Phase 1 Clinical Studies
First-In-Human (FIH)
<Chapter 31>
Pharmacologically-Guided Dose Escalation

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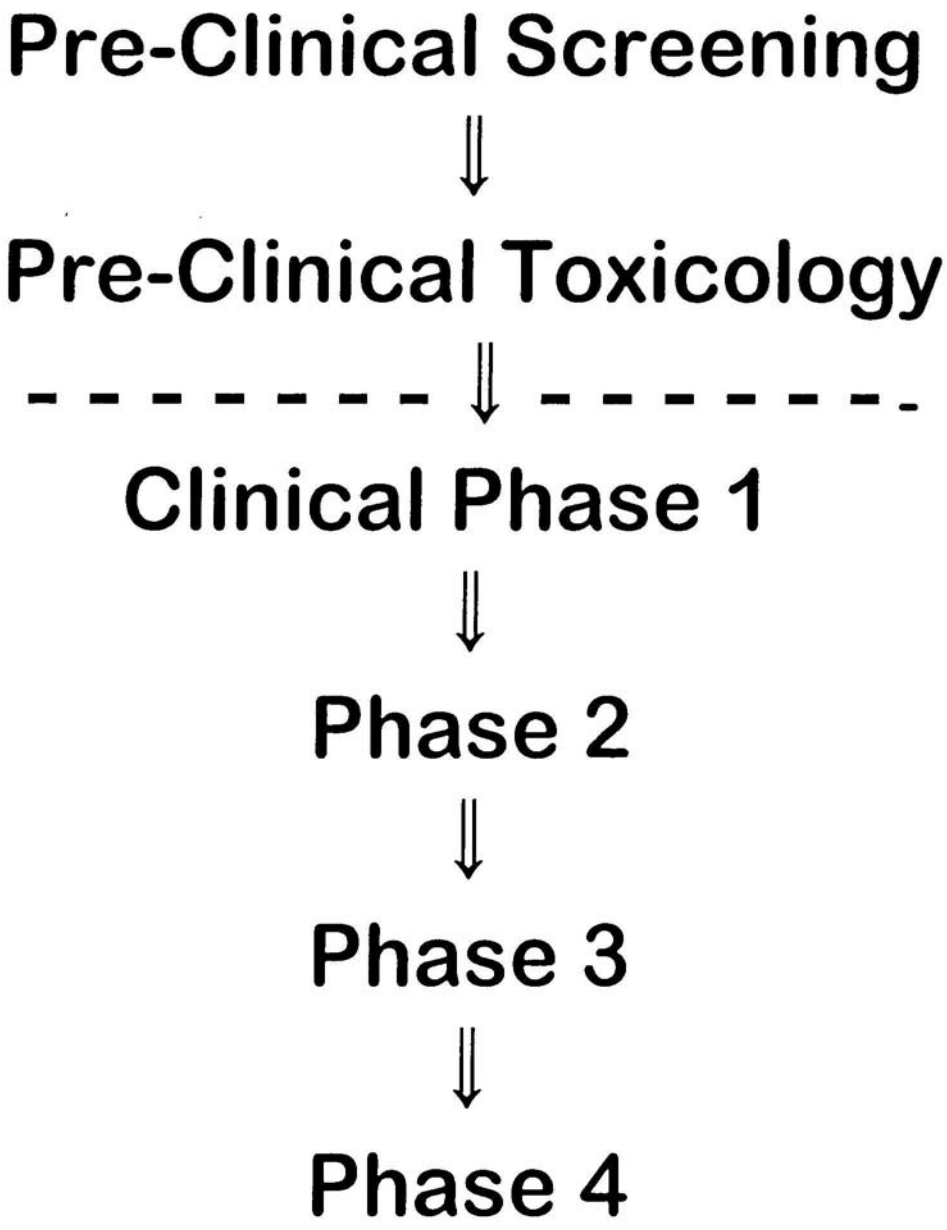
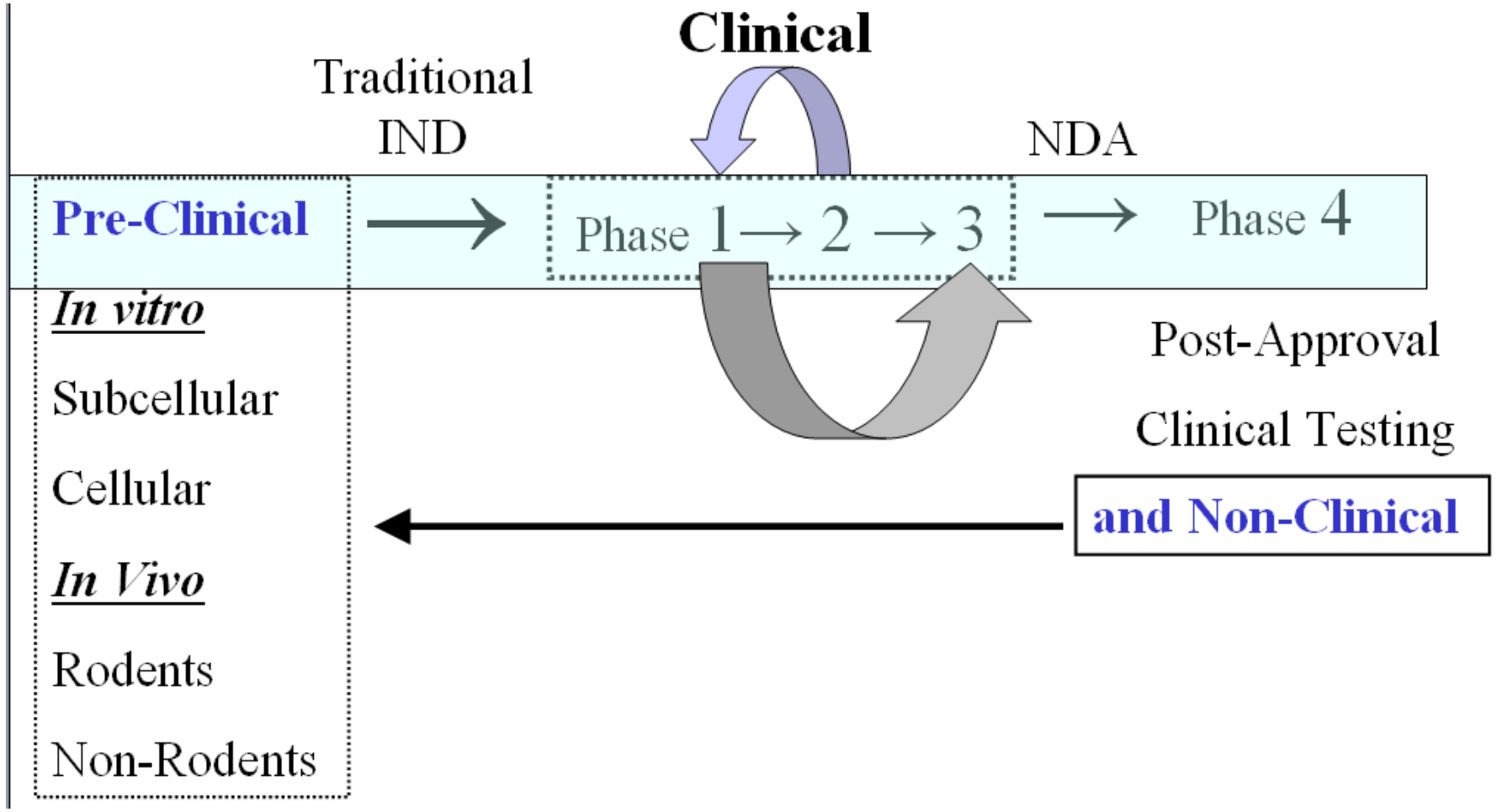
April 3, 2008


Pre-Clinical Screening
Pre-Clinical Toxicology
Clinical Phase 1
Phase 2
Phase 3
Phase 4


Clinical
Traditional
IND
NDA
Pre-Clinical
Phase 1→ 2 → 3
Phase 4
In vitro
Subcellular
Cellular
In Vivo
Rodents
Non-Rodents
Post-Approval
Clinical Testing
and Non-Clinical

Guidance for Industry, Investigators, Reviewers

Exploratory IND Studies

January 2006

Categories of Studies:

[1] Proof-of-Concept (Industry; Academia)

[2] Selection of Lead Candidate from a Set of Options (Industry)

[3] Imaging (parity with EMEA policy)

“Historical” Phases of Human Evauation

Phase 0: Mechanism of Action

Phase 1: Safety, early signs of activity
Phase 2: Is activity promising?
Phase 3: Improve current therapy?

What is: Proof-of-Concept?

What is: Phase Zero?

Can You Articulate the Key Question?

How Do You Answer This Question?

NIH Roadmap

ACCELERATING MEDICAL DISCOVERY TO IMPROVE HEALTH

//nihroadmap.nih.gov

- Overview
- NIH Roadmap Initiatives
- Grants and Funding Opportunities
- Frequently Asked Questions
- Press Release
- Press Briefing Video
- *Science* Magazine Article
- Subscribe to the NIH Roadmap E-mail list

New Pathways to Discovery

- Building Blocks, Biological Pathways, and Networks
- Molecular Libraries and Imaging
- Structural Biology
- Bioinformatics and Computational Biology
- Nanomedicine

Research Teams of the Future

- High-Risk Research
- Interdisciplinary Research
- Public-Private Partnerships

Re-engineering the Clinical Research Enterprise

- Re-engineering the Clinical Research Enterprise

What's New

- Meeting: Nanomedicine Project Launch and Planning – May 4
- Meeting: NIH Roadmap Briefing
- NIH Director's Pioneer Award
- Addendum to RFA-RM-04-005, "National Technology Centers for Networks and Pathways" Page Limits and Budget Pages
- RFTOP-RM-169, Inventory and Evaluation of Clinical Research Networks
- Meeting: Chemistry and Biology: Partners in Decoding the Genome

Re-Engineering Phase I (FIH) Trials

1. **Pipeline/Funnel Pressure: combinatorial/HTS, new Sponsors**
2. **To Phase I Faster, Less Preclinical Work**
3. **Fewer patients, homeopathic doses**
4. **More patients "near-Phase 2" doses**
5. **"Value-Added" factors**
   - **PK only: variability, metabolism/pharmacogenetics**
   - **PD: Decisions to Drop/Continue**

The PINK SHEET October 28, 2002
Daniel Vasella, MD CEO, Novartis
Industry-Wide Trends in Clinical Trials

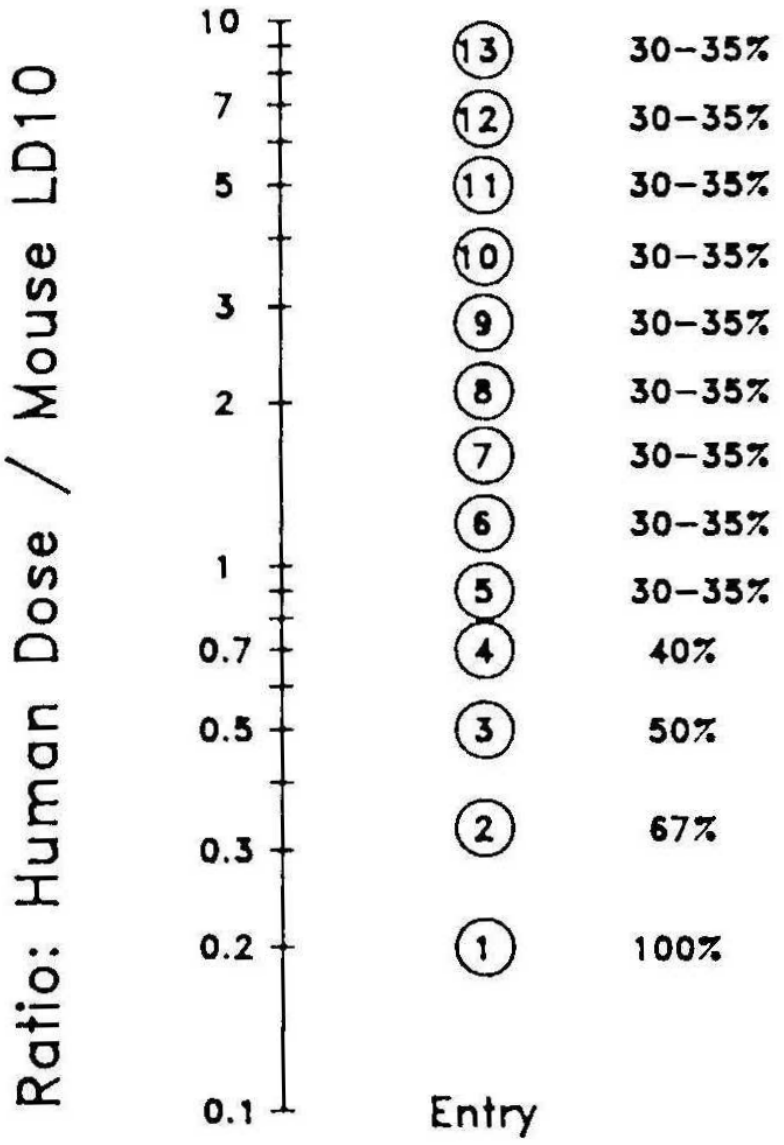
	Change 1995→2001	# Ongoing in 2001
Phase 1	+70%	714
Phase 2	+55%	1,136
Phase 3	(none)	488

Design of Phase 1 (FIH) Trial

* Starting Dose
* Escalation Scheme

For Both Elements, Conflict Between Caution/Safety vs. Efficiency/Efficacy

Modified Fibonacci Escalation



BIBLIOGRAPHY / COLLINS / PHASE 1

J.M.Collins, D.S.Zaharko, R.L.Dedrick, B.A.Chabner. Potential roles for preclinical pharmacology in Phase I trials.
Cancer Treat. Rep. 70:73-80, 1986.

***** Message: we do a lot of preclinical pharm studies;***
- - what do we learn?
- - how is it used?
***** Initial proposal for customized dose escalation.***

J.M. Collins, C.K. Grieshaber, B.A. Chabner.
Pharmacologically-guided Phase I trials based upon preclinical development.
J. Natl. Cancer Inst. 82:1321-1326, 1990.

***** Note that title does not say "PK"***
Intended as an overall platform
Summarizes mostly retrospectively

PK-PD Hypothesis:

When Comparing Animal and Human Doses, Expect Equal Toxicity for Equal Drug Exposure

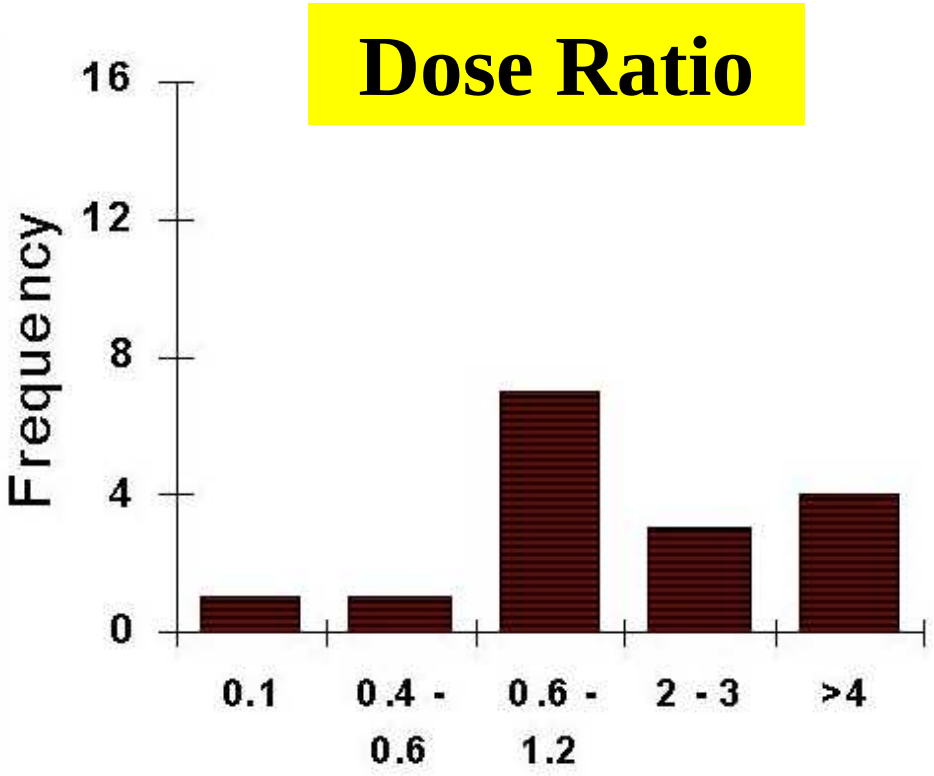
Concentration of Drug as a Biomarker or Endpoint

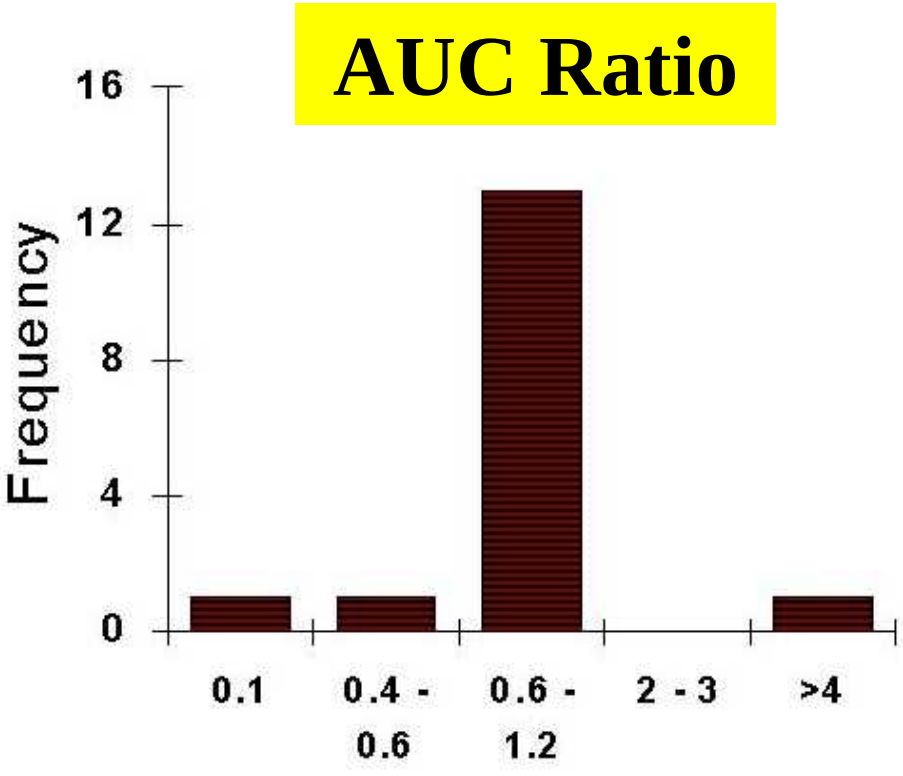
Bridges Between Preclinical and Clinical Development

Preclinical Pharm/Tox	Clinical Phase 1 Trials
Mouse MTD	Starting Dose
↓	↓
Blood Levels	Blood Levels
↘	↙

Escalation Strategy

Acute Toxicity of Anticancer Drugs Human versus Mouse





Conclusion:

Hypothesis has merit.

Follow-Up:

What is underlying reason for interspecies differences?

Additional Effects on Drug Metabolism

Species differences

- Major differences in drug metabolism in different species have been recognized for many years both in gut microflora and CYP proteins

- Example: phenylbutazone half-life is:

  3 h in rabbit
  6 h in rat, guinea pig, dog
  3 days in humans

Metabolism as the Principal Confounding Factor for First-in-Human Trials

Gianni et al, JNCI (1990)

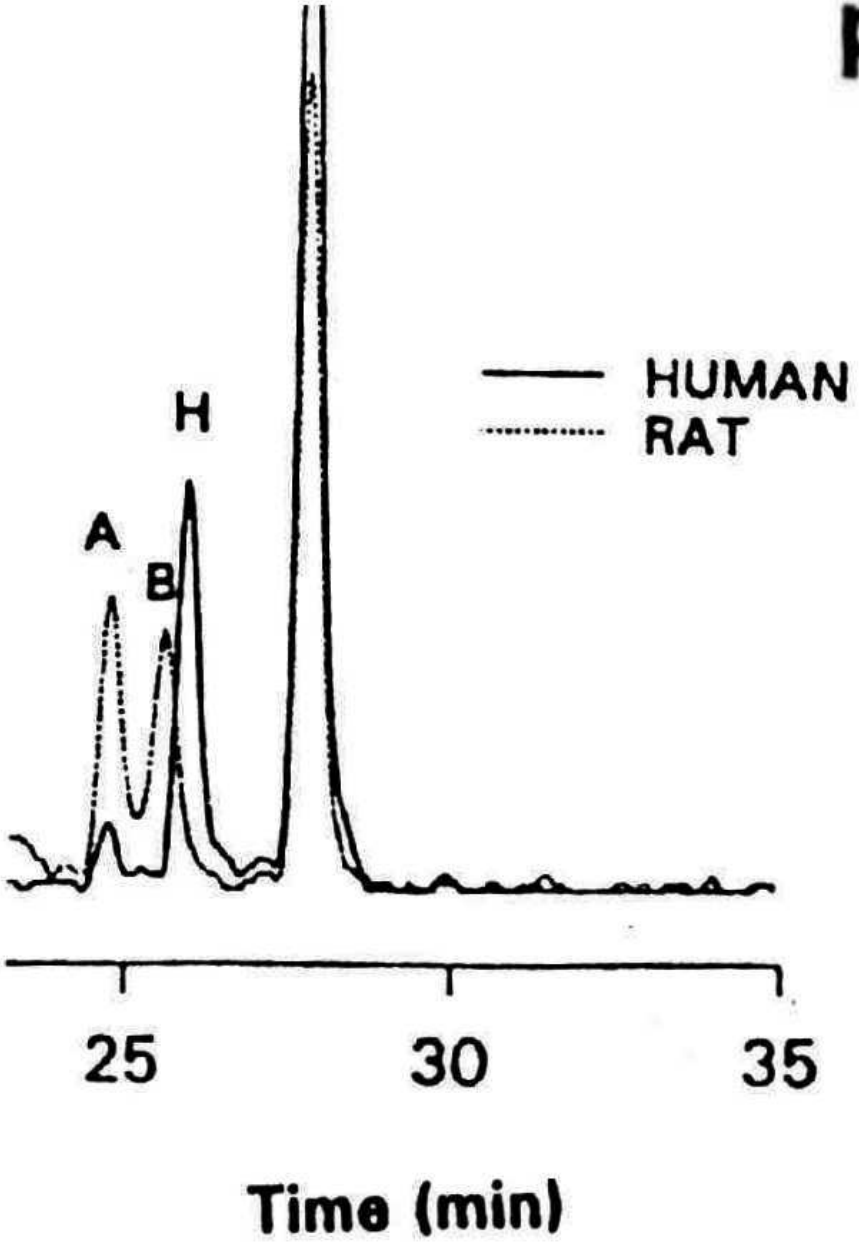
AUC values in plasma for Iododeoxydoxorubicin (I-Dox) in Mouse & Humans at Equi-Toxic Doses

	Mouse	Human
I-Dox	5.0	0.3
I-Dox-ol (metabolite)	1.2	4.0

Rule #1

Always Include Some Data from the Lab

paclitaxel



In Addition to Explaining Interspecies Differences, Other Applications for Metabolism Studies in Phase 1:

Learn/Confirm Major Pathways
Learn/Confirm Active/Toxic Molecules

In Vitro – In Vivo

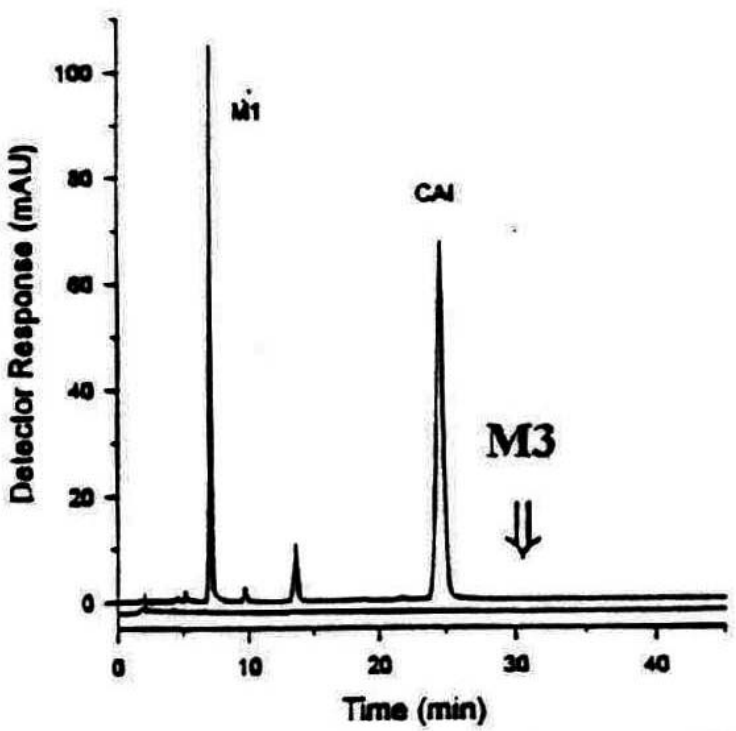
Metabolic Profiling

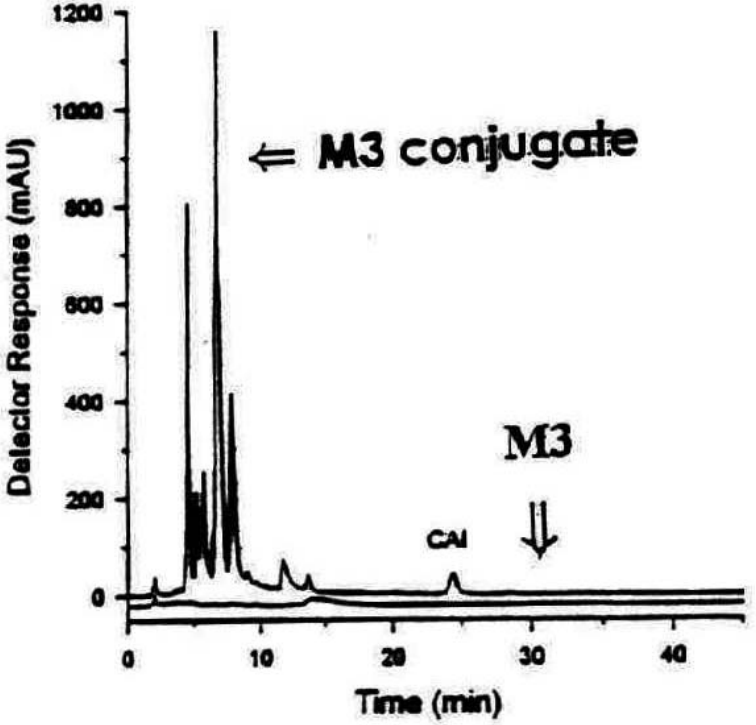
"CAI"

Microsomes

M1 2%

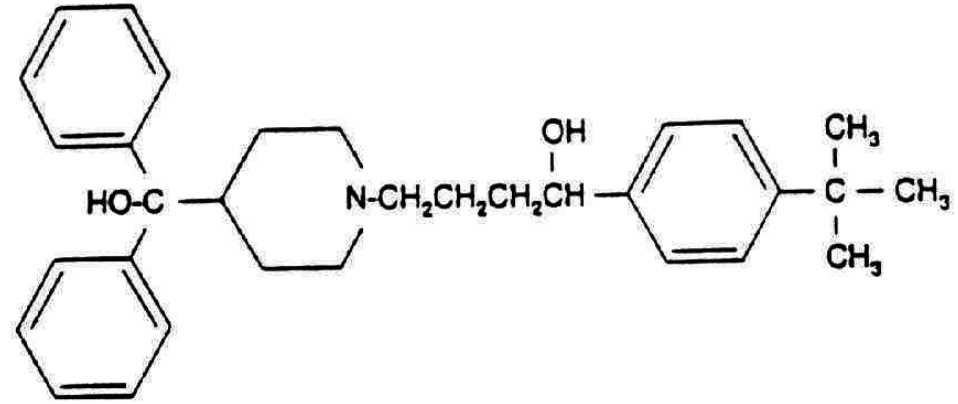
M3 84%

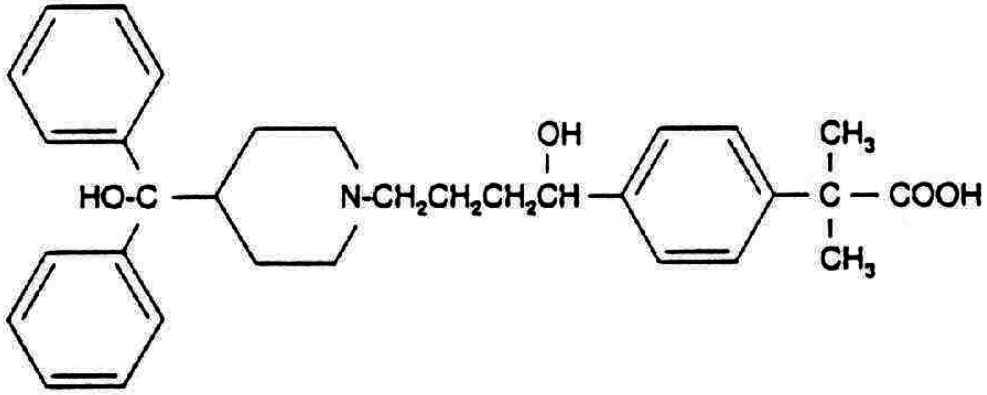




L. Ludden et al Clin Cancer Res, 1995

terfenadine/SELDANE®





fexofenadine/ALLEGRA®

Target-Guided Dose Escalation

Preclinical Pharm/Tox **Clinical Phase 1 Trials**

Safety Factor

Reference Animal Dose ↔ Starting Human Dose

Define Target Goal **Assess Target Impact**

Stop or Escalate?

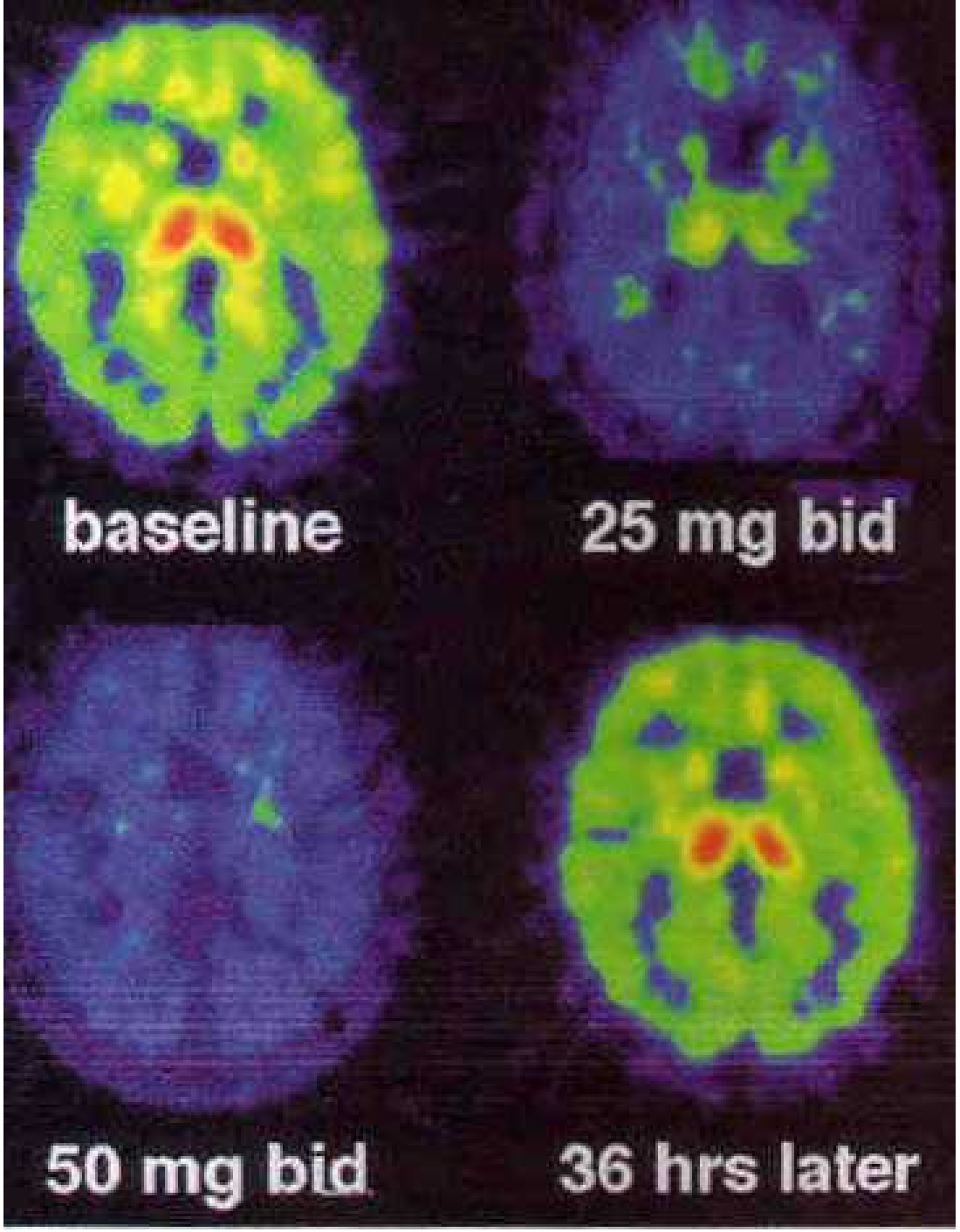
Functional Imaging via PET: Biomarkers for Treatment Evaluation

- **Does treatment impact the desired target?**
- **What is the minimum/maximum dose?**
- **How to select interval between courses?**

CONTEXT:
Individual Patient, or New Agent Development

MAO-B Inhibition by Lazabamide

J.Fowler,BNL Neurology(93)

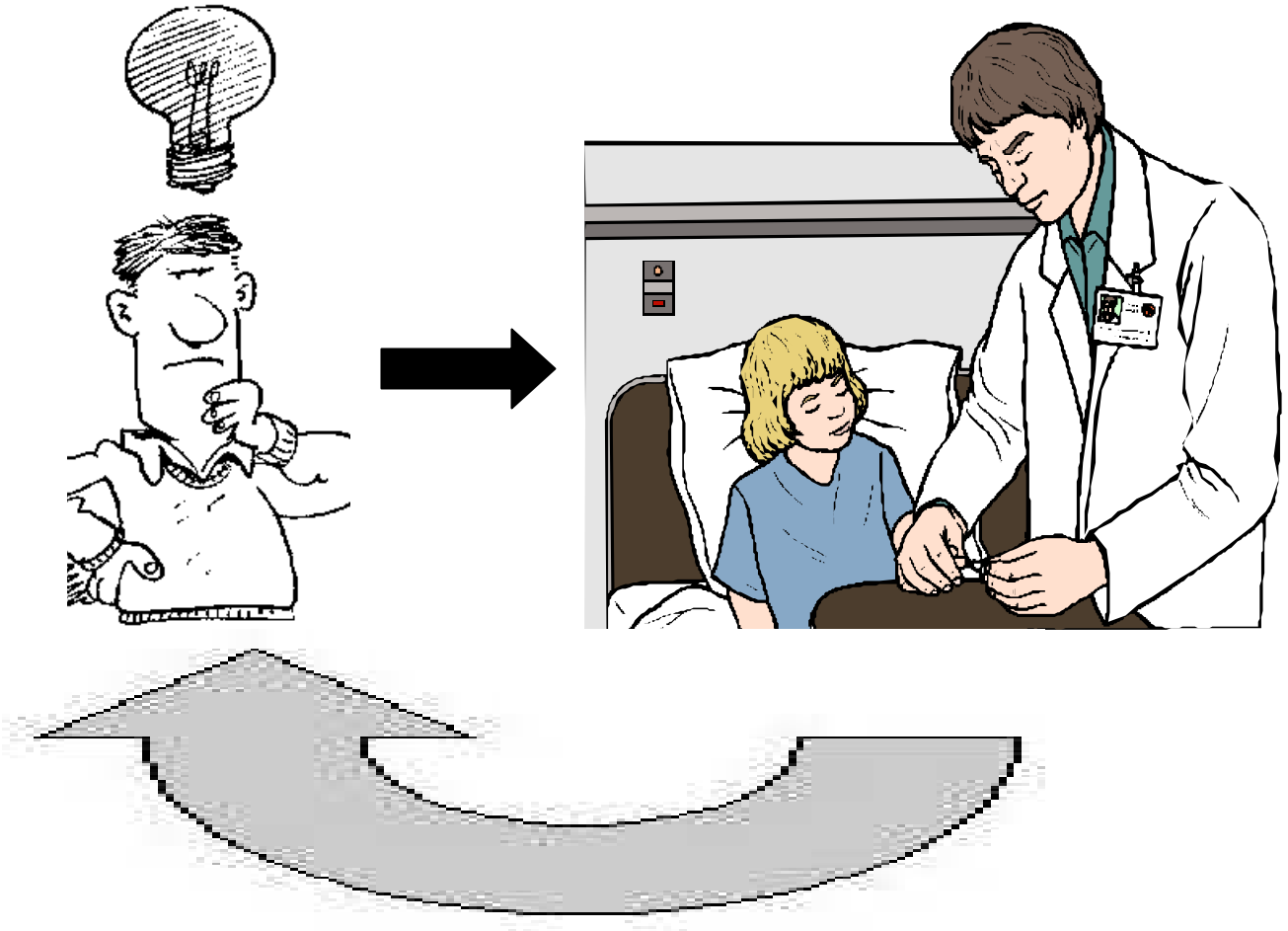


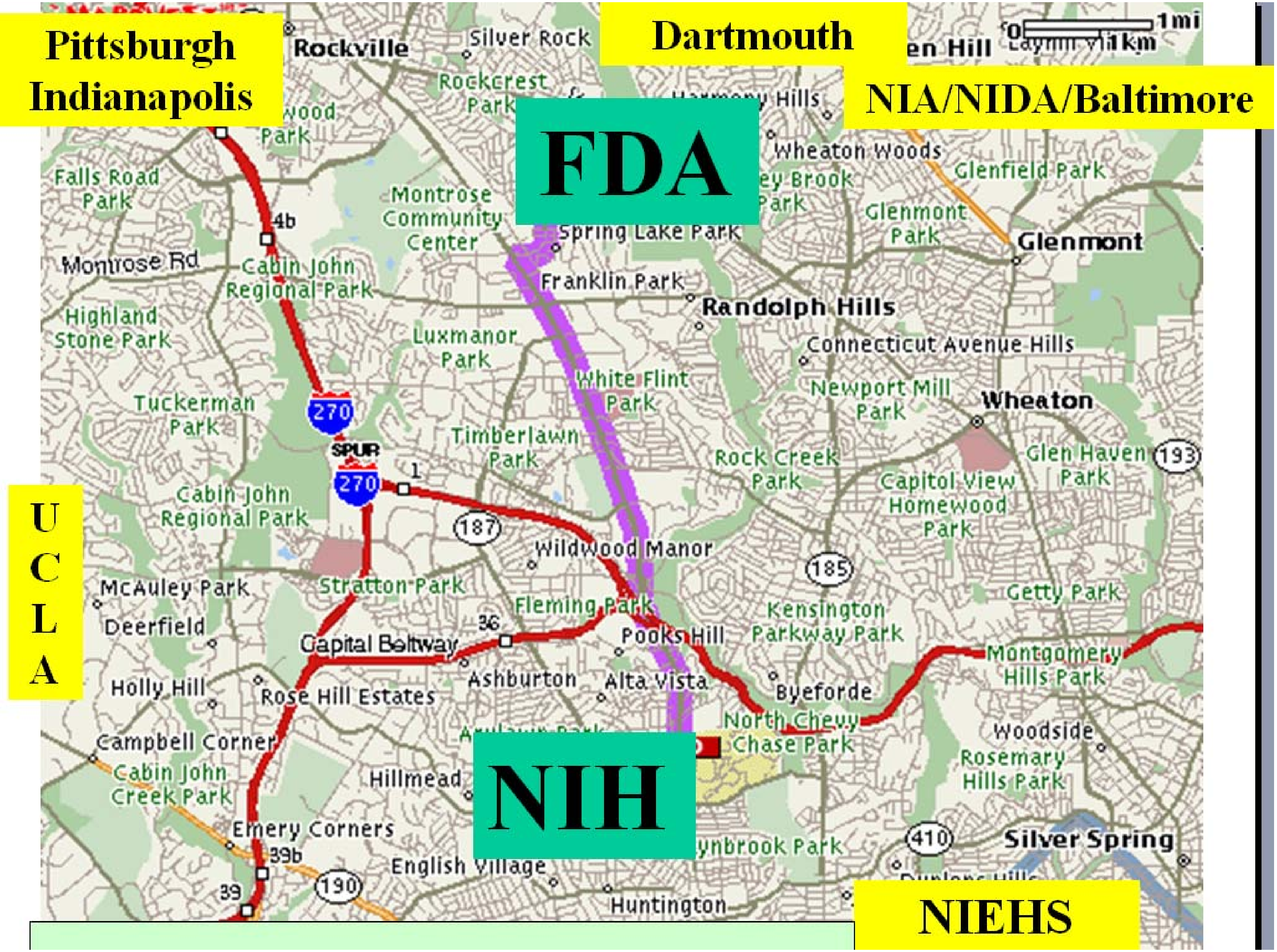
First-In-Human Trials Identity Crisis?

What is Inherent in First-In-Human Trials?

surprise!

Translational Research





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NIA/NIDA/Baltimore
FDA
UCLA
NIH
NIEHS
Rockville
Silver Rock
Rockcrest Park
Harmony Hills
Wheaton Woods
Glenfield Park
Falls Road Park
Montrose Community Center
Spring Lake Park
Glenmont Park
Glenmont
Montrose Rd
Cabin John Regional Park
Franklin Park
Randolph Hills
Highland Stone Park
Luxmanor Park
Connecticut Avenue Hills
White Flint Park
Newport Mill Park
Wheaton
Tuckerman Park
Timberlawn Park
Rock Creek Park
Glen Haven Park
Capitol View Homewood Park
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