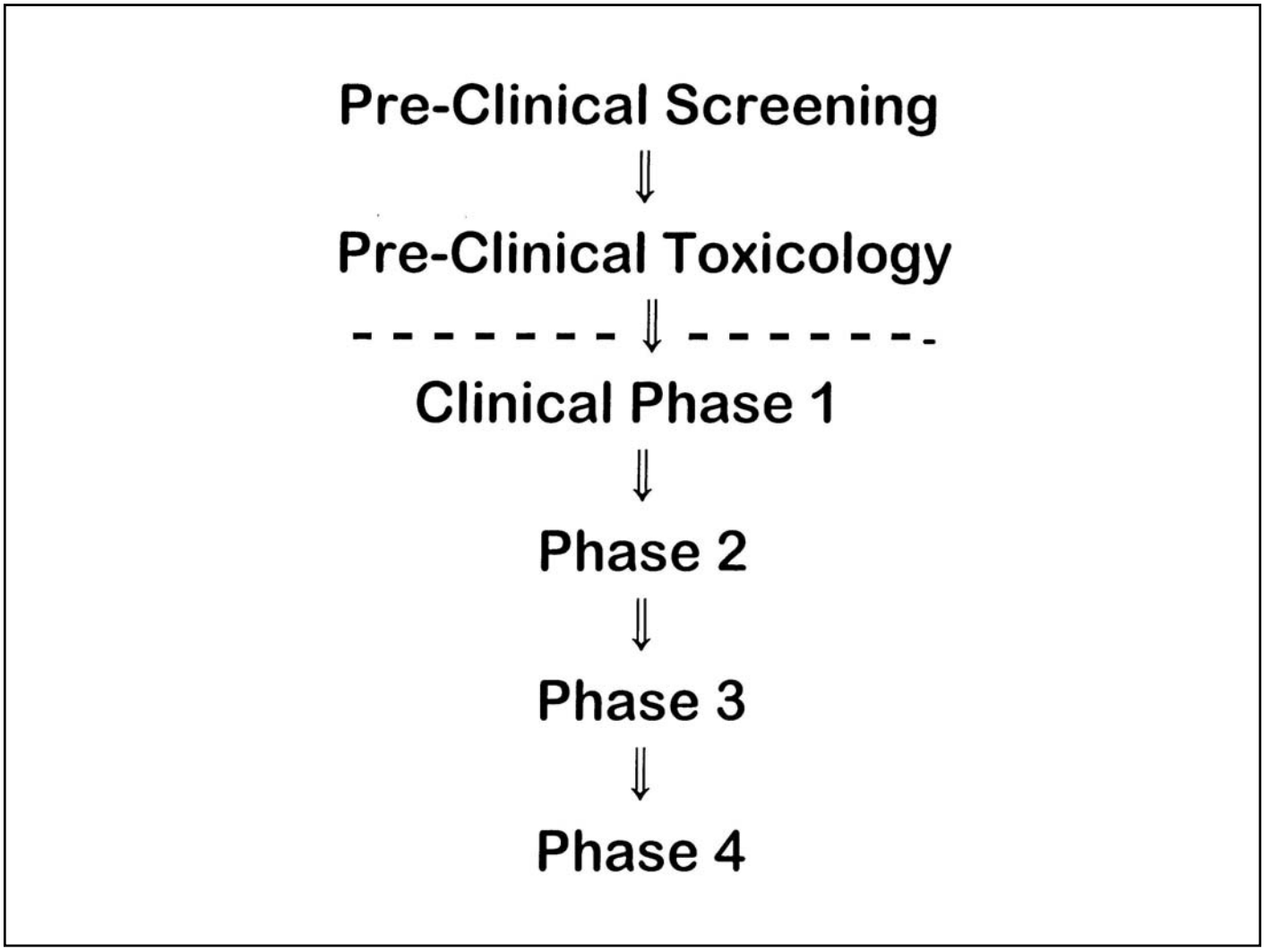
# Phase 1 Clinical Studies
# First-In-Human (FIH)
## *<Chapter 31>*
## *Pharmacologically-Guided Dose Escalation*

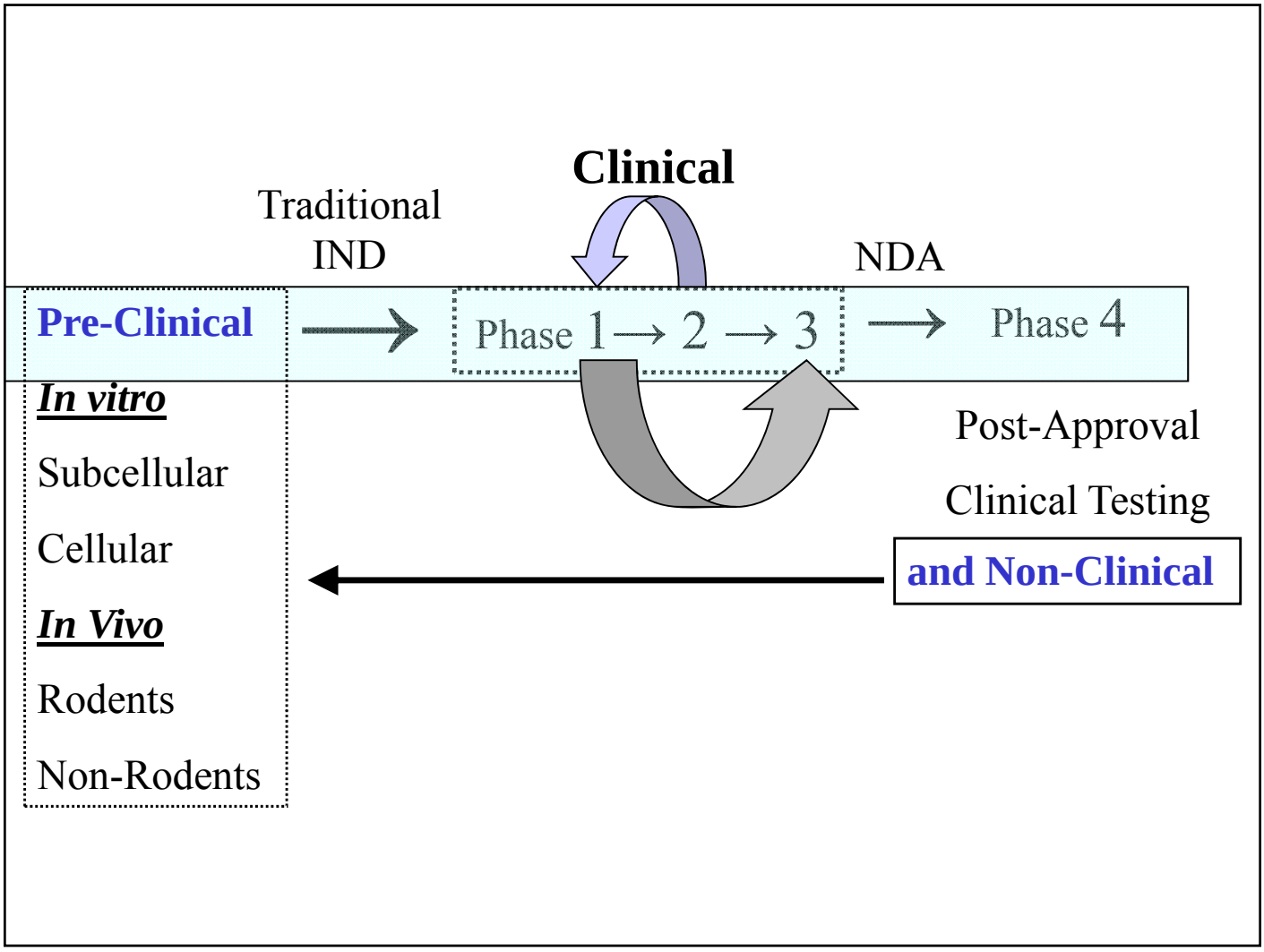
**Jerry M. Collins, Ph.D.**

***Developmental Therapeutics Program***

**Division of Cancer Treatment and Diagnosis, NCI**

**April 1, 2010**


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

//nihroadmap.nih.gov

# NIH Roadmap

ACCELERATING MEDICAL DISCOVERY TO IMPROVE HEALTH

- 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

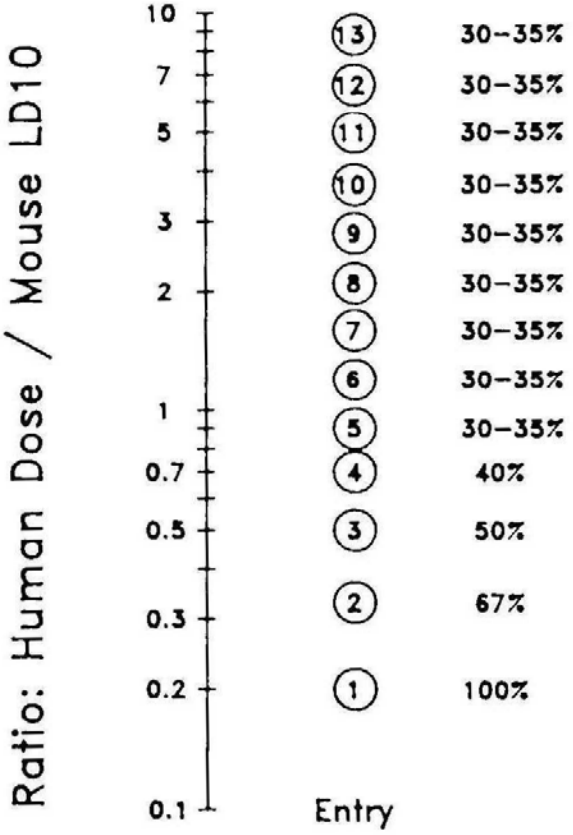
1. **Pipeline/Funnel Pressure: combinatorial/HTS, new Sponsors**
2. **To Phase I Faster, Less Preclinical Work**
3. **Fewer patients, homeopathic doses**
4. **More patients "near-Phase 2" doses**
5. **"Value-Added" factors**
   - **PK only: variability, metabolism/pharmacogenetics**
   - **PD: Decisions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

# 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**

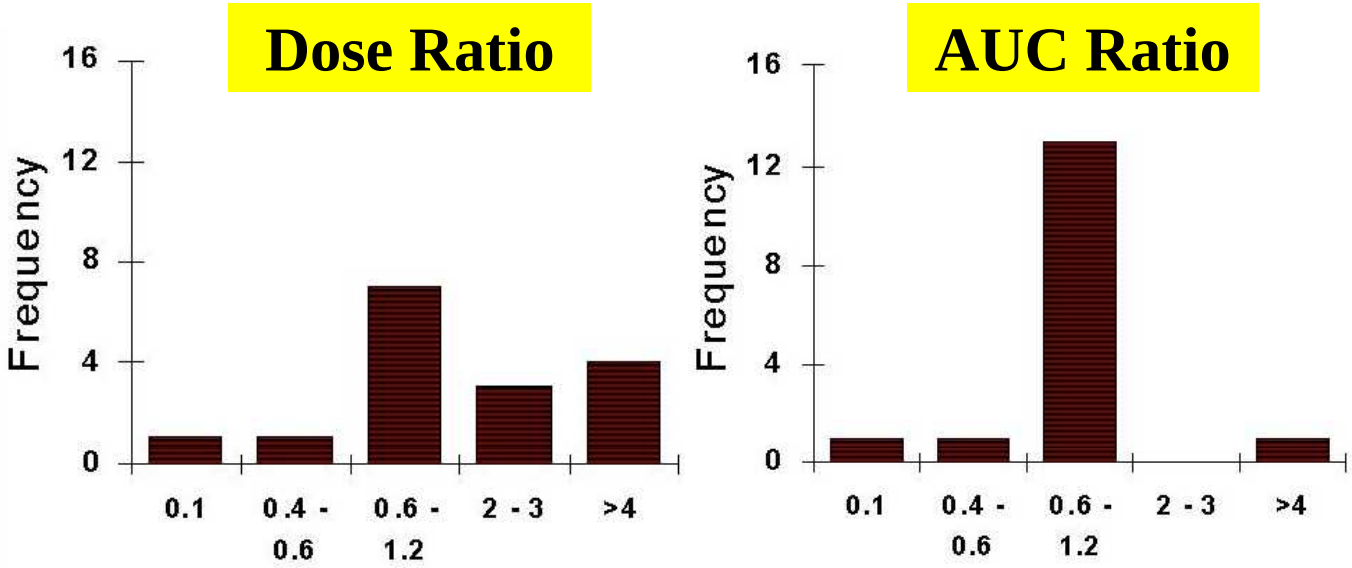
**Concentration of Drug as a Biomarker or Endpoint**

# 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?**

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

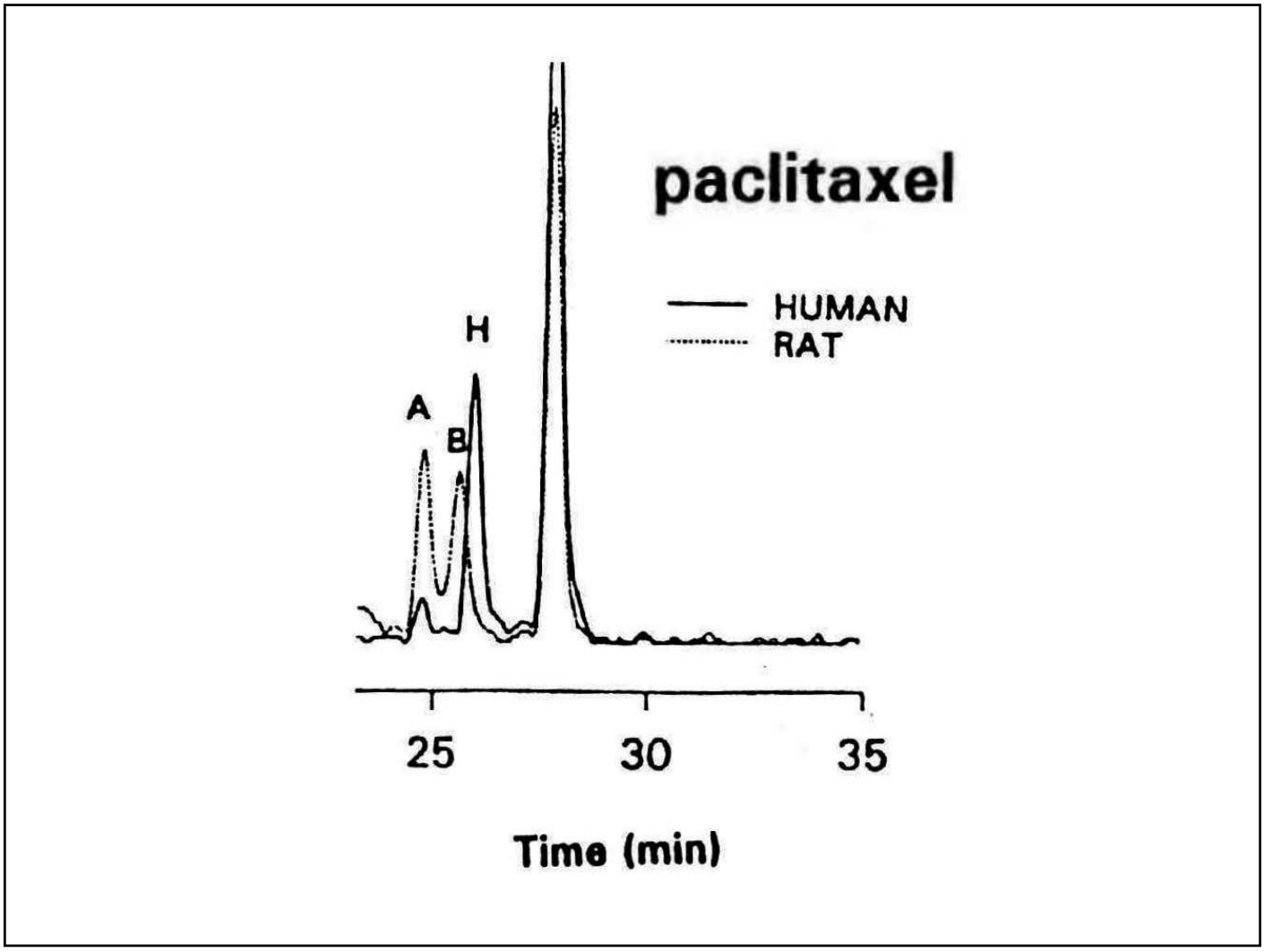
## Additional Effects on Drug Metabolism

# 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

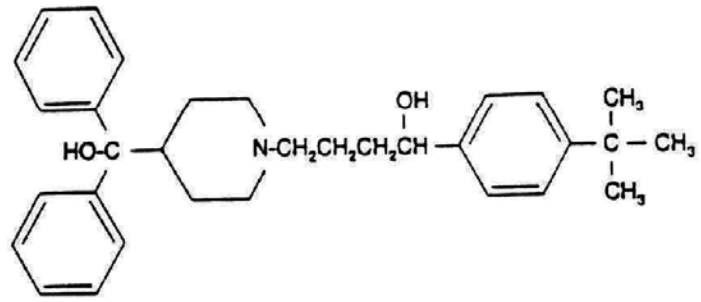
# Metabolism as the Principal Confounding Factor for First-in-Human Trials

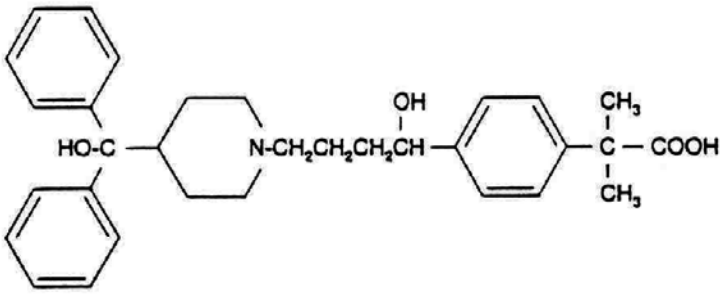

paclitaxel
HUMAN
RAT
A
B
H
25
30
35
Time (min)

***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**

## Chronology of First-in-Human Study Designs

| Era | Primary | Secondary | Correlative |
|---|---|---|---|
| 1960s | Toxicity | Activity | (None) |
| 1980s | Toxicity | Activity | PK |
| 1980s | Toxicity PK-guided | Activity | |
| 1990s | Toxicity | Activity | PK-PD/Biomarkers |
| **2000s Phase Zero** | **PD** | **PK** | **~~Toxicity, Activity~~ (not expected)** |

Role Reversal as Discovery Continues

## Articulate and Answer the Key Question

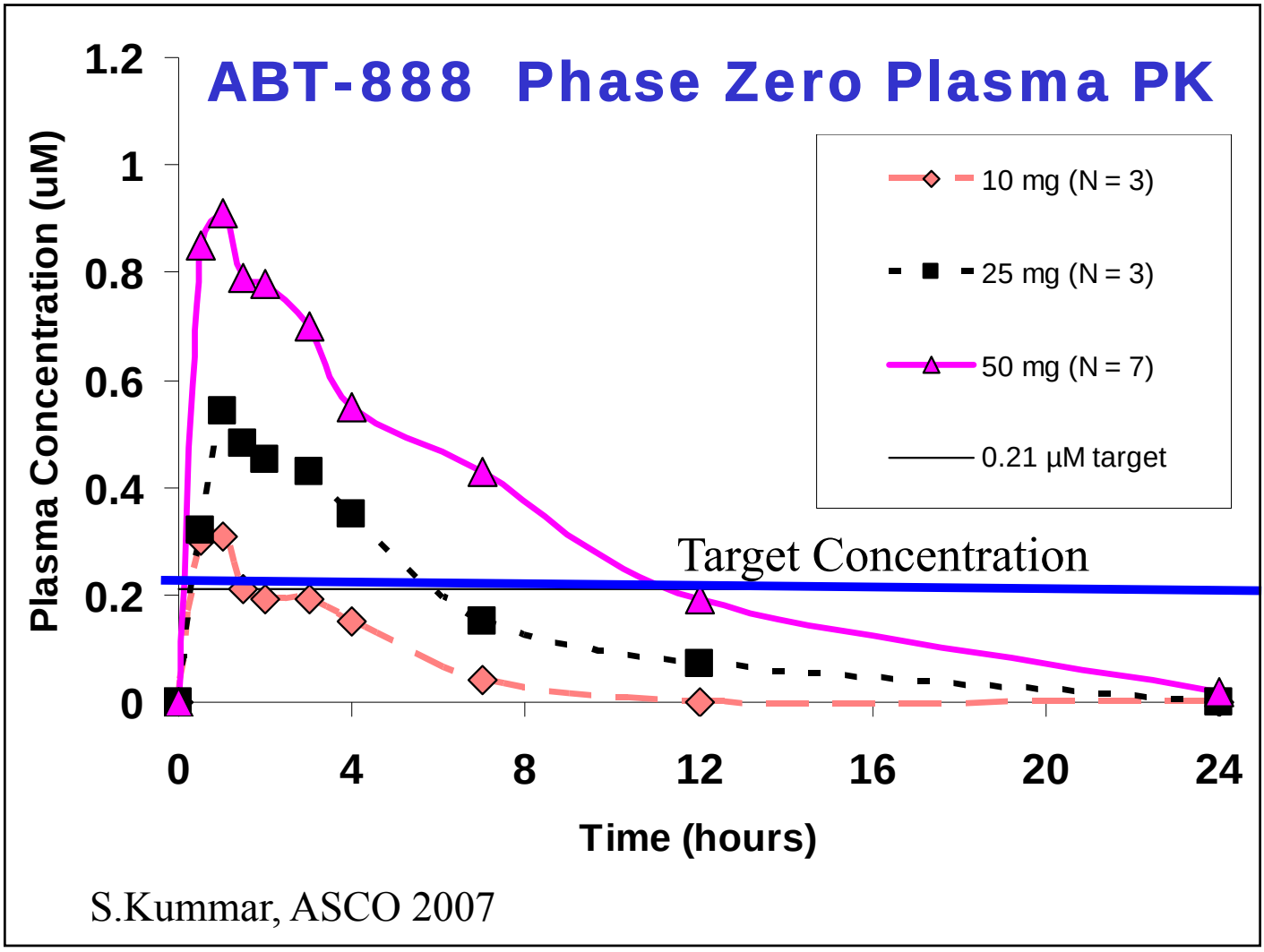
Key question can be as simple as whether drug candidate is absorbed from GI tract

$\Rightarrow$ Readily Answered

Key Question for Phase Zero PARP Project:

Can DNA Repair Enzyme Be Inhibited?

(Need Tumor Sample and Suitable Assay!)



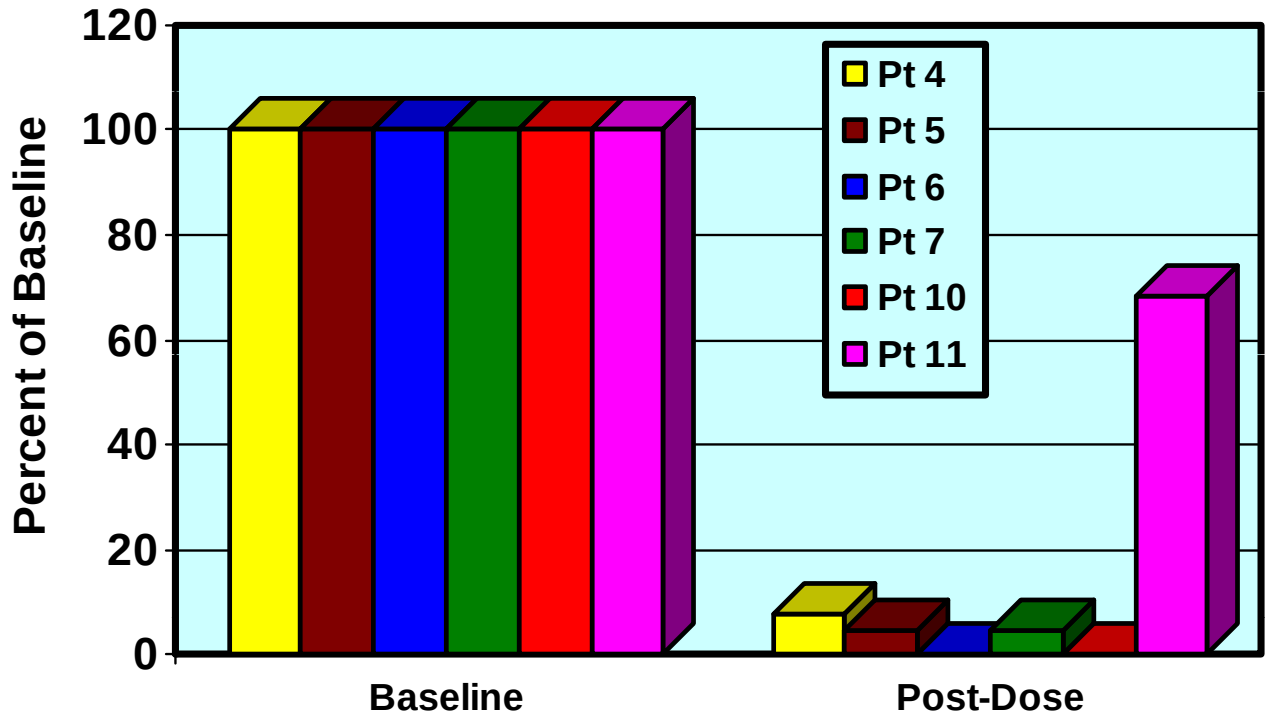

S.Kummar, ASCO 2007

## First NCI Phase Zero Project

PARP enzyme inhibitor

| Goals | Outcomes |
| --- | --- |
| Can Target Plasma Concentration Be Achieved Orally? | YES |
| Can Tumor Biopsy Provide Definitive Results? | |

## PAR Inhibition in Tumor Biopsies 3-6 Hours Post Dose




S.Kummar, T.A.T. 2008

# First NCI Phase Zero Project

## PARP enzyme inhibitor

| Goals | Outcomes |
| --- | --- |
| Can Target Plasma Concentration Be Achieved Orally? | YES — PK |
| Can Tumor Biopsy Provide Definitive Results? | YES — PD |

Inhibition by dose and time

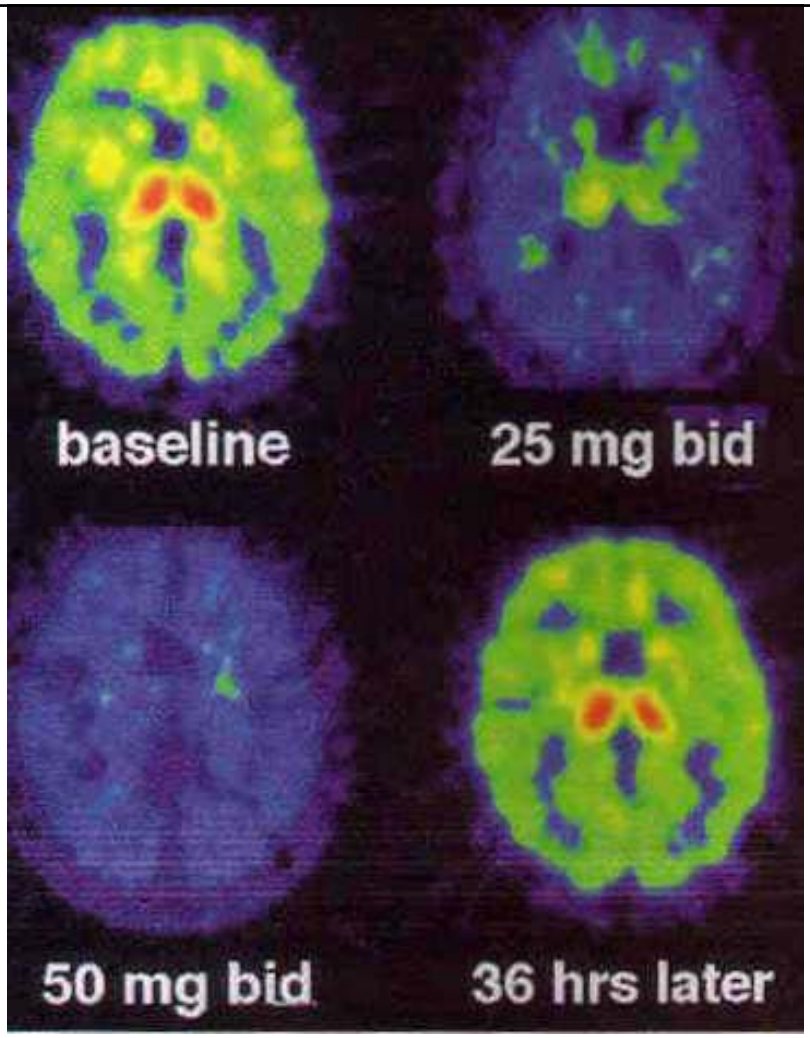
## Functional Imaging via PET: Biomarkers for Treatment Evaluation

- **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)**



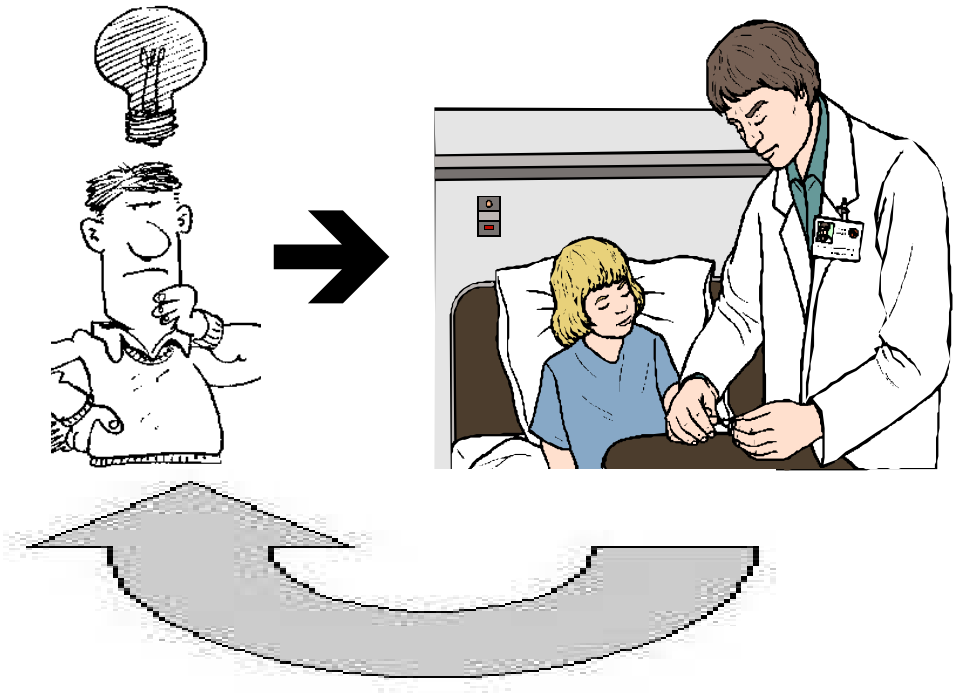
# First-In-Human Trials

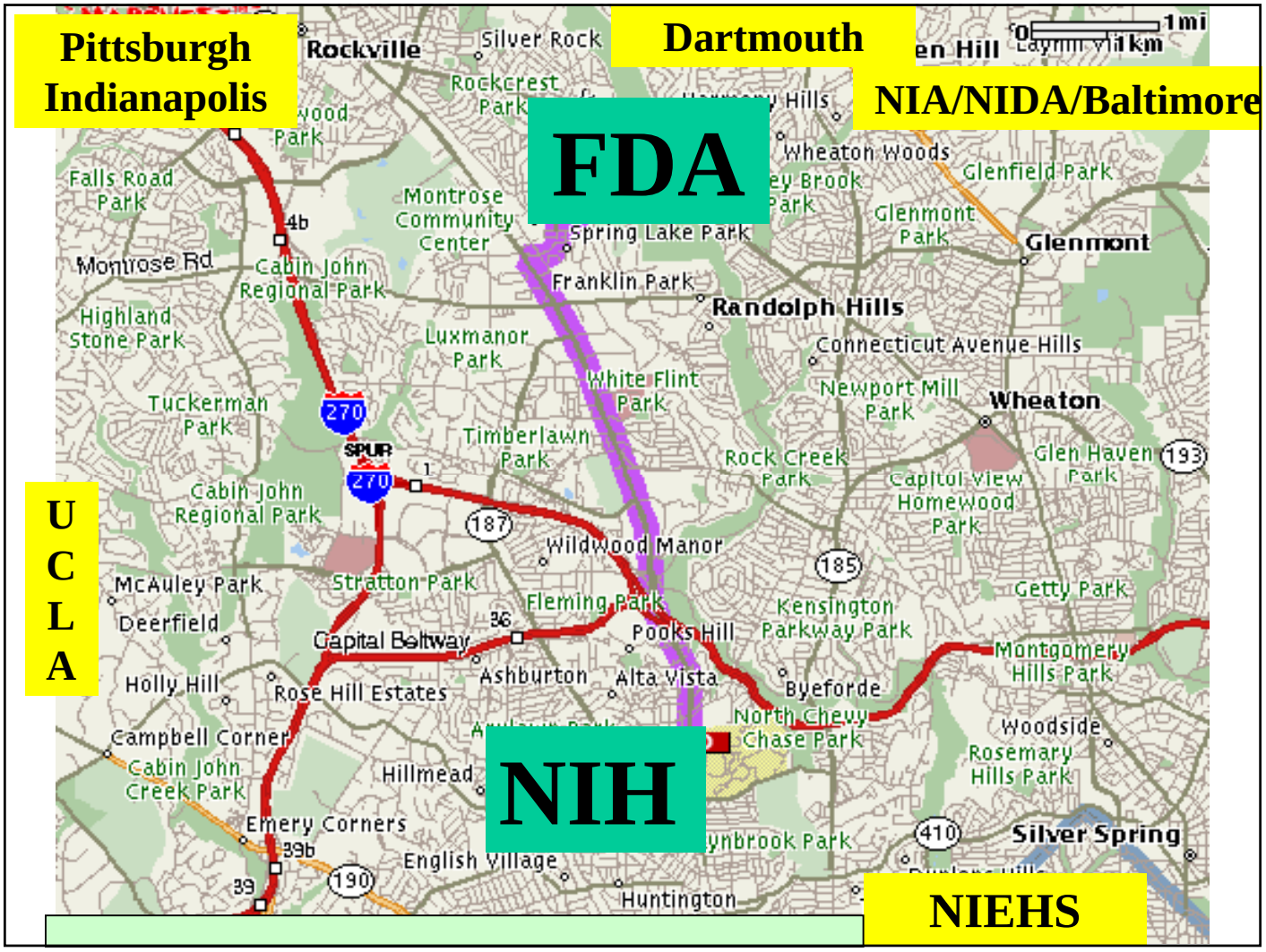
# Identity Crisis?

# What is Inherent in First-In-Human Trials?

# <surprise!>

# Translational Research




Pittsburgh
Indianapolis
Dartmouth
NIA/NIDA/Baltimore
FDA
NIH
NIEHS
UCLA
Rockville
Silver Rock
Rockcrest Park
Wheaton Woods
Glenfield Park
Glenmont Park
Glenmont
Falls Road Park
Montrose Community Center
Spring Lake Park
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
Cabin John Regional Park
Wildwood Manor
McAuley Park
Stratton Park
Fleming Park
Kensington Parkway Park
Getty Park
Deerfield
Capital Beltway
Pooks Hill
Montgomery Hills Park
Holly Hill
Rose Hill Estates
Ashburton
Alta Vista
Byeforde
North Chevy Chase Park
Woodside
Rosemary Hills Park
Campbell Corner
Cabin John Creek Park
Hillmead
Emery Corners
English Village
Silver Spring
Huntington
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SPUR
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190
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1km