

Phase 1 Clinical Studies
First-In-Human (FIH)

<Chapter 31>

Pharmacologically-Guided
Dose Escalation

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Pre-Clinical Screening



Pre-Clinical Toxicology



Clinical Phase 1



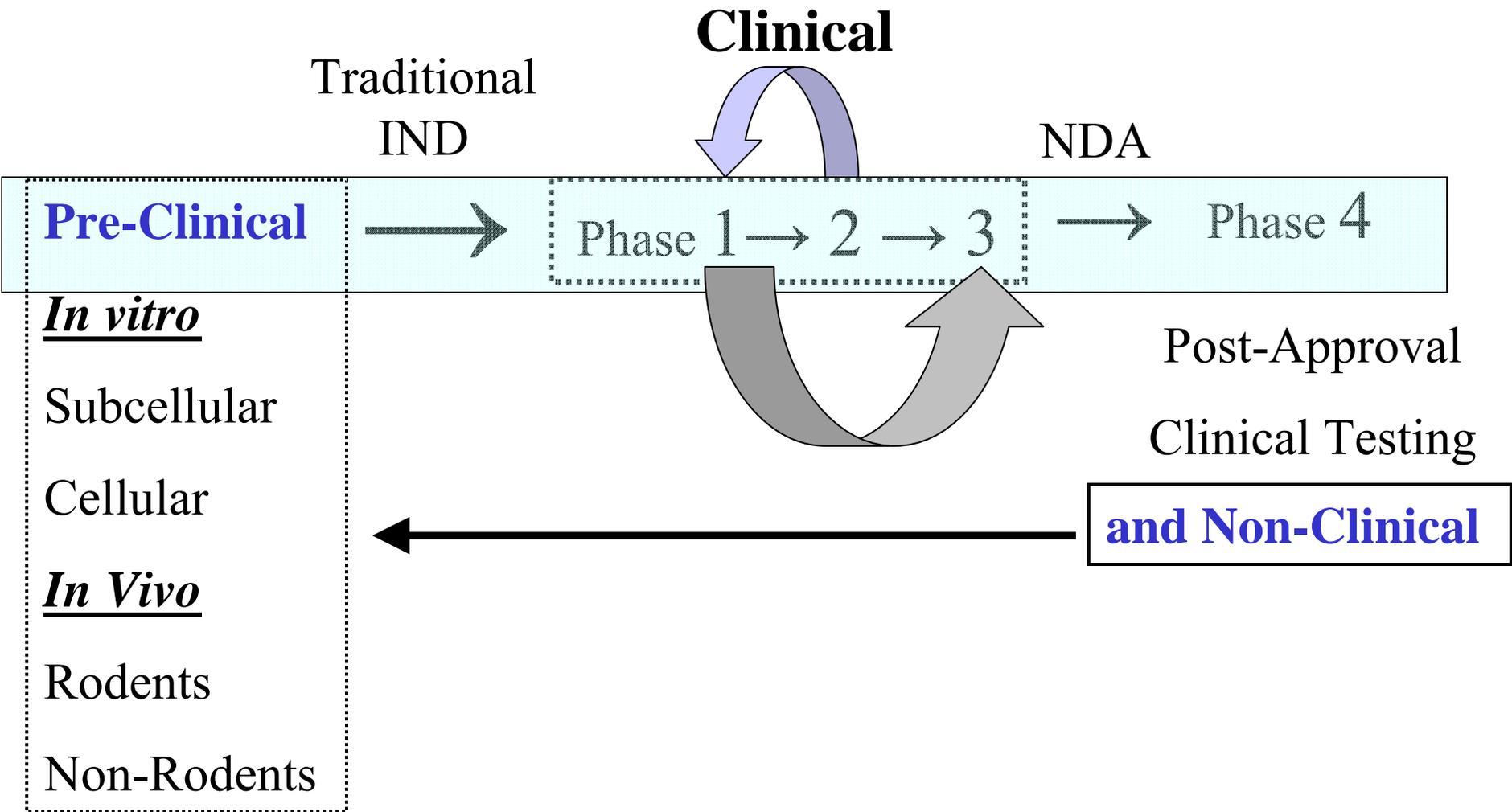
Phase 2



Phase 3



Phase 4





- ▶ [Overview](#)
- ▶ [NIH Roadmap Initiatives](#)
- ▶ [Grants and Funding Opportunities](#)
- ▶ [Frequently Asked Questions](#)
- ▶ [Press Release](#)
- ▶ [Press Briefing Video](#)
- ▶ [Science Magazine Article](#)
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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

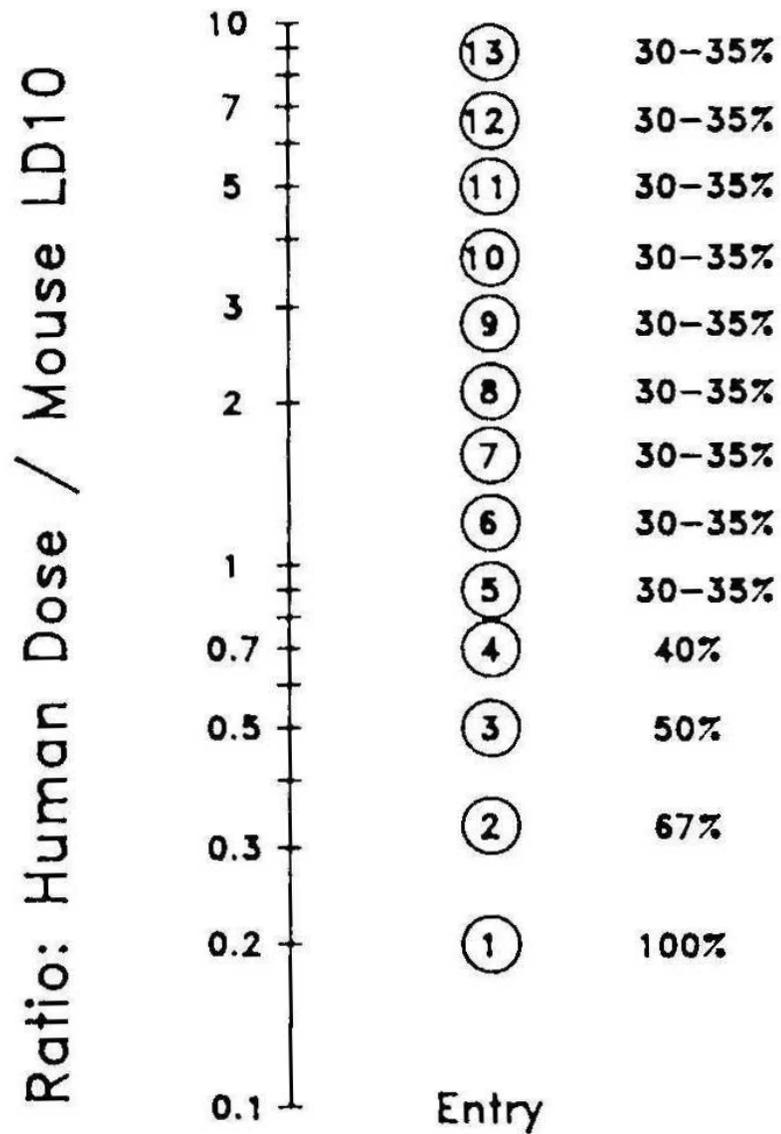
- 1. Pipeline/Funnel Pressure:
combinatorial/HTS, new Sponsors**
- 2. To Phase I Faster, Less Preclinical Work**
- 3. Fewer patients, homeopathic doses**
- 4. More patients “near-Phase 2” doses**
- 5. “Value-Added” factors**
 - PK only: variability, metabolism/pharmacogenetics**
 - PD: Decisions to Drop/Continue**

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**



Mouse MTD



Blood Levels



Clinical

Phase 1 Trials



Starting Dose

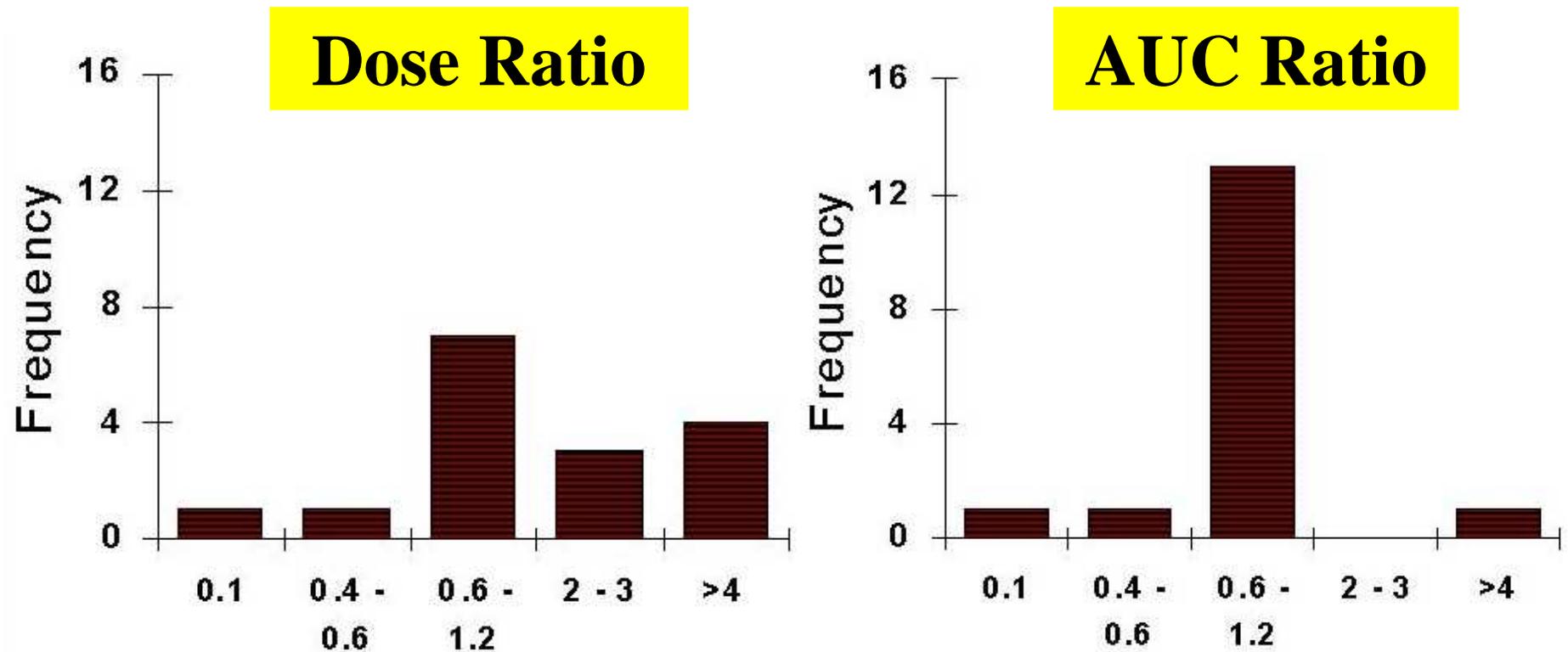


Blood Levels



Escalation Strategy

Acute Toxicity of Anticancer Drugs Human versus Mouse



Conclusion:

Hypothesis has merit.

Follow-Up:

**What is underlying reason for
interspecies differences?**

S.Markey, 8-Nov-01, <not in current year's examples>

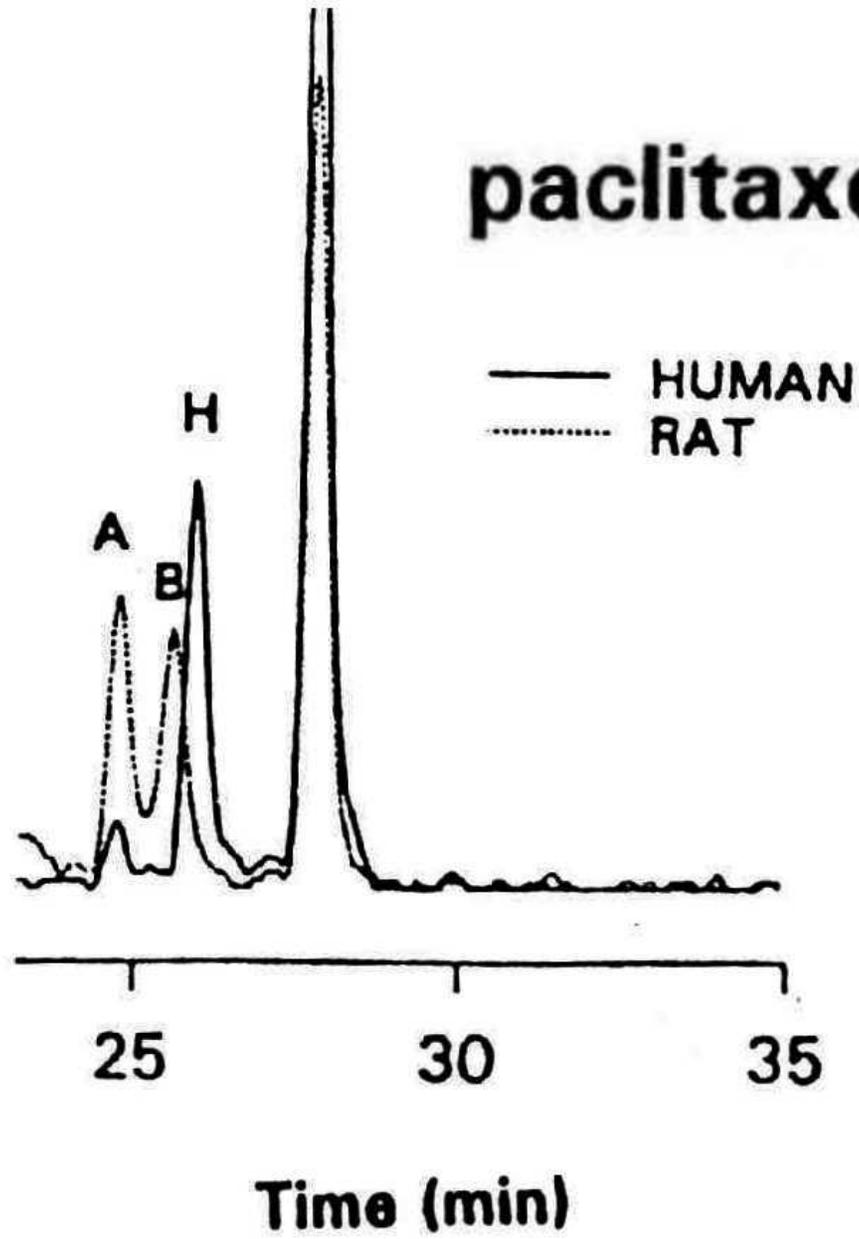
Additional Effects on Drug Metabolism

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**

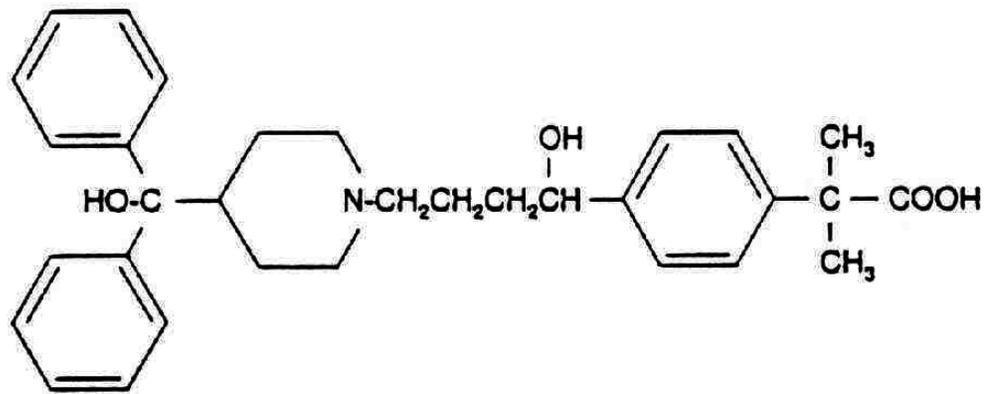
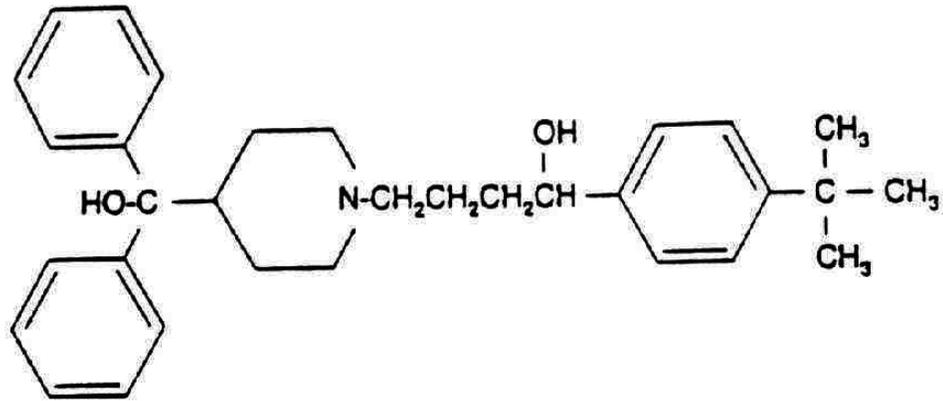
paclitaxel



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

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

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?

Guidance for Industry, Investigators, Reviewers
Exploratory IND Studies
FDA January 2006

Categories of Studies Include:

- [1] Molecular Proof-of-Concept
(pharmacologic concentrations)**
- [2] Functional Imaging**

**FDA's Exploratory IND
enables NCI's Phase Zero**

“Historical” Phases of Human Evaluation

Phase 0: Mechanism of Action

Phase 1: Safety, early signs of activity

Phase 2: Is activity promising?

Phase 3: Improve current therapy?

**NCI is working to re-engineer its pipeline
of new candidate molecules in the context of
Exploratory IND**

Articulate and Answer the Key Question

Key question can be as simple as whether drug candidate is absorbed from GI tract

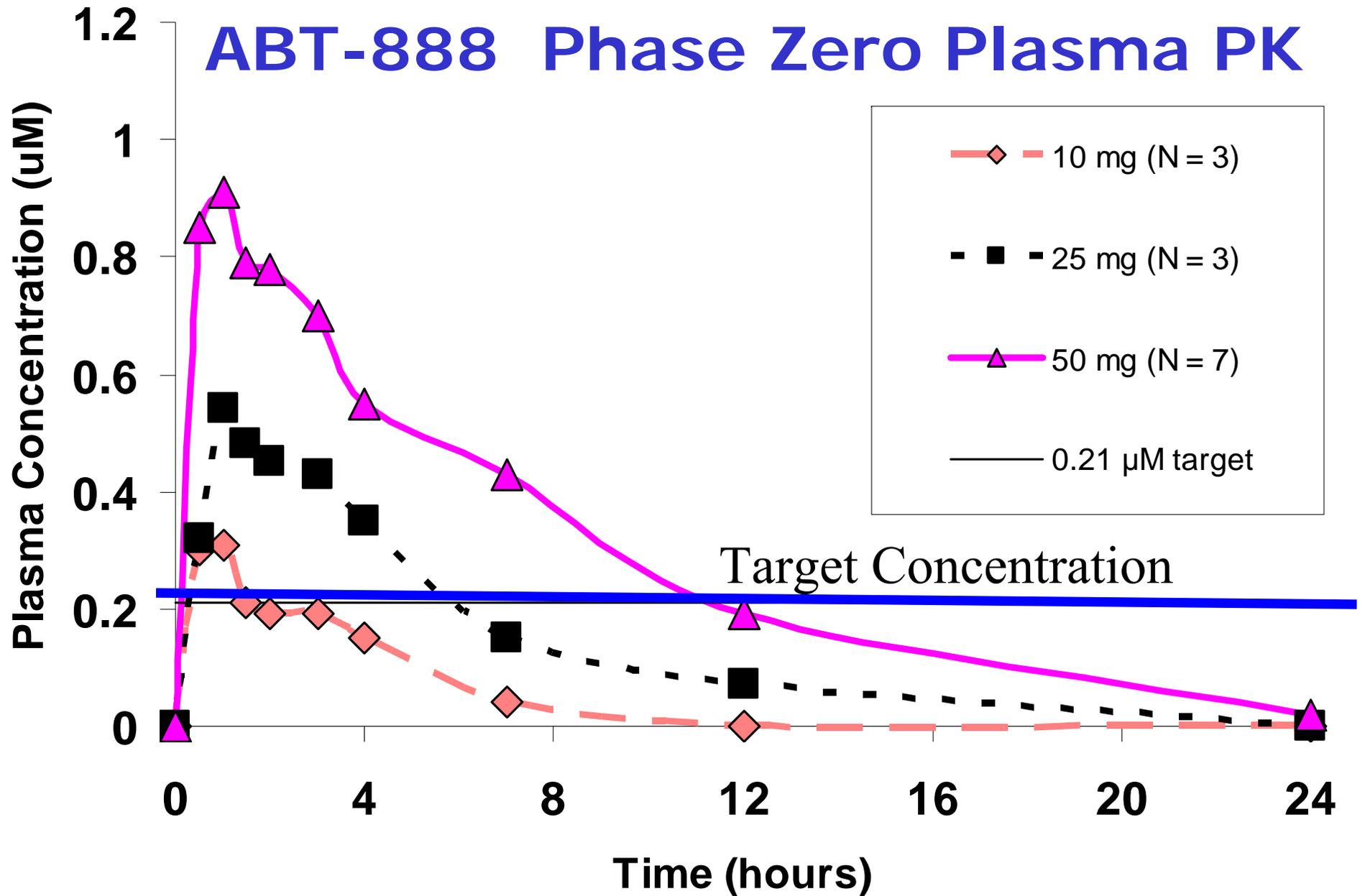
⇒ Readily Answered

Key Question for Phase Zero PARP Project:

Can DNA Repair Enzyme Be Inhibited?

(Need Tumor Sample and Suitable Assay!)

ABT-888 Phase Zero Plasma PK



S.Kummar, ASCO 2007

First NCI Phase Zero Project

PARP enzyme inhibitor

Goals

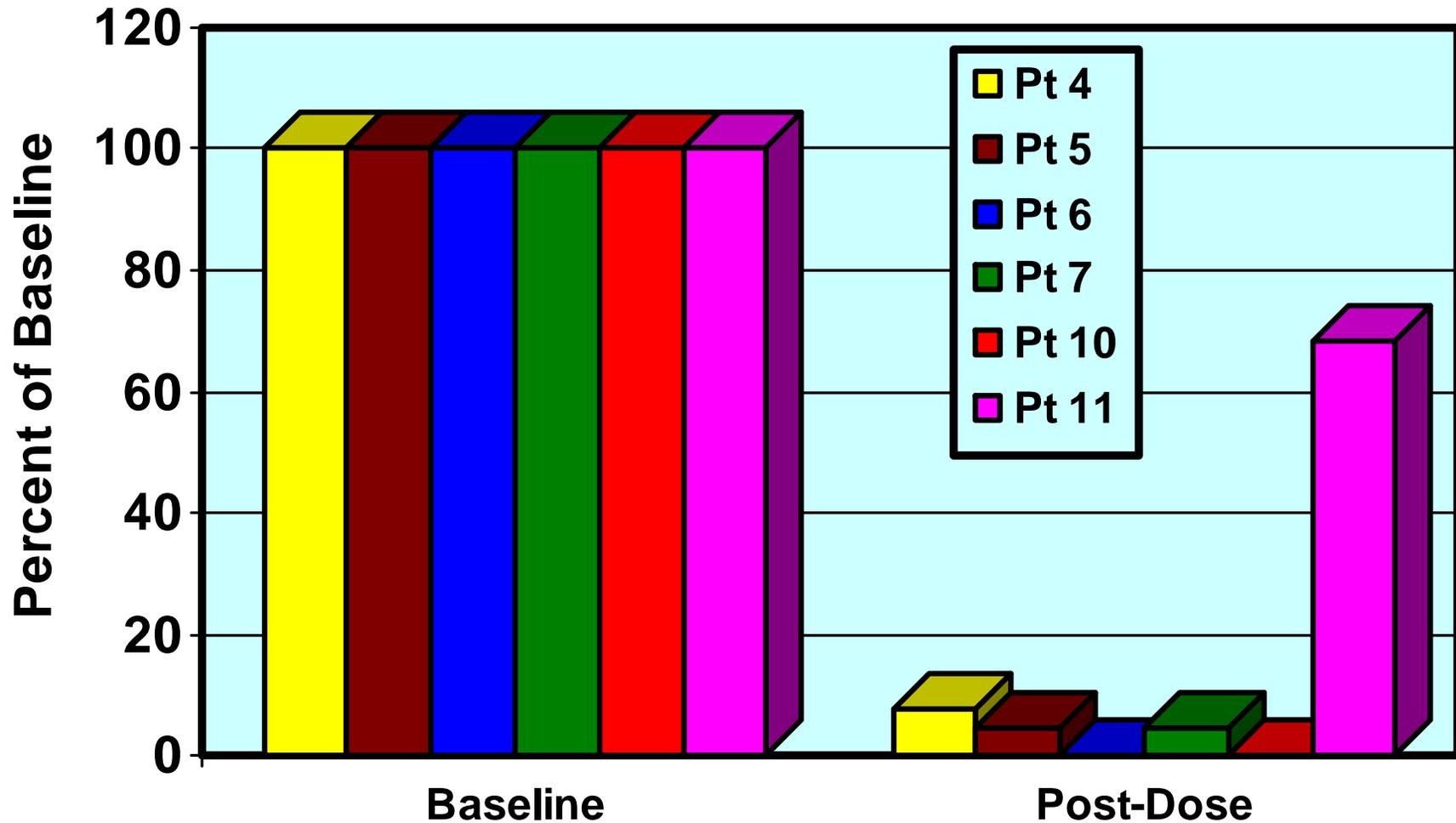
Can Target Plasma
Concentration Be
Achieved Orally?

Outcomes

YES

Can Tumor Biopsy
Provide Definitive
Results?

PAR Inhibition in Tumor Biopsies 3-6 Hours Post Dose



First NCI Phase Zero Project

PARP enzyme inhibitor

Goals

Can Target Plasma
Concentration Be
Achieved Orally?

Can Tumor Biopsy
Provide Definitive
Results?

Outcomes

YES

PK

YES

PD

Inhibition by dose and time

Functional Imaging via PET: Biomarkers for Treatment Evaluation

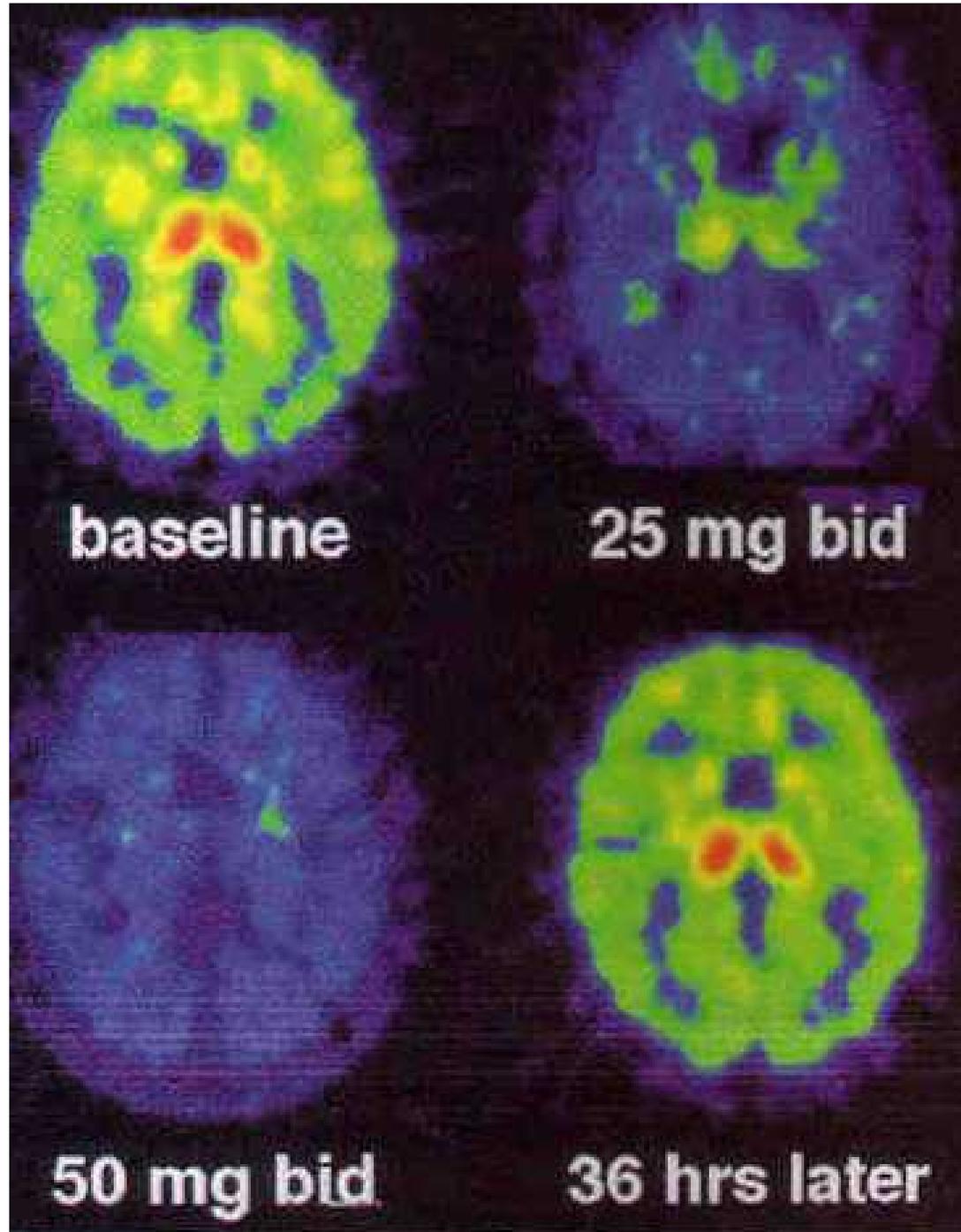
- **Does treatment impact the desired target?**
- **What is the minimum/maximum dose?**
- **How to select interval between courses?**

CONTEXT:

Individual Patient, or New Agent Development

**MAO-B
Inhibition by
Lazabamide**

**J.Fowler,BNL
Neurology(93)**



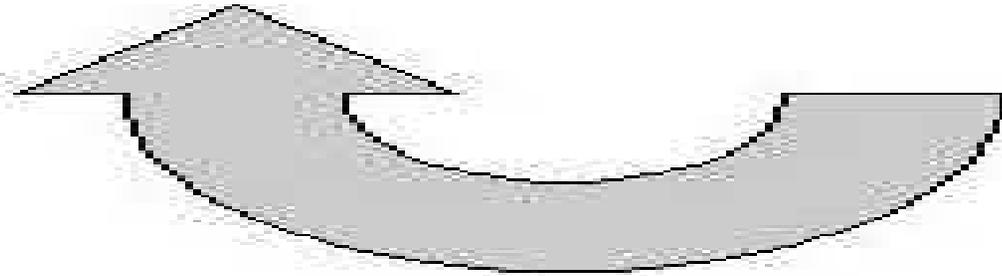
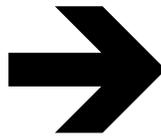
First-In-Human Trials

Identity Crisis?

What is Inherent in First-In-Human Trials?

<surprise!>

Translational Research



**Pittsburgh
Indianapolis**

Dartmouth

NIA/NIDA/Baltimore

FDA

**U
C
L
A**

NIH

NIHHS

