What's Down the Road for Drug Metabolism Support of Drug Discovery?

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Why Do We Need DMPK Support of Drug Discovery?

We want to build "drug-like" properties into our clinical candidates:

Efficacy: the intrinsic potency and effectiveness of the compound to produce a desired pharmacological effect.

Availability: the ability of the compound to pass through multiple biological barriers to reach the target receptor. Includes oral bioavailability and adequate distribution to the target organ.

Persistence: sufficient residence time at the target receptor so that pharmacological effects have a clinically meaningful duration. Persistence is usually expressed as the plasma elimination half-life.

Safety: sufficient selectivity for the target receptor so that an adequate dose range exists in which the intended pharmacological action is essentially the only physiological effect of the compound.

Practicality: pharmaceutical properties of the compound, including solubility, chemical stability, crystallinity, *etc*., which allow the drug substance to be synthesized and formulated, and the drug product to be distributed, handled and dosed in a practical manner.

White, *Annual Reviews of Pharmacology & Toxicology* **40**:133 (2000)

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Methodology Has Narrowed Over the Years

"If you are holding a hammer, everything looks like a nail."

The big hammer these days is LC/MS/MS.

Very powerful – can investigate many problems

Has limitations – for example,
- only answers the exact question asked
- often does not give an exact structure for a metabolite

We try to do everything with LC/MS/MS. But if LC/MS/MS doesn't do a good job, we tend to just not get that kind of information.

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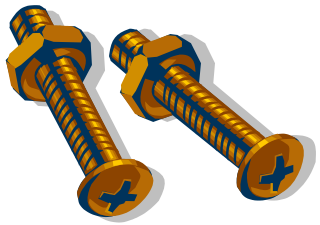
“Old Time” Methodology

When we encounter a screw or a nut instead of a nail, we need to remember that the toolbox also contains screwdrivers and wrenches.



Back in the “old days”, we had effective methods for investigating some problems, but they had limitations and have been almost completely replaced by LC/MS.

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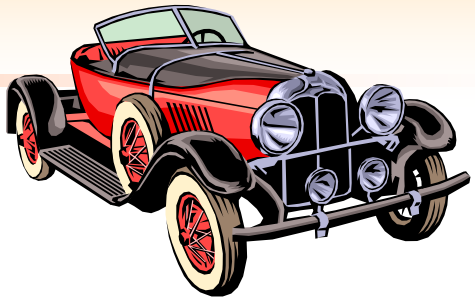
“Old Time” Methodology (continued)



What are some of these “old time” methodologies?

- UV – to the extent that background interference allows, can often find all the metabolites. Usually gives a reasonable estimate of the amount of a metabolite in a sample, since the extinction coefficient doesn’t change very much compared to parent. The cases where it will change are evident from the structure.
- Scale up and isolation of metabolites
- Hydrolysis of conjugates by glucuronidase and sulfatase
- NMR – provided that a “clean” sample can be isolated, almost always gives an exact chemical structure of a metabolite.
- Sometimes, these methods can still be useful today.

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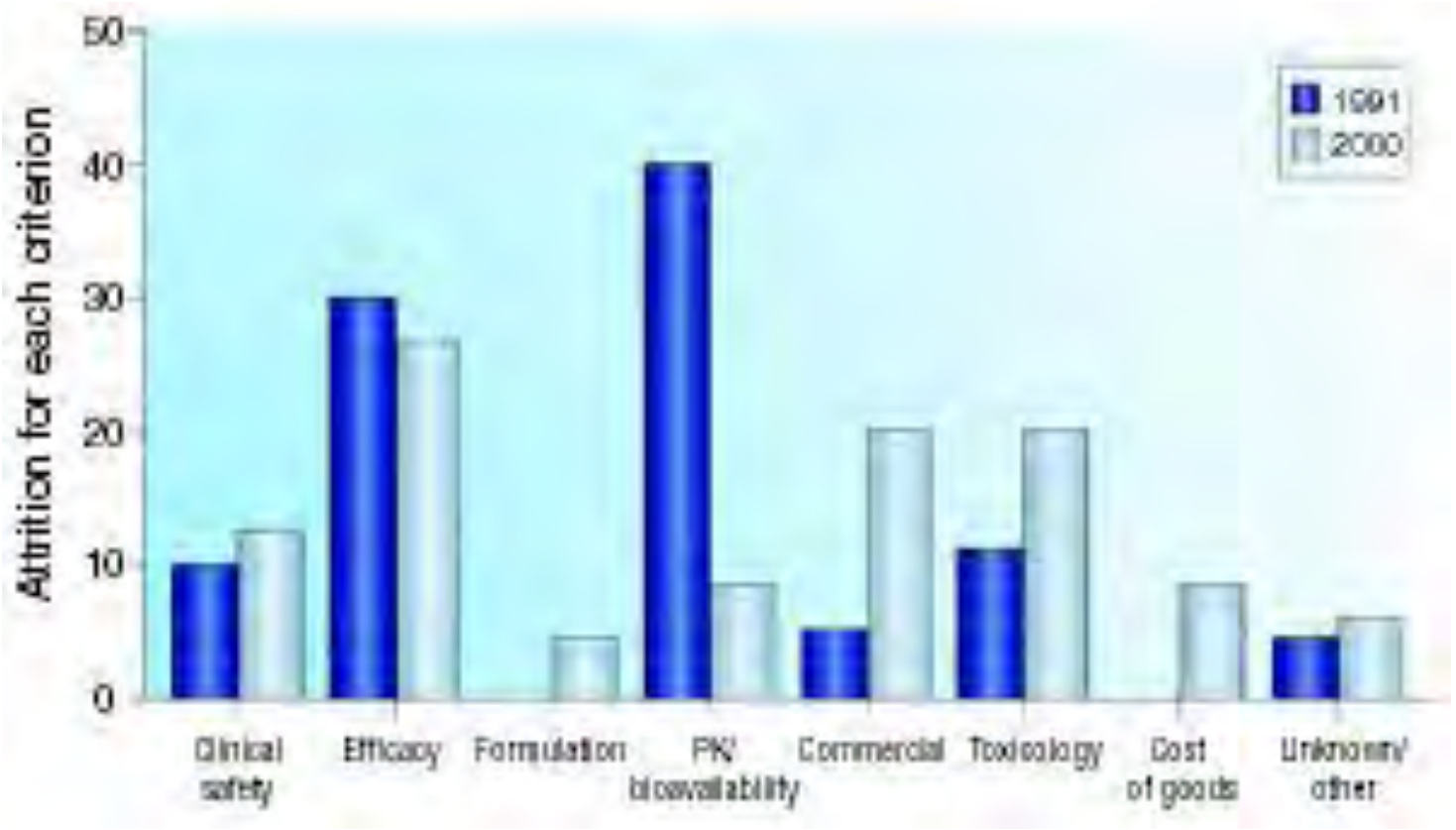
Drug Metabolism Support of Discovery Is "Mature" at This Point

Most of the potential benefit has already been realized.



Kola (2008) *Clinical Pharmacology and Therapy* **83**, 227

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Unmet Needs in Drug Metabolism Support of Discovery

Areas where strategically meaningful improvements are still possible:

- PK/PD
- Drug-Drug Interactions
- Metabolite Recognition
- Exact Structures of Metabolites
- Reactive Metabolites
- Transporters

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PK/PD

Projection of Human PK

Several approaches to this. Best to use more than one and then decide if discrepancies in the different approaches are telling you something. Considered a "home run" if projected PK parameters such as half-life and dose are within a factor of two of the actual values. Sometimes way off, so improvement still needed.

Understanding Animal and Human PD

Most big companies are doing this now, at least partially. Ideally, we would have enough PK data from the actual pharmacology experiments to establish the animal PK/PD model (simple E_{max}, indirect model, hysteresis, *etc.*). Most pharmacologists don't like their animals to be "disturbed" by blood sampling during effect measurements, so cooperation is needed for PK/PD to be a reality.

Projection of Human PK/PD

Assess the relation of animal model of disease (if any) to human. Include comparisons of intrinsic activity, plasma protein binding, distribution into target organ. Combination with projected human PK allows us to estimate human dose.

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PK/PD (continued)

Why do we project PK/PD at the discovery level?

- Clinical Pharmacology – They determine initial dose based on FDA "*Maximum Starting Dose*" Guidance, and top dose is determined by safety in Phase I SAD/MAD. But if projected dose in discovery is less than pre-IND animal tox NOAEL, everyone feels good to go forward.
- R&D Management – How developable is this drug? Is it a good bet?
- Drug Safety Evaluation – the projected human AUC helps them estimate what exposure multiples they can access in pre-IND tox studies
- Pharmaceutics R&D – approximately how many milligrams will they have to pack into a tablet or capsule: 1-10, 10-100, 100-1000?
- Chemical Process Research – approximately how many kilograms will they need in order to advance the drug to the next GO/NO GO decision: 1, 5, 10, 20?

How accurate do we need to be?

- Only as accurate as required to make strategic decisions.
- 90% Confidence Interval would be a better way to express our PK and dose projections.
- Instead of saying the dose will be 57 mg and the half-life 12.6 hours, we should say that we are 90% confident that the dose will be in the range of 40-60 mg and the half-life 10-15 hr.

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Accurate Assessment of Drug-Drug Interaction Potential

- CYP Inhibition

  What concentration do we use in [*I*]/K_i term?

- PXR Transactivation

  What concentration do we use in [Drug]/EC_{50} term?

- Software simulations such as *SimCyp*® or *Gastro Plus*®

  A lot of fitted or empirical parameters. Not much trusted by clinicians and regulators right now.

- Monkey DDI studies

  Have to be very careful that critical factors are similar in monkeys and humans (*e.g.*, C_{max}, protein binding, DMEs, static and time-dependent K_i-values, *etc.*). Really only feasible for late-stage discovery candidates.

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Finding Metabolites Without Radioactivity

- Already do this in clinical development in response to FDA 'MIST' Guidance

- Should adapt these methodologies to discovery

  Numerical scanning

  Constant neutral loss scanning

  Precursor ion scanning

  Mass Defect Filtering

  Background subtraction

  etc.

- Lots of interesting papers in the literature, but the techniques are not much available in actual everyday discovery support

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Exact Structures of Metabolites

Categories of Structure Knowledge

1. Recognition of a chromatographic peak as a metabolite

   flagging a peak as being drug-derived during scanning based on experiments such as constant neutral loss, baseline subtraction, mass defect filtering, *etc*. Metab

2. What is the chemical transformation?

   determining the general nature of the metabolic change based only on change in molecular mass; *e.g*., oxygen atom added, methyl removed, glucuronide added, sulfate added, *etc*. Transform

3. Regionalization of transformation

   determination of the region of the parent molecule that was modified; *e.g*., left side of molecule or bicyclic core, *etc*. Region

4. Exact chemical structure of metabolite

   e.g., hydroxylation at 5-position on the heterocyclic ring Exact

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Exact Structures of Metabolites

Value of Various Levels of Structure Knowledge in Discovery

Info Type	Ease	Nature of Conclusion	Utility to Program	NMR Needed?
1. Metab	Easy	Metabs present	Relative importance of CL pathways	No
2. Transform	Easy	Main type of metabolism	Relevance of *in vitro* data	No
3. Region	Mod	Similarity across species; hot spot	Fix metabolism	No
4. Exact	Diff	Exact site of metabolism	Fix metabolism; Mets active?	Yes

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Reactive Metabolites

OBJECTIVE:

Detect that a substantial portion of the dosed was converted to metabolites that rapidly react with intracellular nucleophiles.

More about this later in *Toxicology* discussion.

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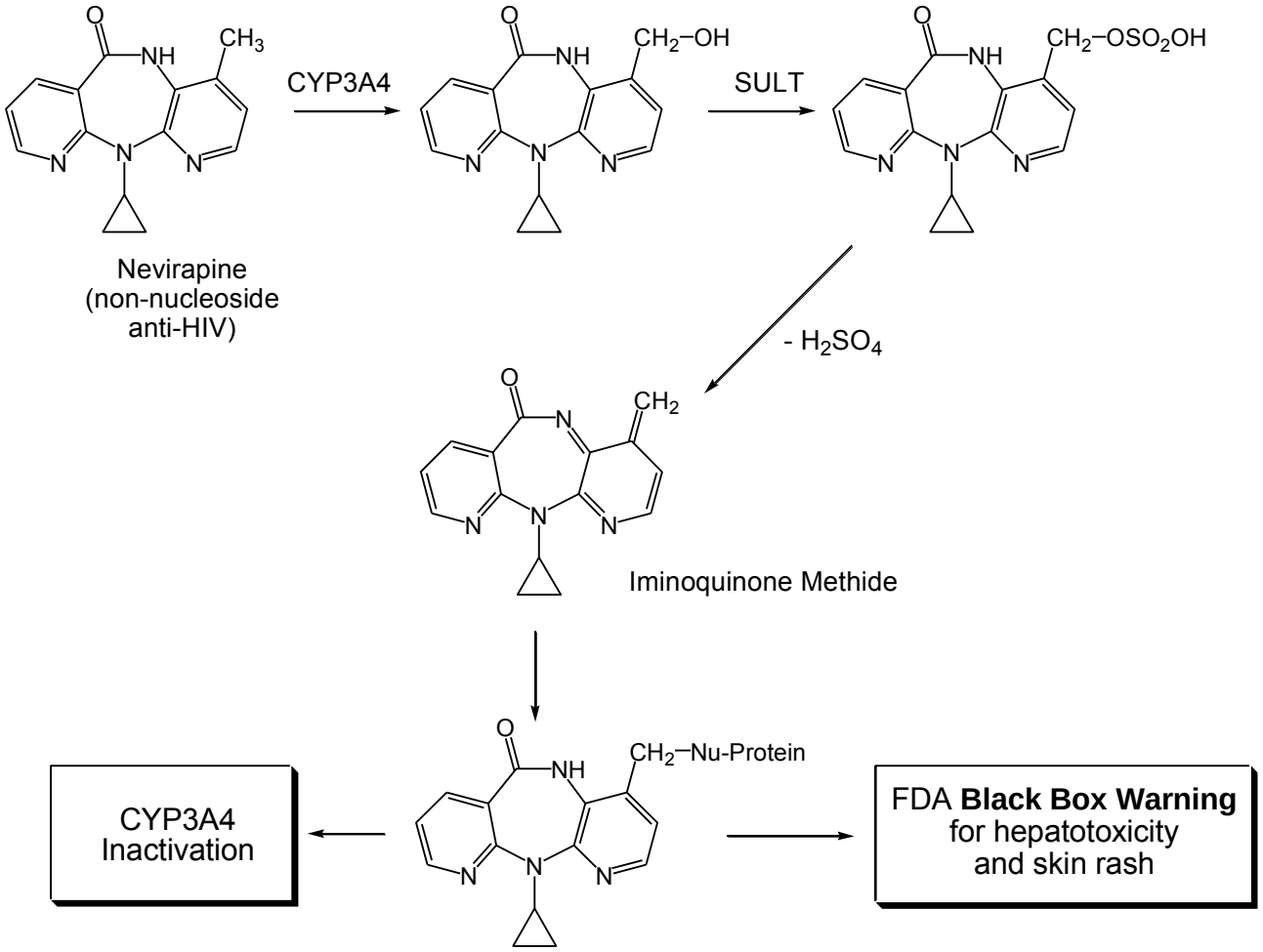
The Literature is Full of Examples of Reactive Metabolites



Wen *et al.*, *Drug Metabolism and Dispo*sition **37**: 1557 (2009)

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Transporters

- At this point, we seldom have to consider the transporter profile when screening in lead optimization and in characterizing late state discovery candidates.
- Reason is that we have only a poor understanding of exactly how transporters affect the clinical suitability of a drug.
- This is changing. The *International Transporter Consortium Report** was issued last month, and it emphasizes that transporters are fundamental to distribution and disposition of many drugs.
- The FDA** has signaled its interest in transporters in clinical development:
  - Interplay of DMEs and transporters
  - Drug-drug interactions
  - Transporter polymorphisms
- Just a matter of time before transporter characterization has the same status as CYP characterization in discovery support

*Giacomini *et al*., *Nature Reviews, Drug Discovery* **9**: 215 (2010)
Huang & Woodcock, *Nature Reviews, Drug Discovery* **9: 175 (2010)

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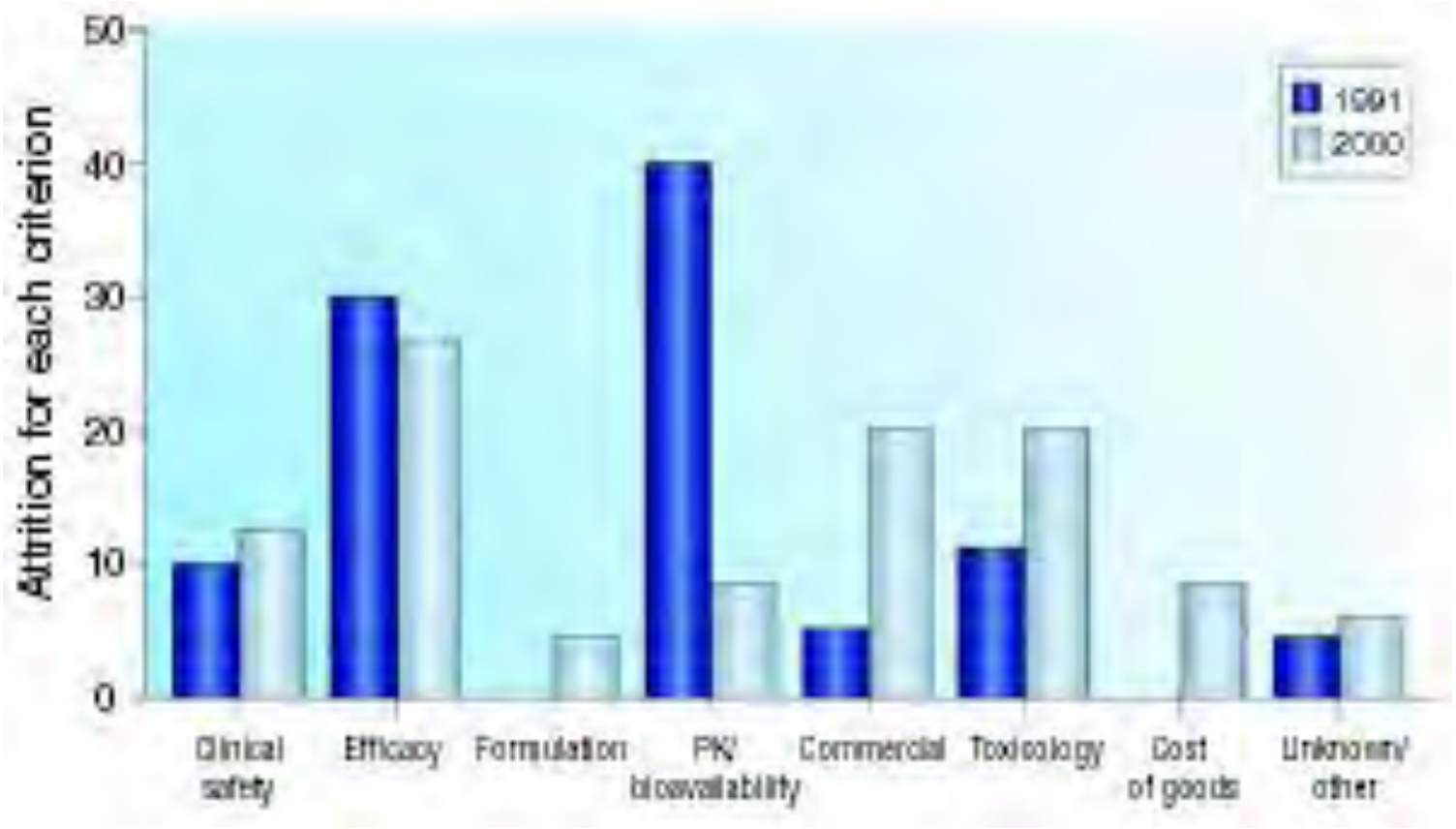
Attrition Rates Increased in Toxicology



Are today's molecules more toxic?

Is the bar for toxicity higher today?

Is this just a "zero-sum" exercise?

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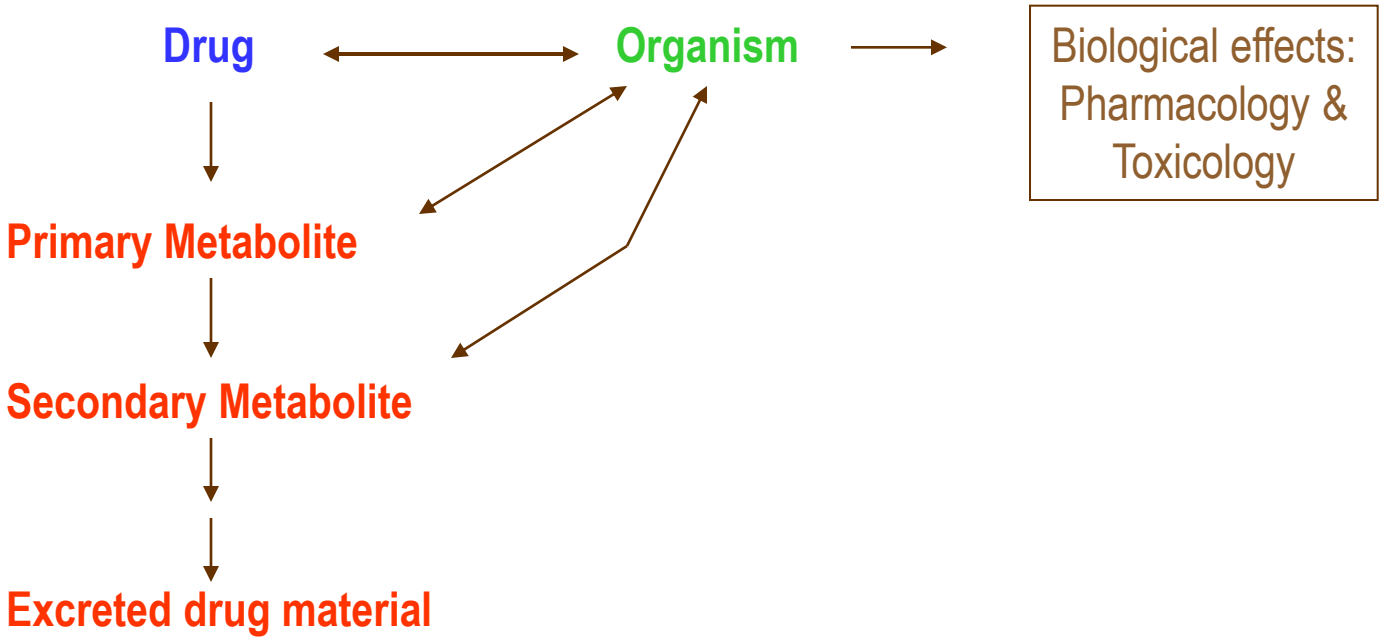
Let's Do Toxicology in Discovery Just as We Did With DMPK!

How is Toxicology Different From DMPK?

"Toxicology" is what the drug does to the organism.

"Drug Metabolism" is what the organism does to the drug.



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We "Understand" Drug Metabolism

Early PK/ADME screening is possible because:

- we have a fair understanding of the quantitative link between either human *in vitro* or animal *in vivo* and human *in vivo* behavior of drugs

$$CL = \frac{f_u \times CL_{\text{int}} \times Q_B}{f_u \times CL_{\text{int}} + Q_B}$$

- we understand the chemistry and enzymology of biotransformation of drugs and can even predict the metabolism (to some degree)

We know "who done it".

Hydroxylations are done by CYPs

N-Demethylations are done by CYPs

Glucuronidations are done by UGTs

Acetylations are done by NATs

et cetera

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Toxicology is a “Black Box"

- In contrast to DM, we have extremely limited ability to predict toxicities, or even to understand them after the fact.
- Thus, the typical preclinical safety program is exploratory in nature, and the major findings are descriptive and seldom predictable in advance.
- Even worse, we have little ability to relate observed toxicities in animals to probable human toxicities.
- Equally bad, we have many examples of human-specific toxicities (*i.e.*, the toxicity was not seen in animals).

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Drug Metabolism Is Now Important in a New Way

Drug Metabolism has come back around through the backdoor to be on the cutting edge of reduction of attrition of clinical candidates.

Table 12. Mechanistic Causes of Toxicology Attrition[a]

	percent of all advanced molecules[b]
biotransformation-related	27
target-based	28
single or multiple ion channel inhibition	18
immune-mediated	7
all other mechanisms	36

[a] Based on experience (in animal models) from DuPont-Merck and Bristol-Myers Squibb, 1993−2006. This information was kindly provided by B. D. Car, Bristol-Myers Squibb. [b] $n = 88$. Because categories are partially overlapping, the total is > 100%.

Guengerich & MacDonald, *Chemical Research in Toxicology* **20**, 344 (2007)

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Reactive Metabolites are "Hot"

- Contemporary recognition of significance of reactive metabolites in toxicity.

- How can we relate reactive metabolites to toxicity?

  1. Capture of electrophiles by protein or thiol nucleophiles:
     - Baillie (Merck) method
     - Pfizer method
     - Daiichi Sankyo method
     - BMS method
  2. Anticipate reactive metabolite formation based on chemical structure.
  3. Identify chemical form of drug residues covalently bound to protein.
  4. Identify target proteins

These methods are chemical and statistical in nature,
with little, if any, biochemical tox understanding.

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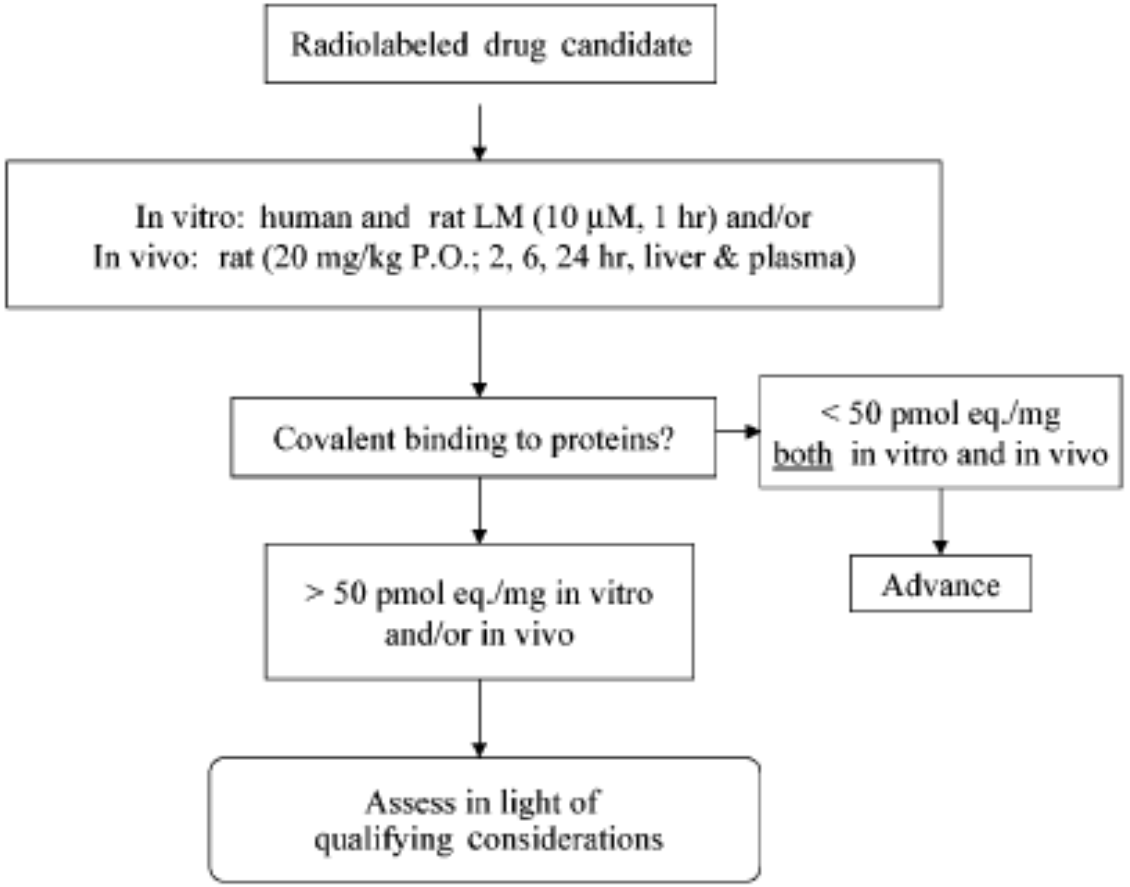
Baillie Method (Merck)

First attempt to quantitatively relate reactive metabolites to toxicity.

Measure production of covalently bound radiolabel to proteins in a metabolically competent system such as liver microsomes or rats



Evans *et al.*,
Chemical Research in Toxicology
17: 3 (2004)

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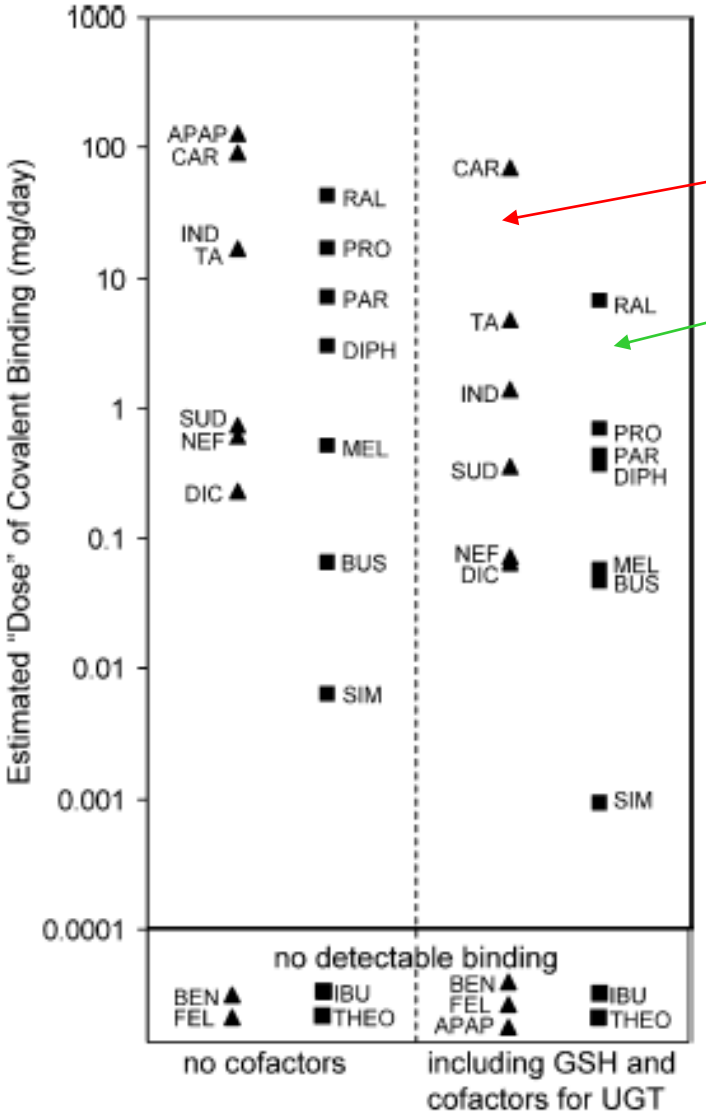
Dose/Clearance-Corrected Covalent Binding (Pfizer)



Hepatotoxins (▲)

Non-hepatotoxins (■)

Estimation of the "dose" or "body burden" of a reactive metabolite based on fraction of dose cleared through reactive metabolite pathway.

Very little discrimination of the two groups.

Obach *et al.*, *Chemical Research in Toxicology* **21**: 1814 (2008)

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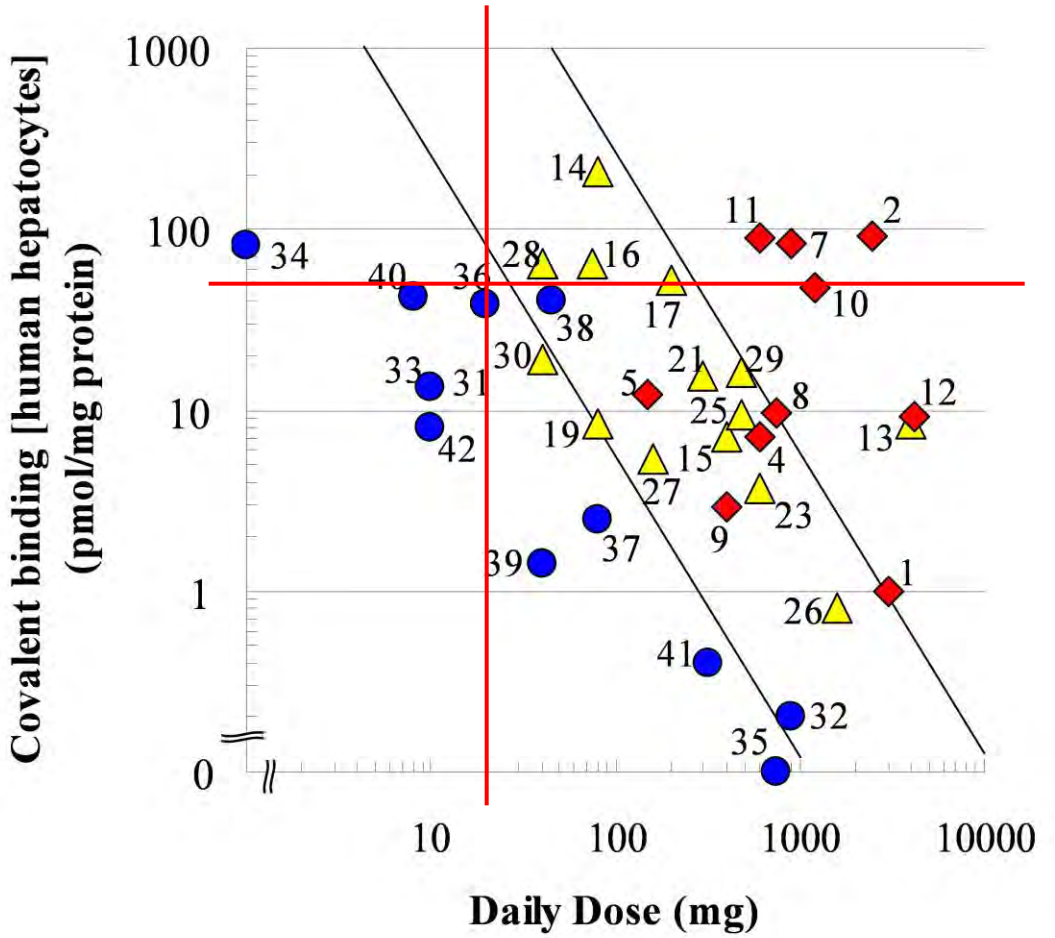
Zone Classification System (Daiichi-Sankyo)



Safe
Toxic
Withdrawn

How does this fit with "conventional" wisdom about dose and covalent binding?

Daily dose < 20 mg

Binding < 50 pmol/mg

Nakayama *et al.*, *Drug Metabolism and Disposition* **37**: 1970 (2009)

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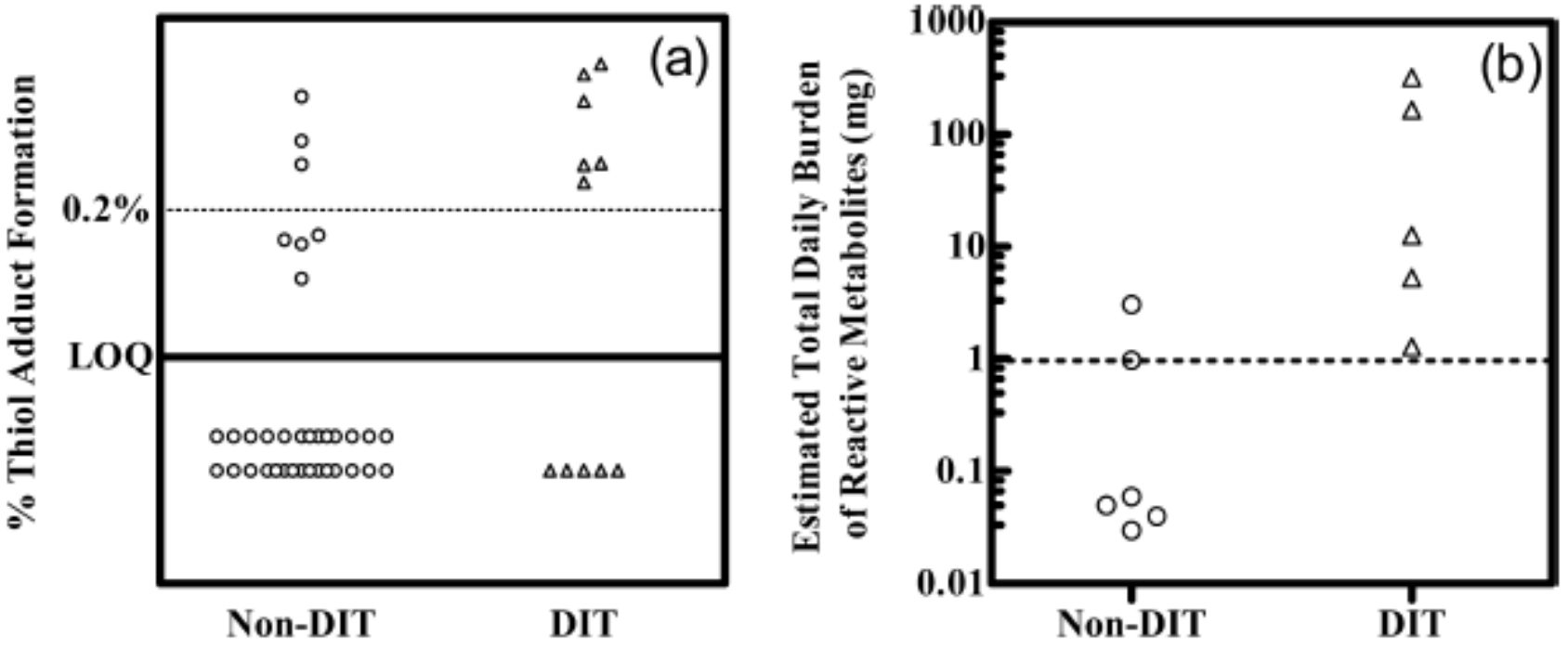
Dose-Corrected Thiol-Adduct Method (BMS)



The "body burden" of reactive metabolite determined in this way is a moderately effective predictor.

Gan *et al.*, *Chemical Research in Toxicology* **22**: 690 (2009)

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Current State of Preclinical Screening for Reactive Metabolites

- Fundamental problem is that DM scientists expect to get definite, quantitative answers out of the “Black Box” of toxicology (Black Hole?)
- These are blind assays with little chemical or biological understanding of what they mean.
- Assays are not validated.
- Nobody likes these assays, especially chemists.
- Much improvement needed, but not clear if it is possible.

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Conclusion

- Although most of the benefit of discovery-level DMPK work has already been accrued, important improvements are still possible.
- Transporter characterization will likely become more important in drug discovery support in a few years.
- To the extent that some toxicities are attributable to metabolites, DM screening and characterization may be able to help reduce post-nomination attrition of clinical candidates.
- However, the science relating metabolism to toxicity is still immature.

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