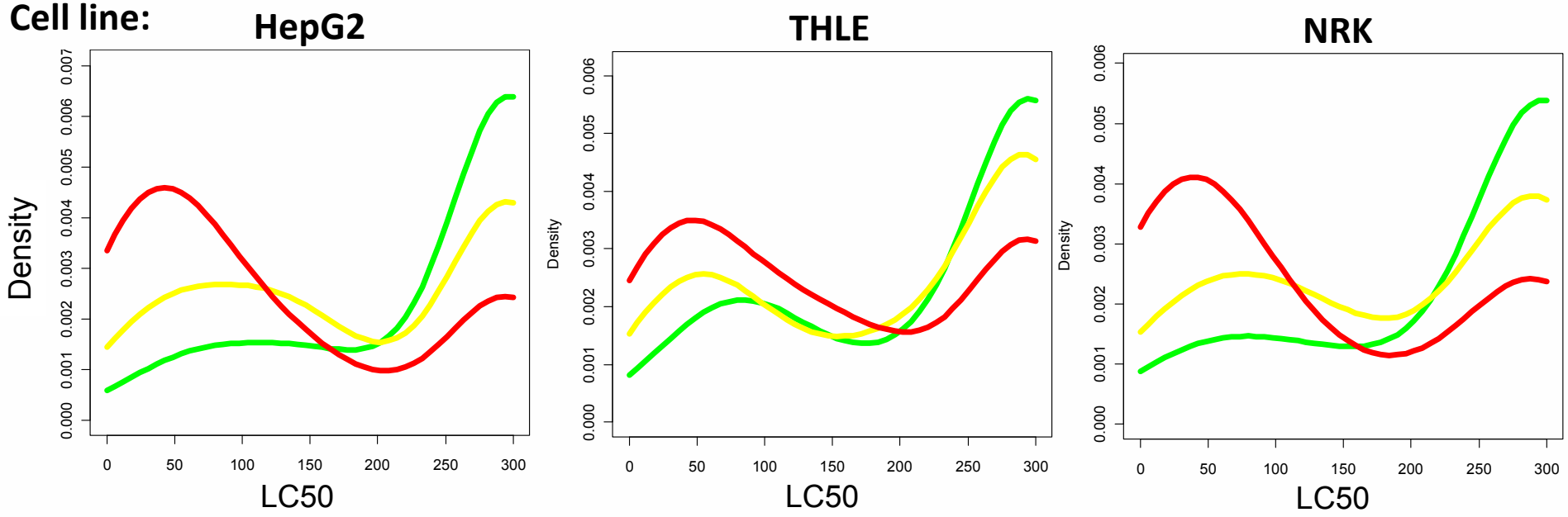
Comparing Assays to Toxic Cmax

Tox_Cmax < 3μM

3μM < Tox_Cmax < 30μM

Tox_Cmax >30μM

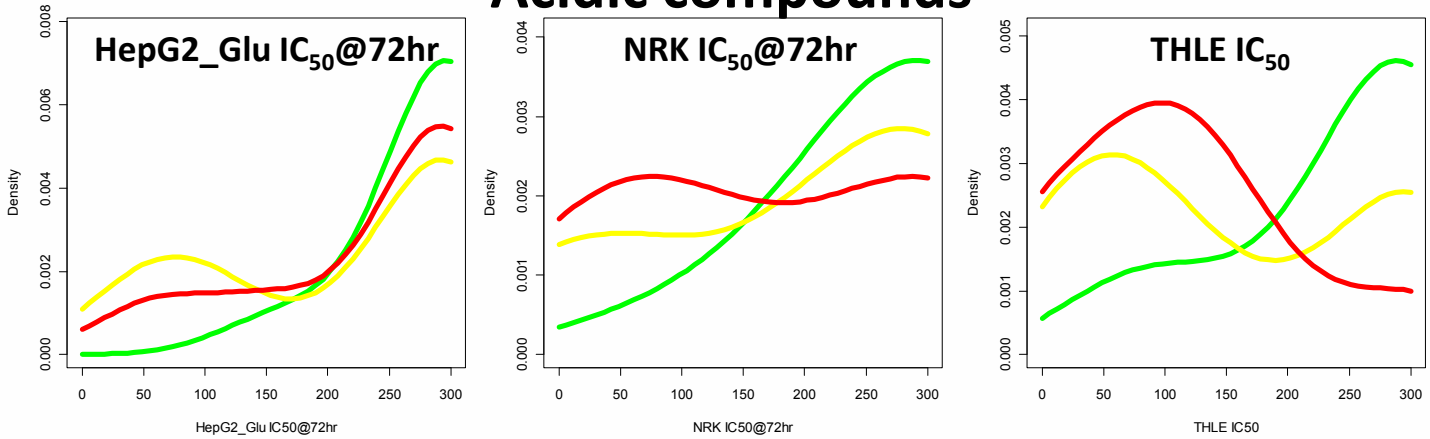
Cell line:



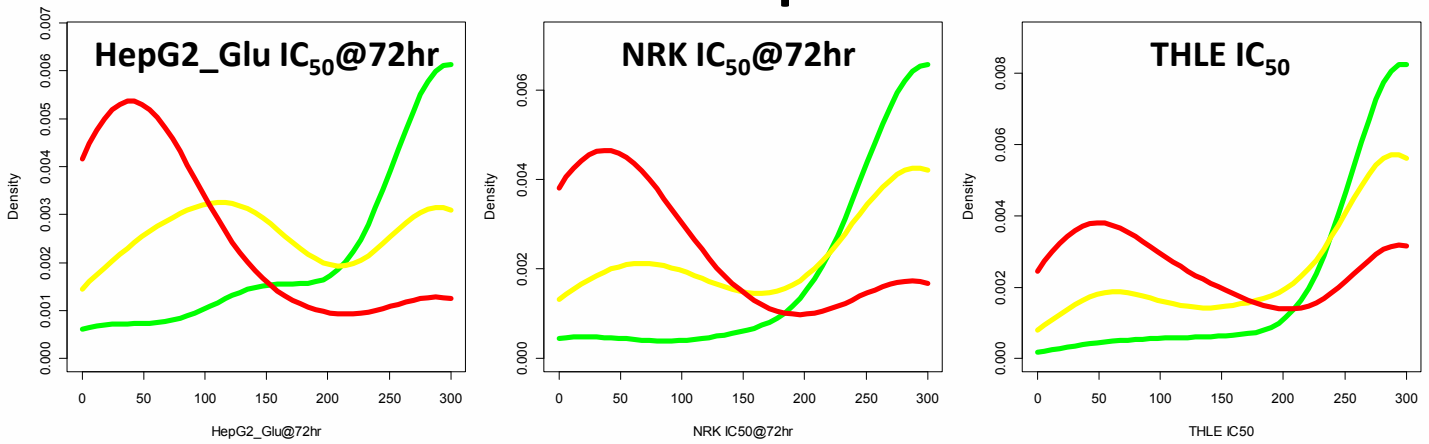
- "Diverse" dataset combining of basic, netrual and acidic compounds

The Importance of Ionization State

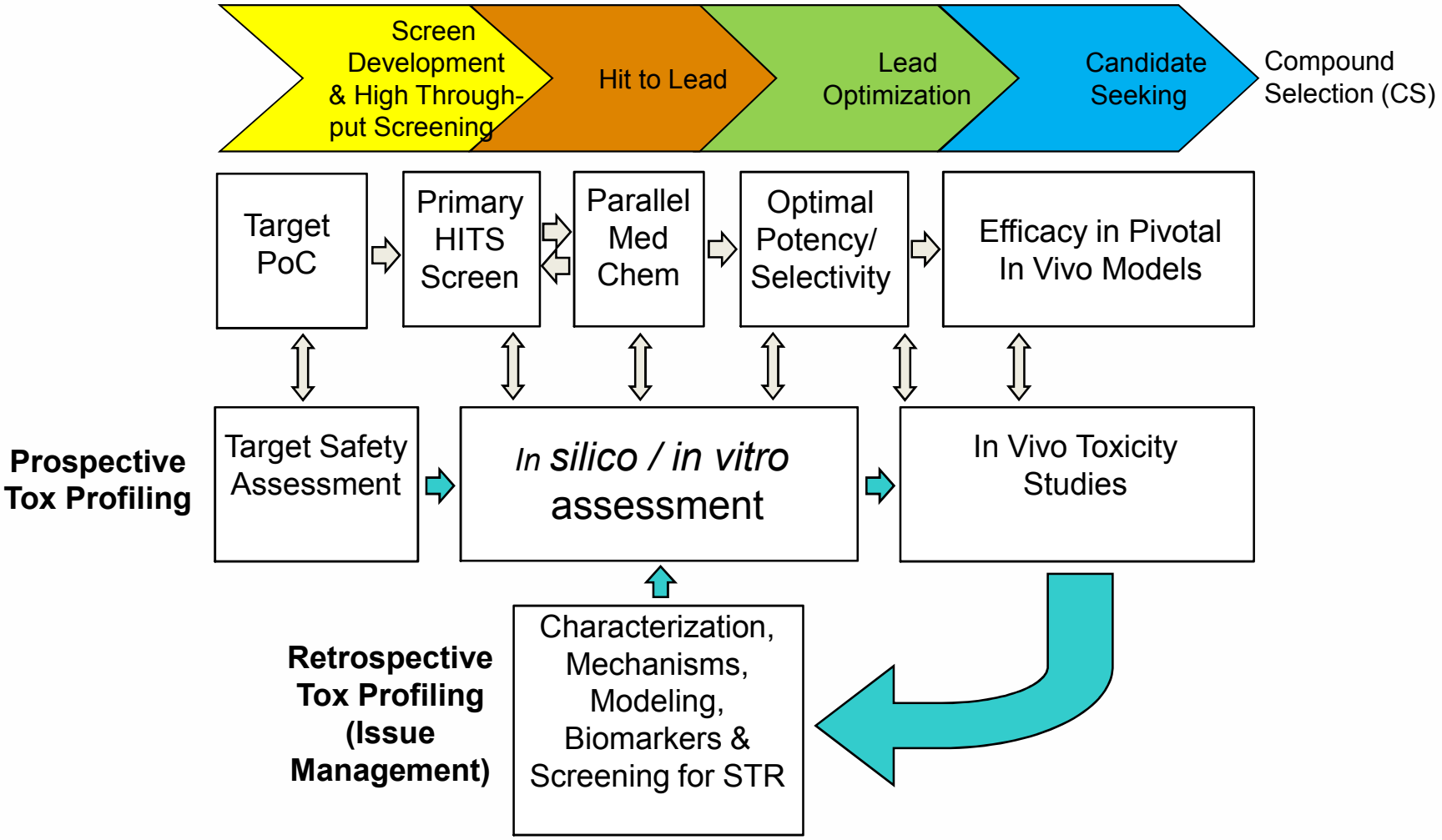
Acidic compounds



Basic compounds



Toxicity Profiling in Drug Discovery



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

Acknowledgements

- William Pennie
- Karen Leach
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- Sarah Skerratt
- Ian Storer
- Rob Owen
- Kevin Dack

And many others!!

Q&A