DM/PK-guided Lead Optimization
A Historical Perspective of a Paradigm Shift

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NEDMDG
Gerald Miwa Retirement Symposium
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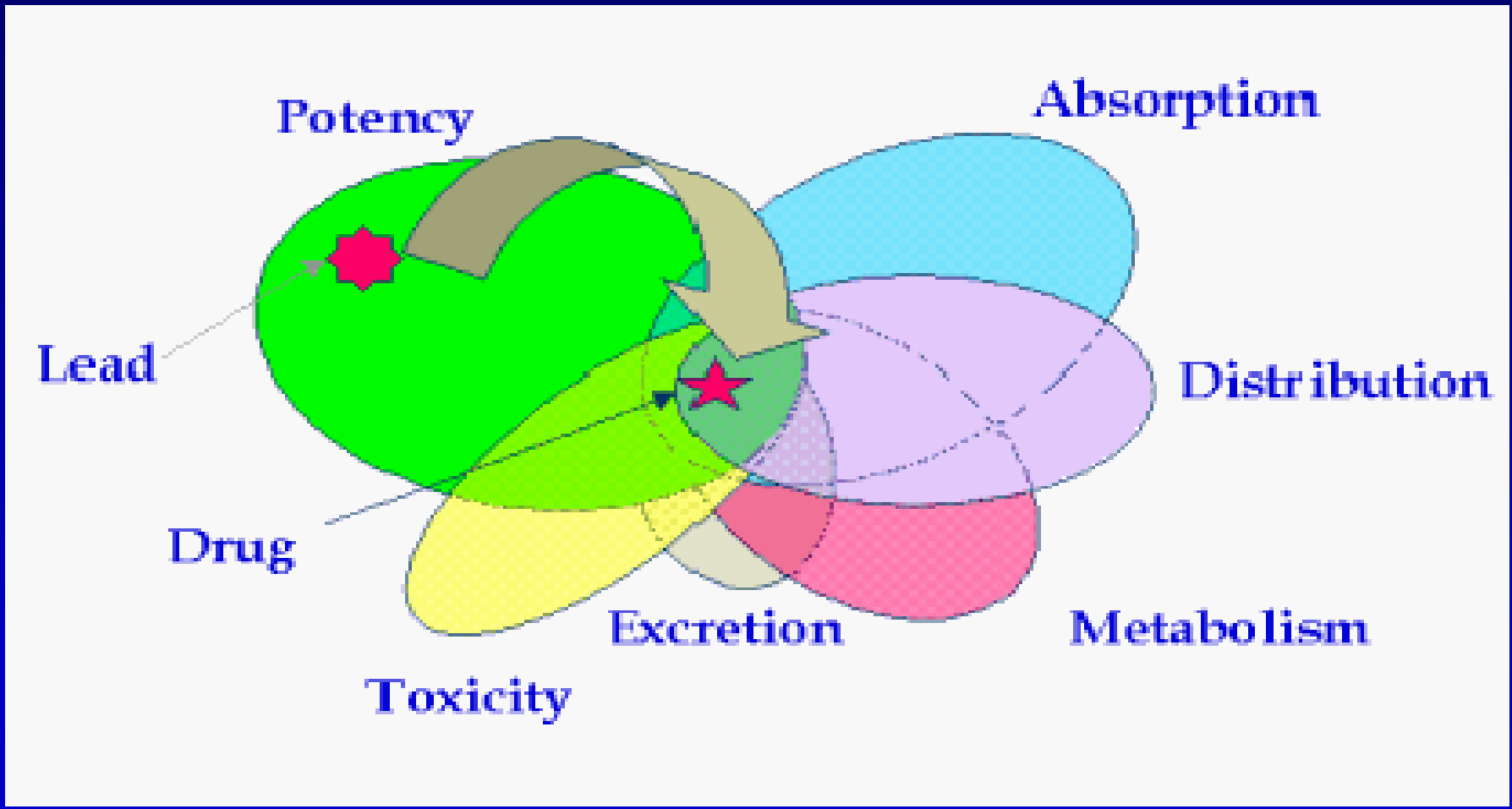
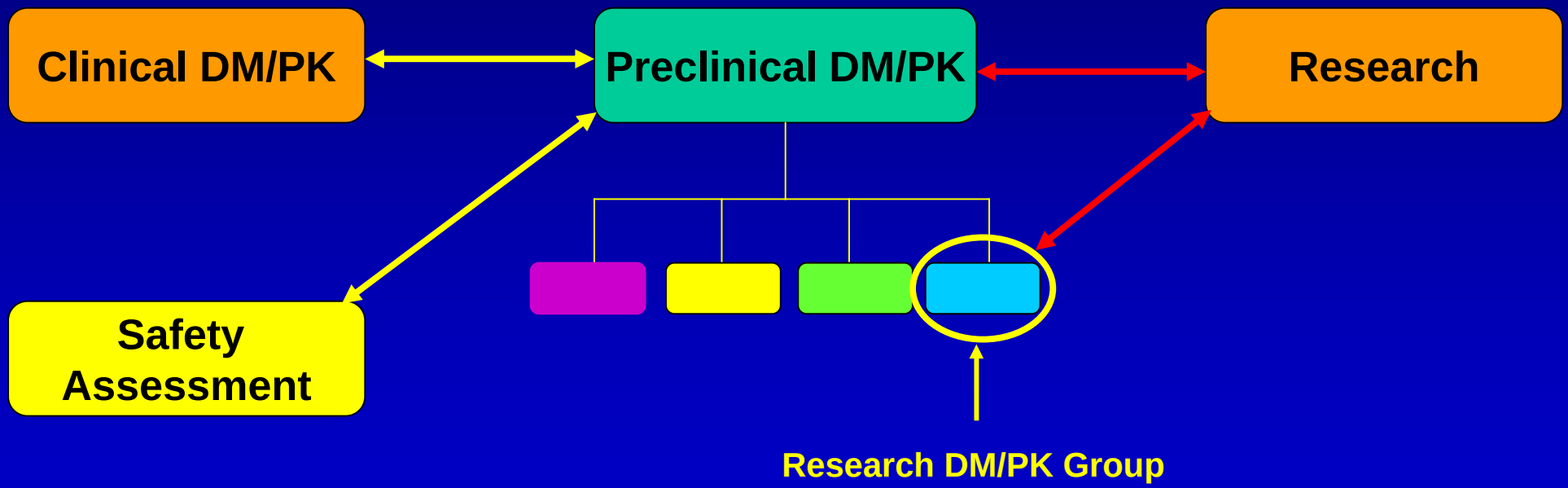
Current Paradigm

Optimizing Biology and ADME Synchronously



C. Breneman, Krisitn Bennett, J. Bi., M. Song, M. Embrechts
– Rensselaer Polytechnic Institute www.drugmining.com

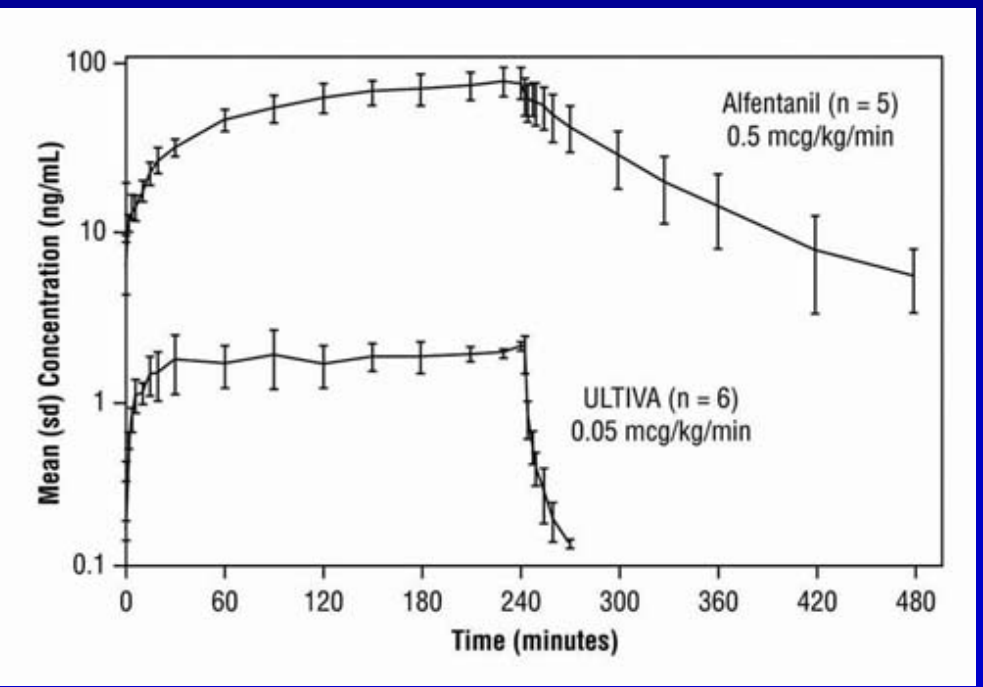
DM/PK – Research Interface at Glaxo
Late 1980's – Early 1990's

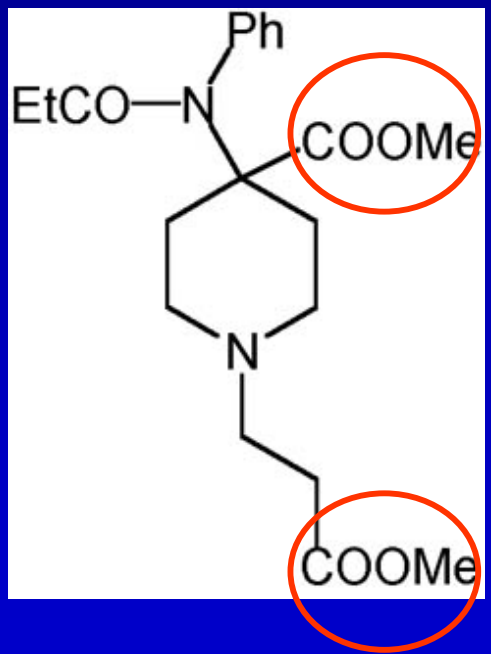


Ultra Short Acting Opioid Remifentanil - ultiva

Rapid Offset of Action

Within 5 to 10 minutes after the discontinuation of ULTIVA, no residual analgesic activity is present.



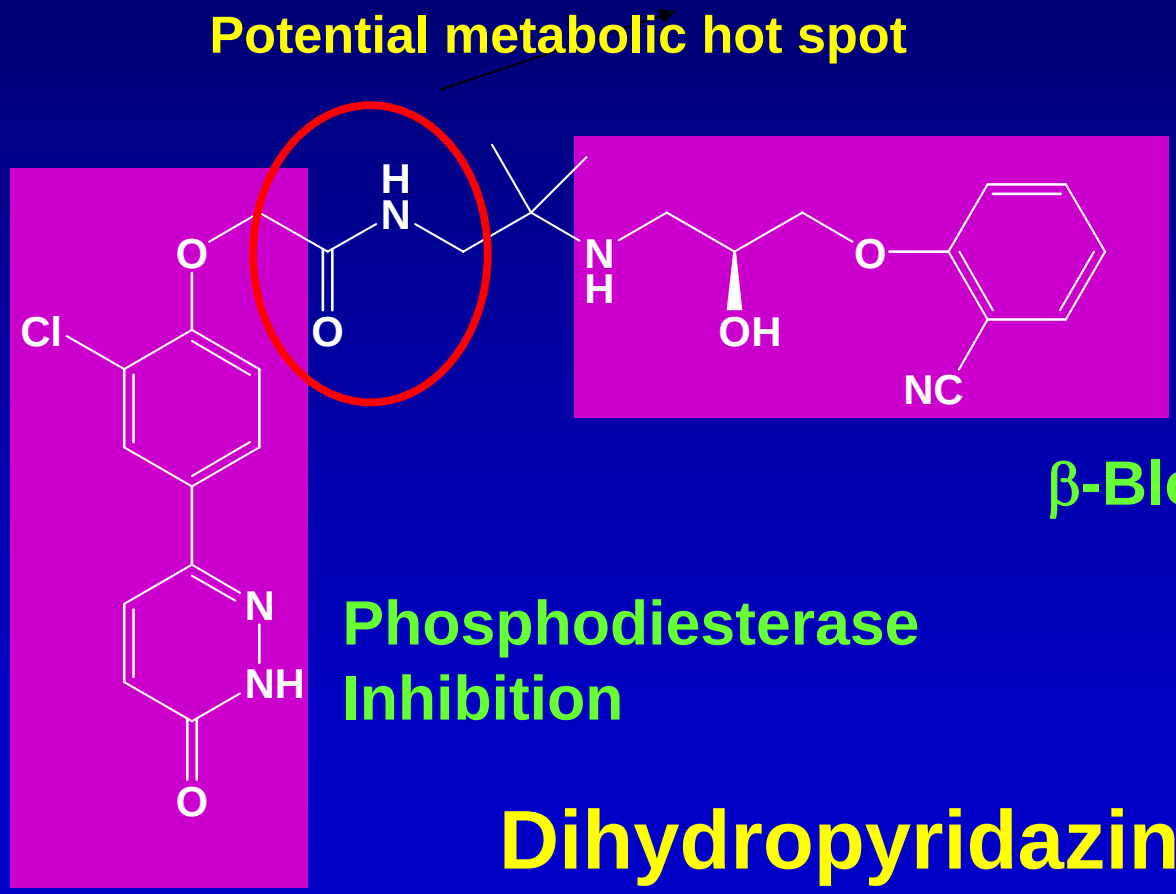


Chemical vs. Enzymatic Hydrolytic Rates

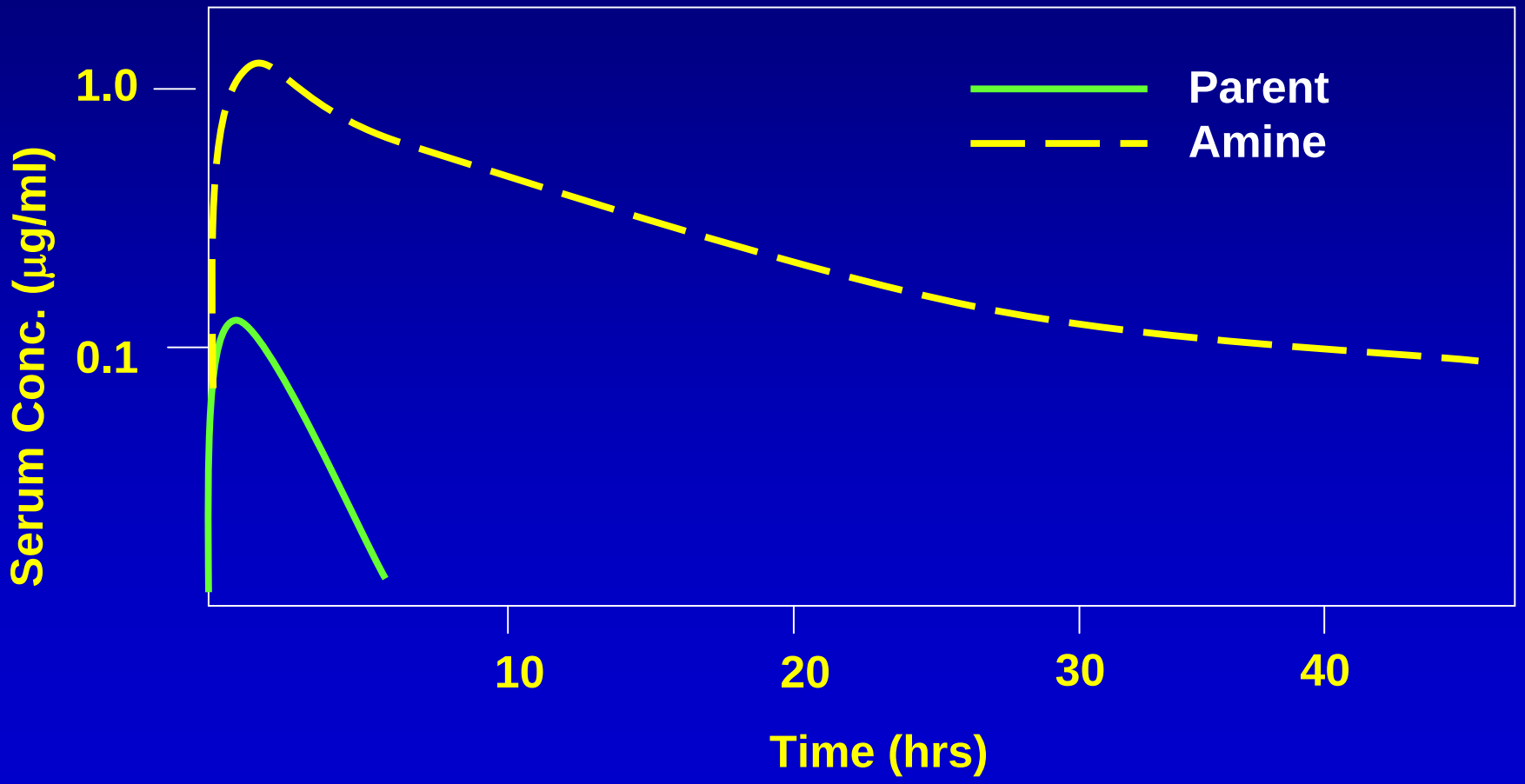
Source: Ultiva® product label

Use of *in vitro* metabolism screen to identify "Metabolic Hot Spot"

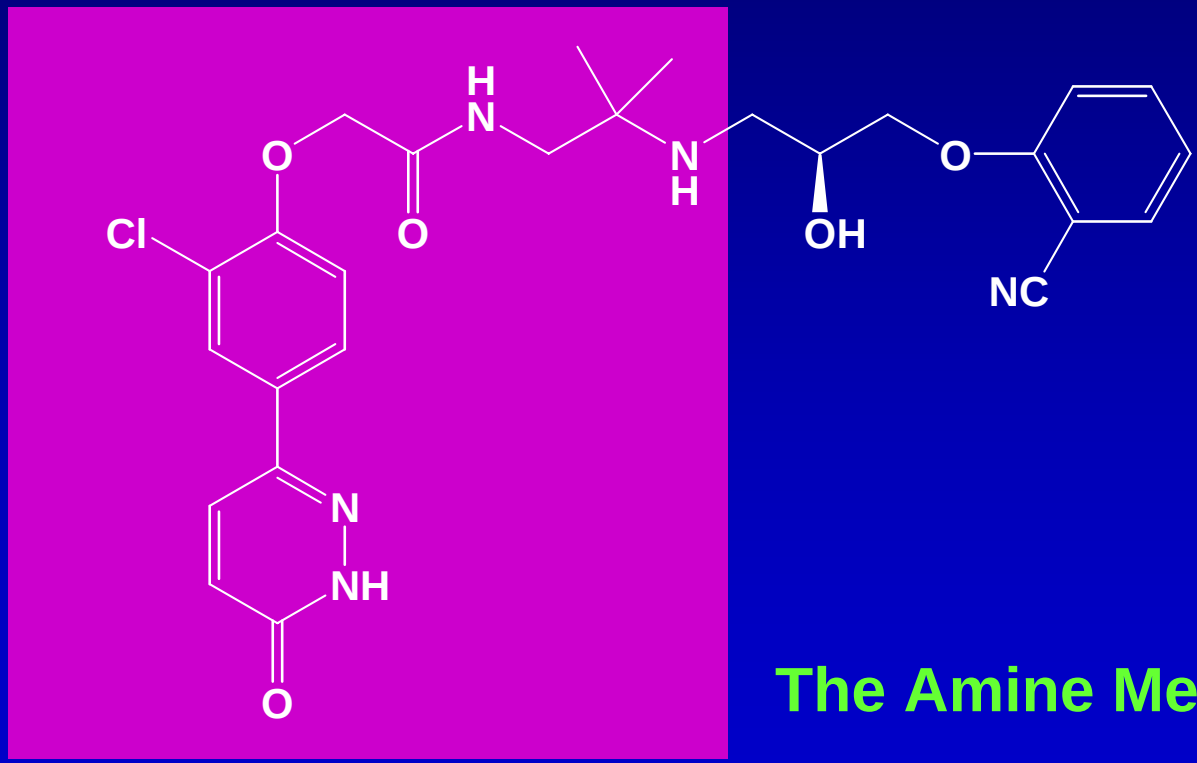
Rationale for Incorporating Metabolic Studies Early in the Discovery Program



PK of Parent and the Amine Metabolite Following Oral Administration of DHP-1 (5 mg/kg) to Male Beagle Dog Suggests First Pass Metabolism

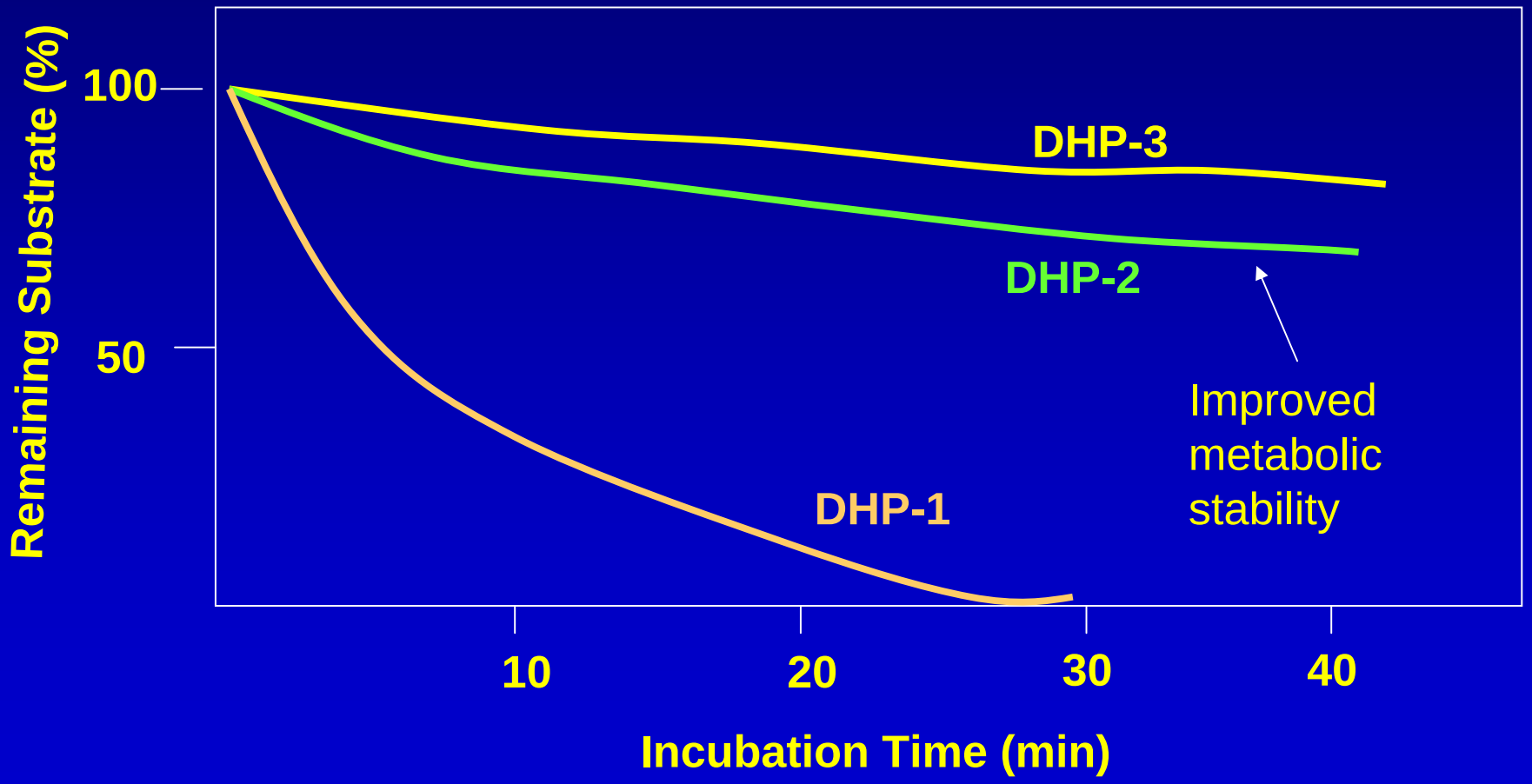


Major Metabolite of DHP-1

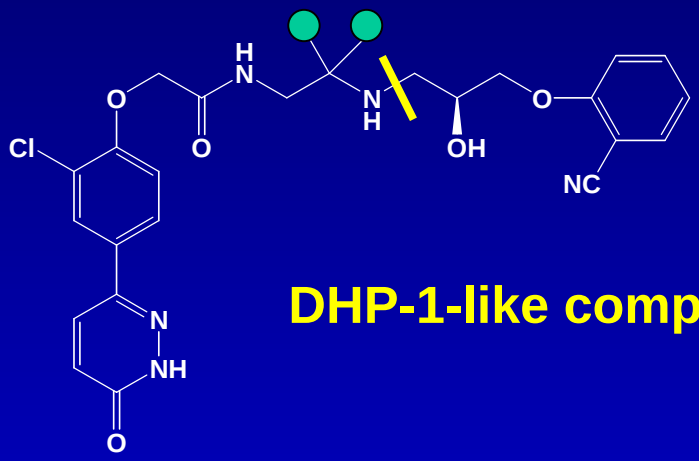


The Amine Metabolite

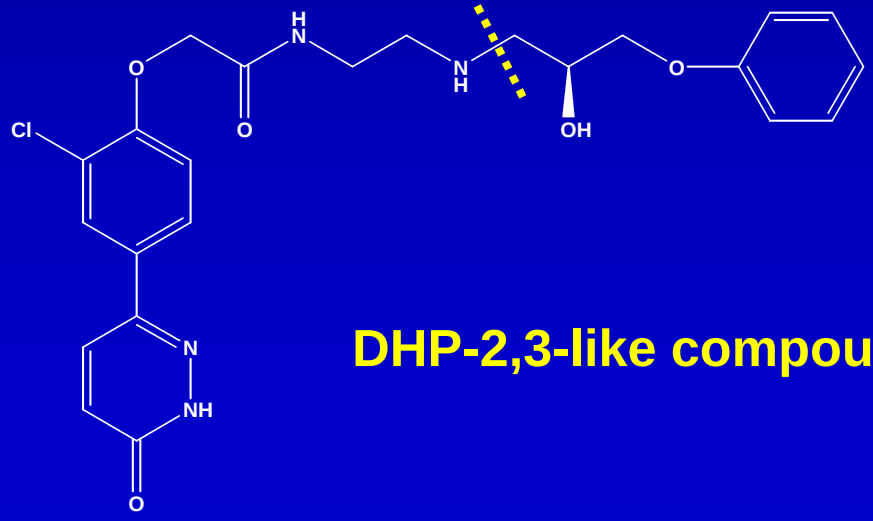
Relative Rates of *In Vitro* Metabolism for Dihydropyridazinone Leads



Functional Group Contributing to the Metabolic Hot Spot for Dihydropyridazinones

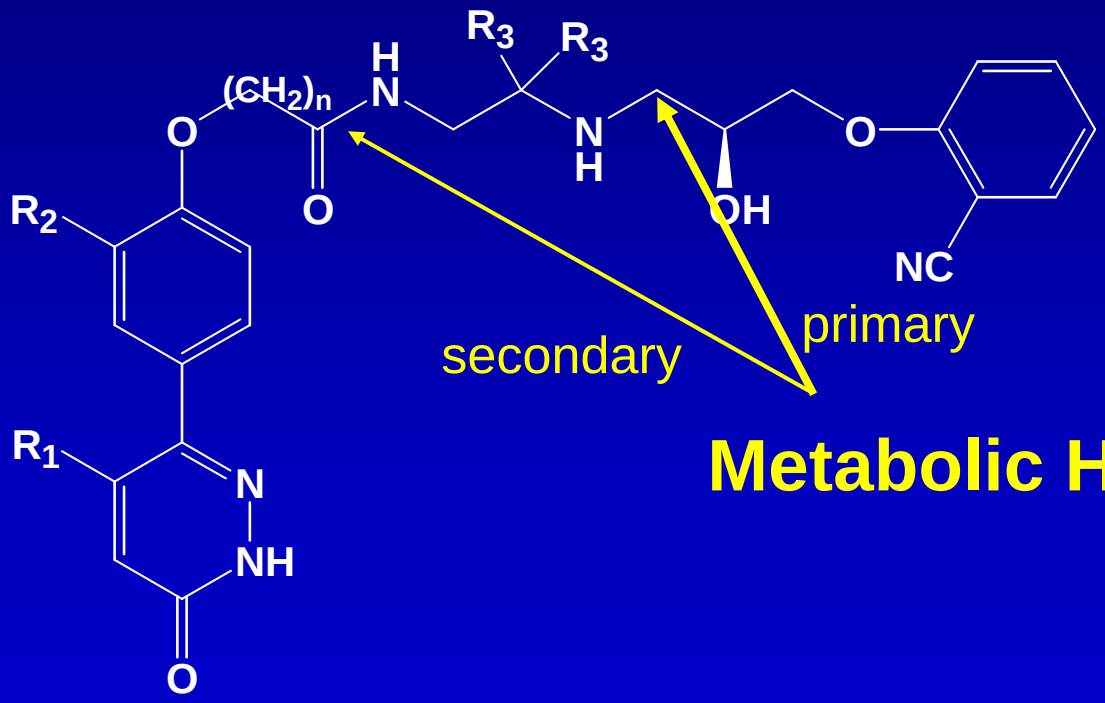


DHP-1-like compounds



DHP-2,3-like compounds

Stabilizing a metabolic hot spot can uncover a secondary hot spot



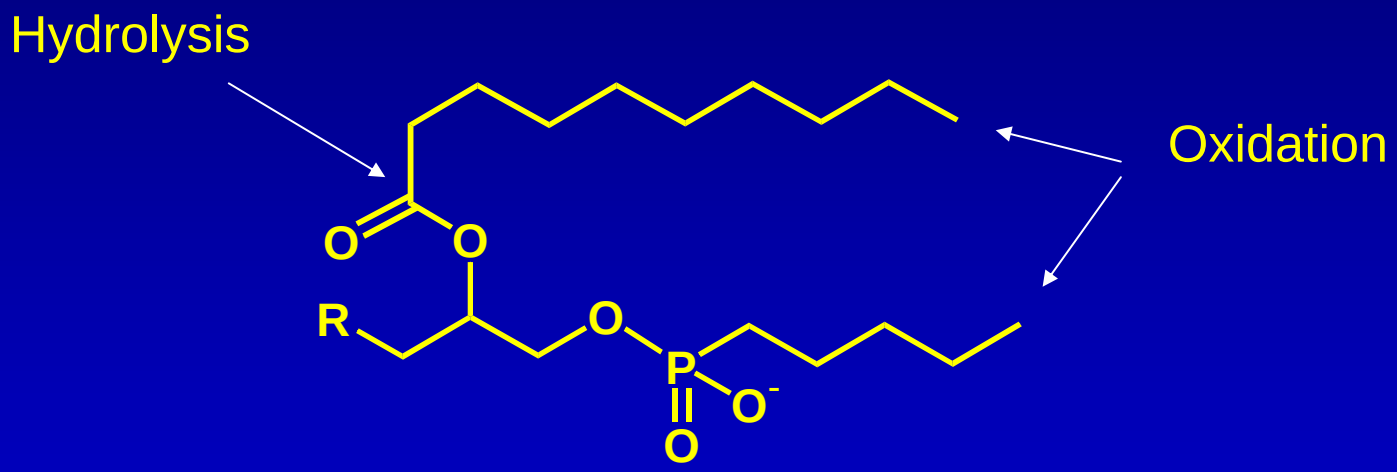
Metabolic Hot Spots

Rationally designed *in vitro* metabolism study, based on a good understanding of likely metabolic pathways, could lead to a rapid solution

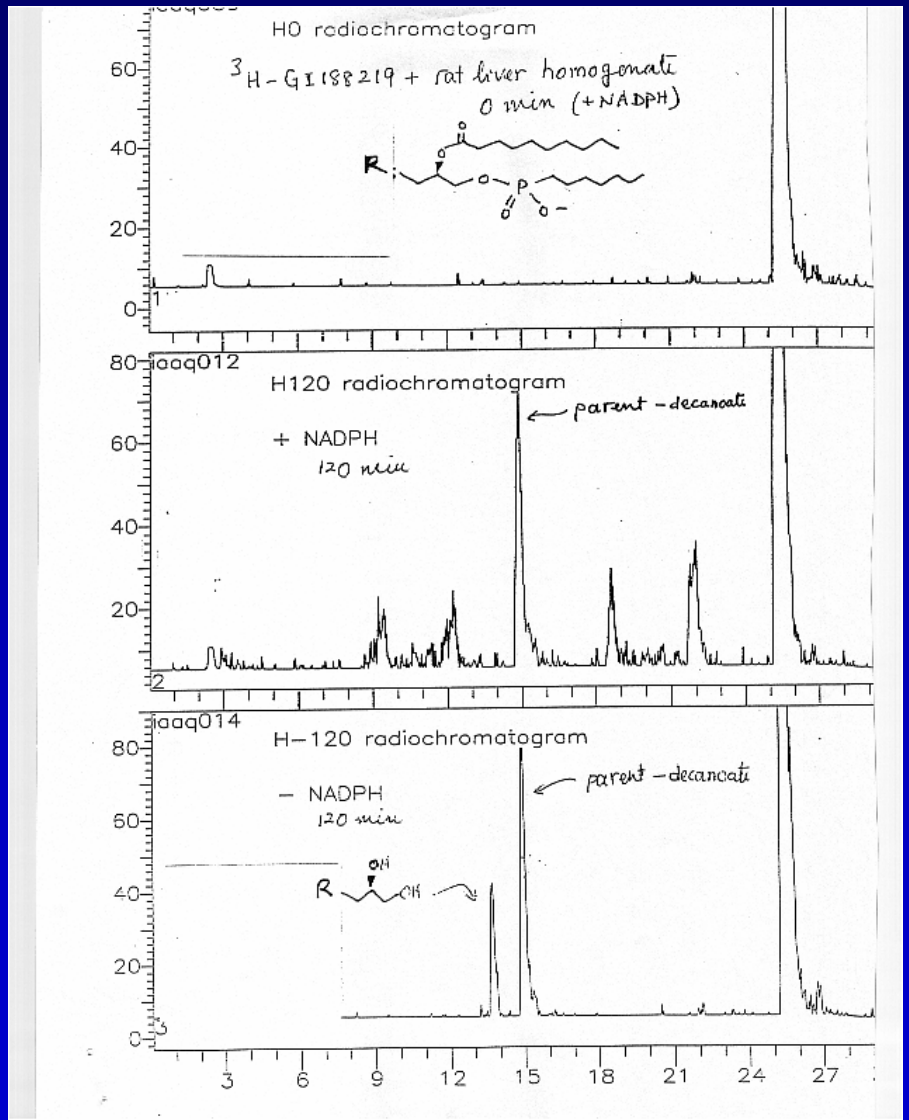
Background

- Phospholipase A-2 Inhibitors for Inflammatory Diseases (Arthritis, Asthma)
- Glycerophospholipid derivatives
- Major problem – Poor bioavailability in rats
- First pass metabolism was implicated – absorption (permeability) was not a problem (Caco-2 studies, in vivo studies with radiolabeled compounds)

Likely Metabolic Hot Spots



Evidence for Oxidative and Hydrolytic Metabolism of the Lead Compound



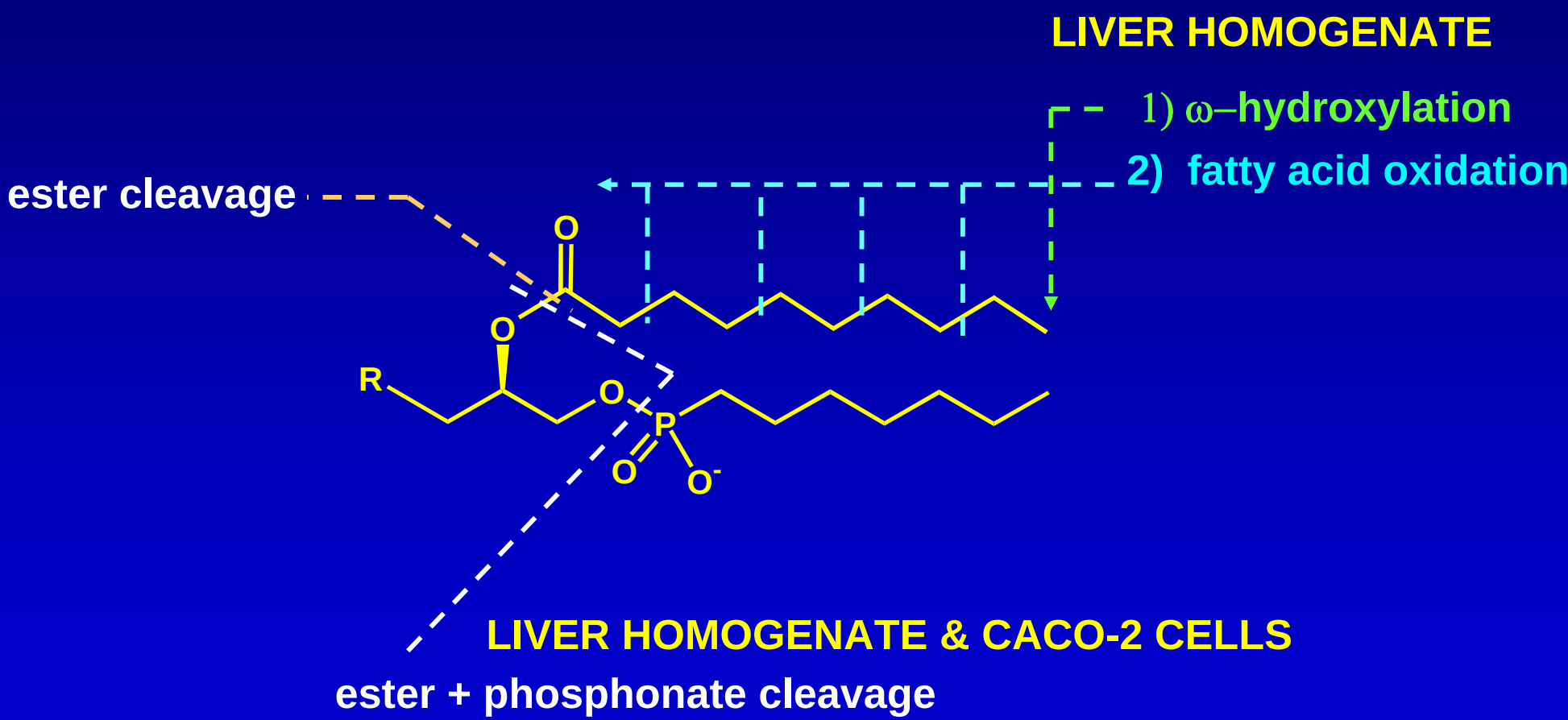
Oxidative metabolism

Incubation with
liver homogenates + NADPH

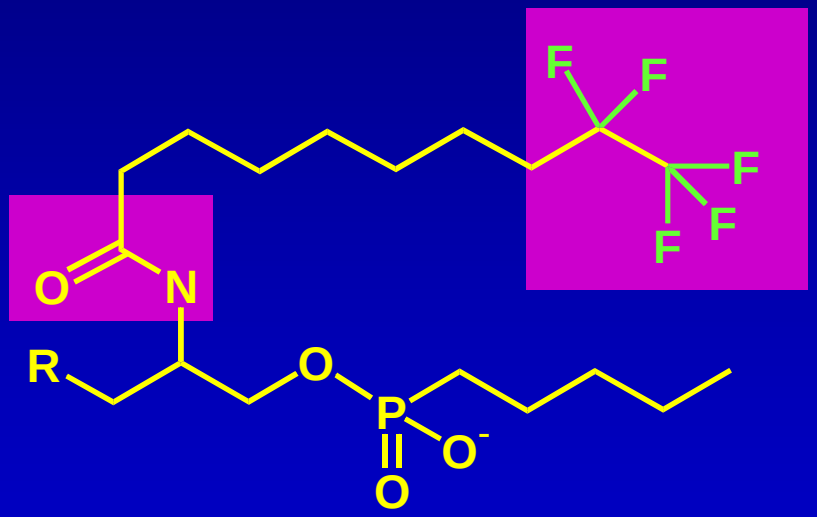
Hydrolytic metabolism

Incubation with
liver homogenates - NADPH

In Vitro Metabolism of the Lead Compound by Rat Liver Enzymes and Caco-2 Cells



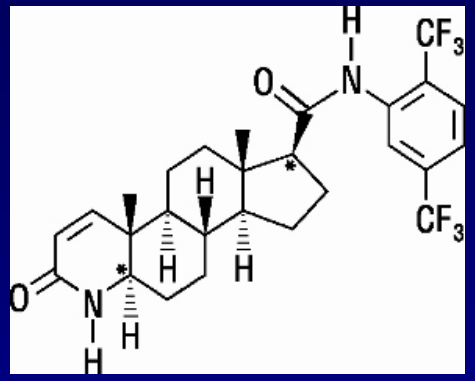
Modification of Metabolic Hot Spots

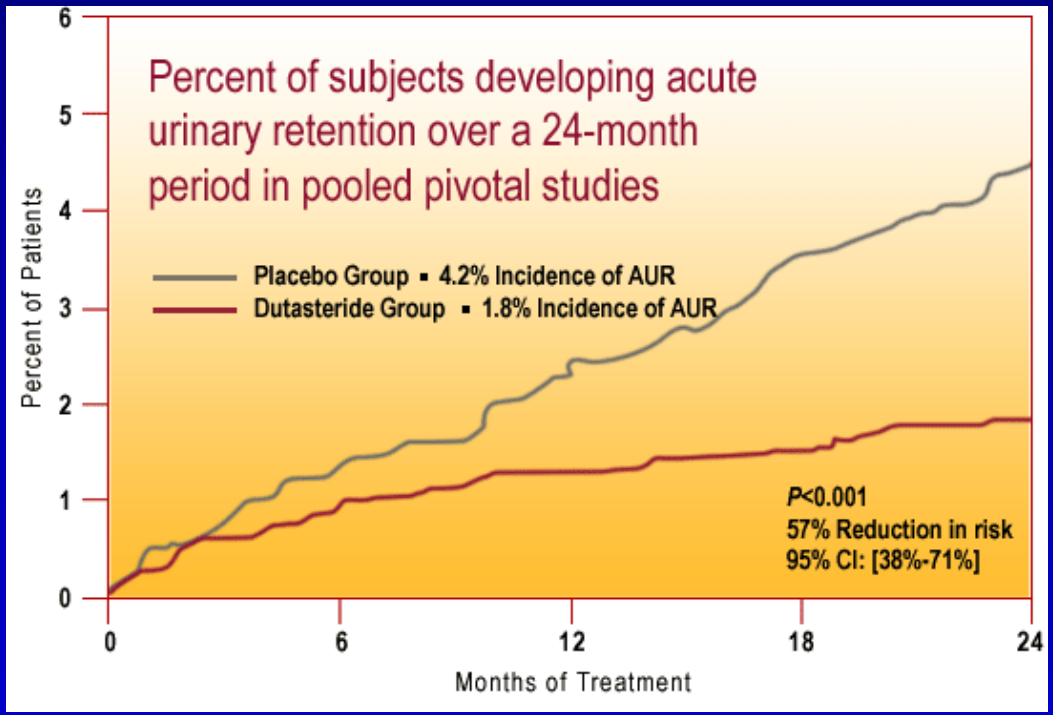


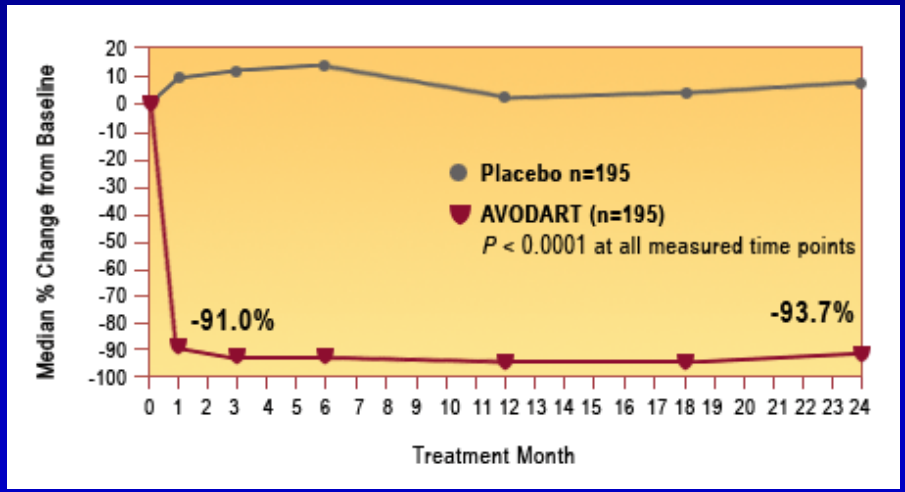
In vitro studies do not provide guidance for improving *in vivo* metabolic clearance

A case for n-in-one *in vivo* PK studies

Dutasteride® for BPH



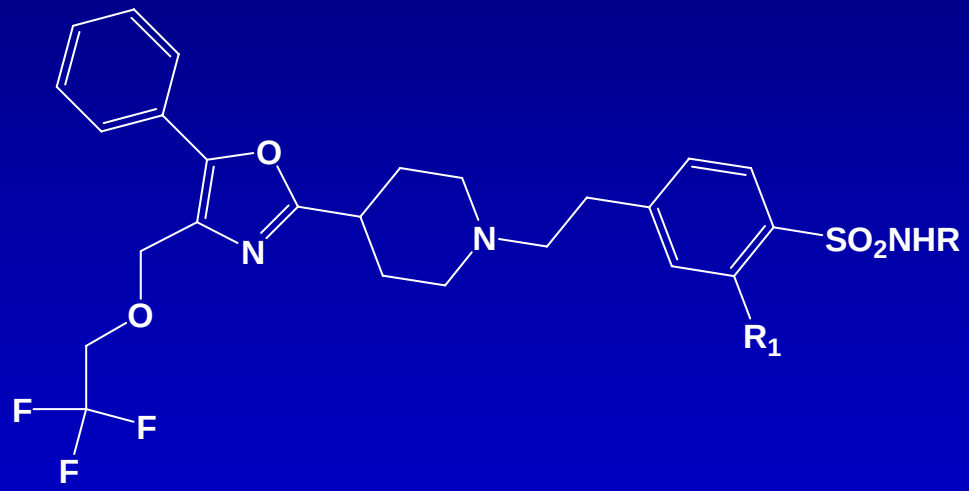




The terminal elimination half-life of dutasteride® is 5 weeks at steady state
Frank Lee et al.

Profile of the Lead Series

- Alpha-1 antagonists for BPH
- Once-a-day dosing
- MW: 400-600, basic, clogP 5-7
- Well-absorbed
- Short half-life
- Elimination predominantly by metabolism
- Highly protein bound



Dog Microsomal Metabolism Screen

- Poor correlation between *in vitro* metabolism rate and *in vivo* $T_{1/2}$ or CL
- Several possible reasons considered
  - » Sequential metabolism
  - » Phase II metabolism
  - » Protein binding
- Follow-up studies showed that none of these reasons could explain the lack of correlation between *in vitro* and *in vivo* studies

PK of Mixtures?????

Origin of Cassette Dosing

The Challenge

- Screen over 150 compounds to find a lead appropriate for once-a-day dosing
- The only predictive screen was *in vivo* PK in dogs
- *In vivo* screen would be too slow

The Solution

- *In vivo* PK studies of mixtures!!!

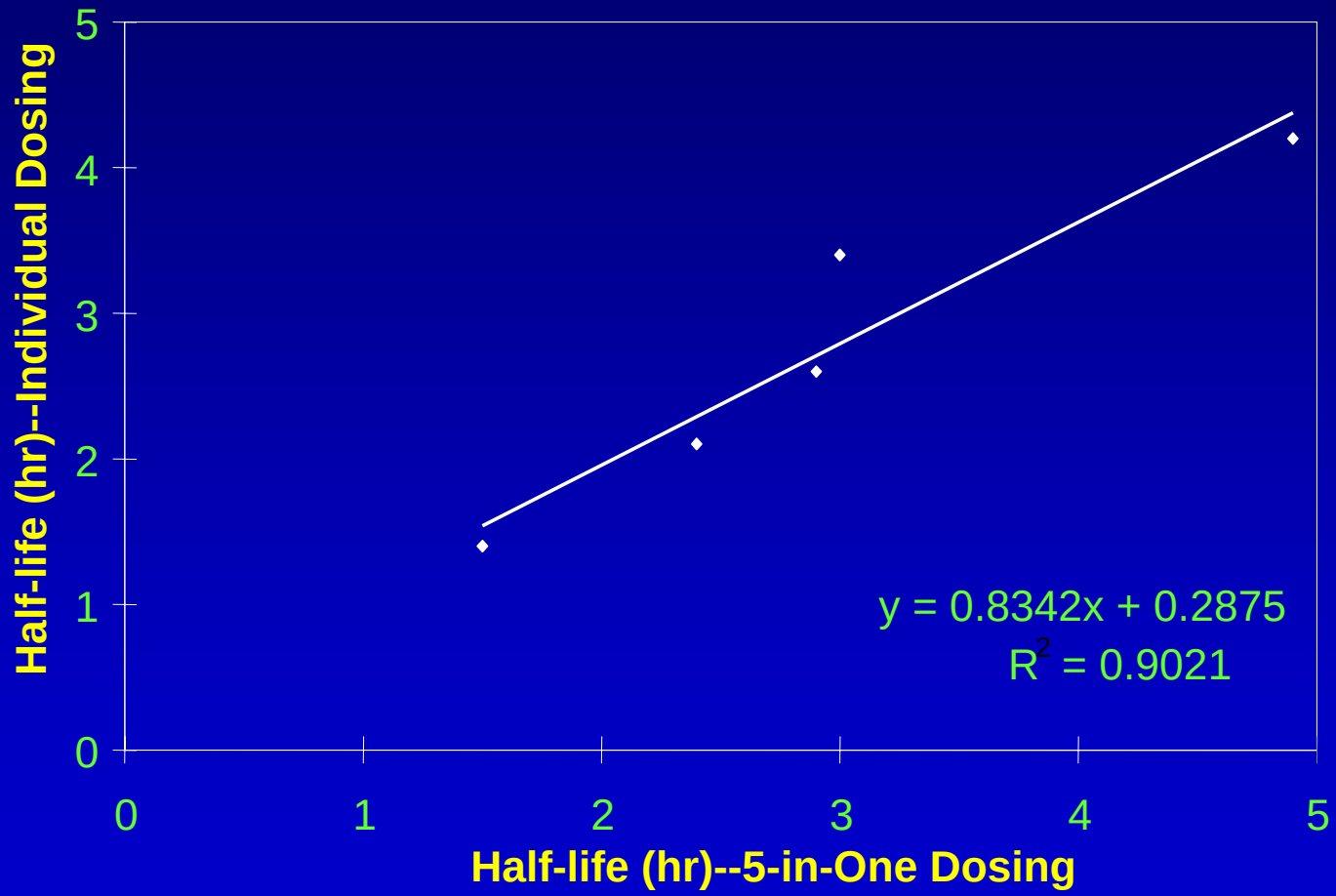
Judd Berman

Cassette Dosing “Validation” (5-in-One)

- Five compounds of known CL, V_{SS}, and $T_{1/2}$ administered concomitantly to a dog
- Dose=0.25 mg each compound/kg IV
  - » *1/4th the dose of compounds administered individually*
- Plasma samples assayed by LC/MS/MS
  - » Assay for simultaneous analysis of 5 compounds without interference from any of the metabolites
- Pharmacokinetic parameters compared to those previously obtained

5-in-One Dog *vs.* Individual Dosing

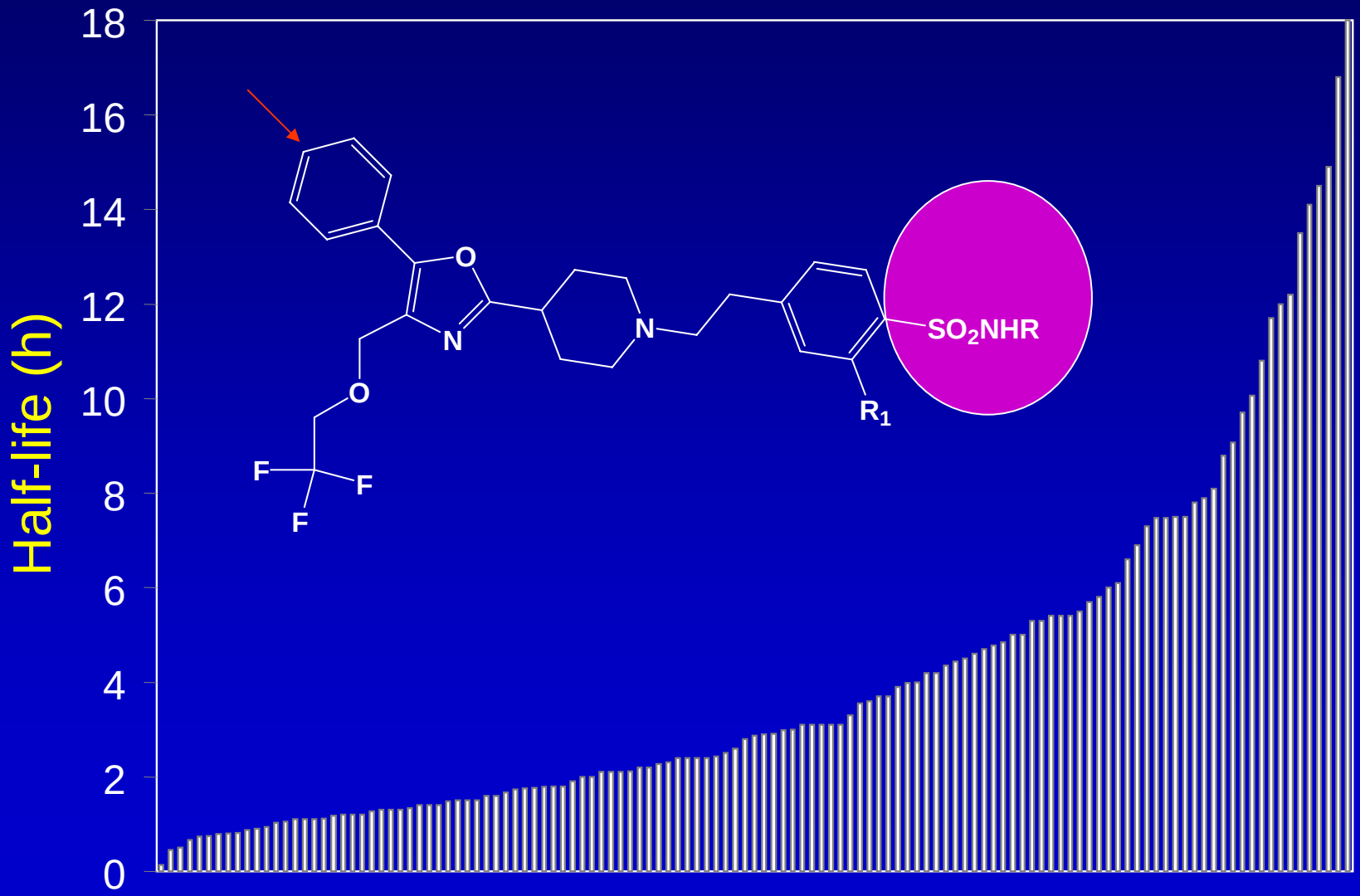
Half-life comparison



N-in-one in vivo screen worked

- Good correlation in PK parameters.
- Useful for ranking compounds
- 125 compounds screened in 10 dog studies in 2 months.
- Approximate structure-PK relationships developed
- Compounds with a wide range of $T_{1/2}$ could be identified from which leads could be selected for further evaluation

Half-lives of 125 Compounds in Dogs as Determined by Cassette Dosing



Acknowledgments

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- Leslie Hudson

Gerald Miwa