

# 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 2, 2009

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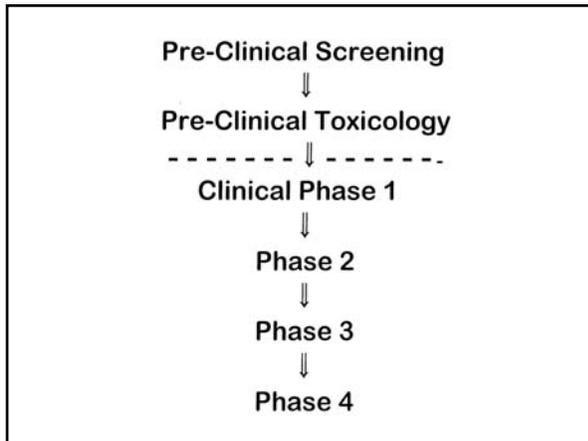
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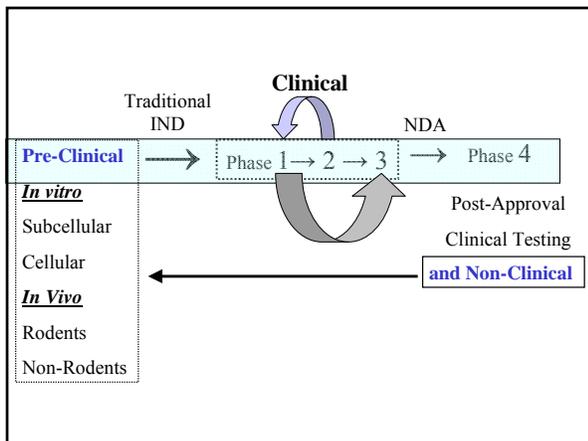
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### Re-Engineering Phase I (FIH) Trials

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

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### Design of Phase 1 (FIH) Trial

- Starting Dose
- Escalation Scheme

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

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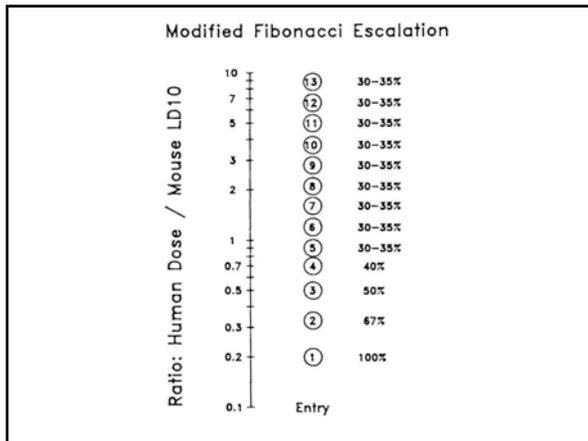
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**BIBLIOGRAPHY / COLLINS / PHASE 1**

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*

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**PK-PD Hypothesis:**

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

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

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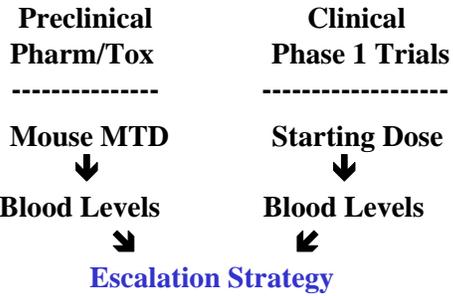
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## Bridges Between Preclinical and Clinical Development



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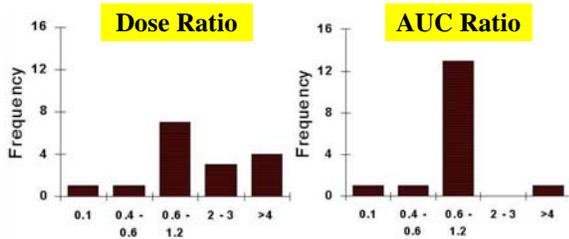
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## Acute Toxicity of Anticancer Drugs Human versus Mouse



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### Conclusion:

Hypothesis has merit.

### Follow-Up:

What is underlying reason for interspecies differences?

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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

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

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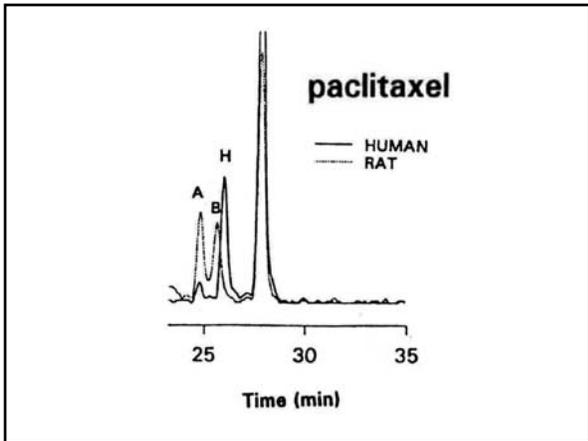
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***In Addition to Explaining  
Interspecies Differences,  
Other Applications for  
Metabolism Studies in Phase 1:***

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

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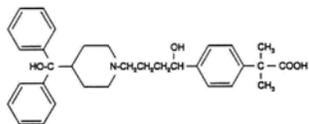
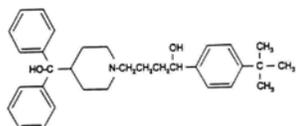
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**terfenadine/SELDANE®**



**fexofenadine/ALLEGRA®**

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**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?**

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**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**

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**"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**

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**Chronology of First-in-Human Study Designs**

<u>Era</u>	<u>Primary</u>	<u>Secondary</u>	<u>Correlative</u>
1960s	Toxicity	Activity	(None)
1980s	Toxicity	Activity	PK
1980s	Toxicity PK-guided	Activity	
1990s	Toxicity	Activity	PK-PD/Biomarkers
2000s Phase Zero	PD	PK	<del>Toxicity, Activity</del> (not expected)

Role Reversal as Discovery Continues

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**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!)

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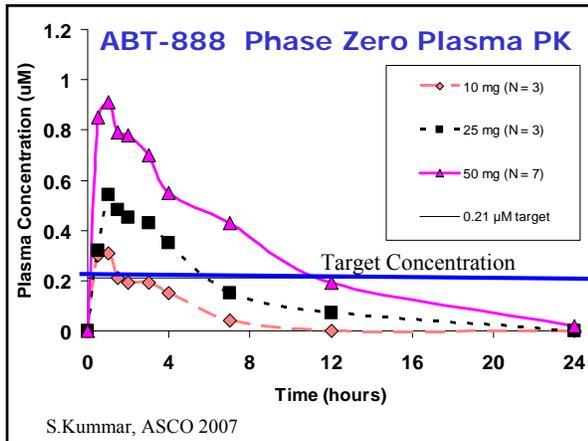
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**First NCI Phase Zero Project**  
PARP enzyme inhibitor

**Goals**

Can Target Plasma Concentration Be Achieved Orally?

**Outcomes**

**YES**

Can Tumor Biopsy Provide Definitive Results?

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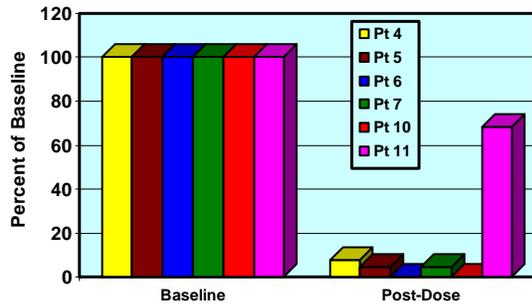
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PAR Inhibition in Tumor Biopsies 3-6 Hours Post Dose



S.Kummar, T.A.T. 2008

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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

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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

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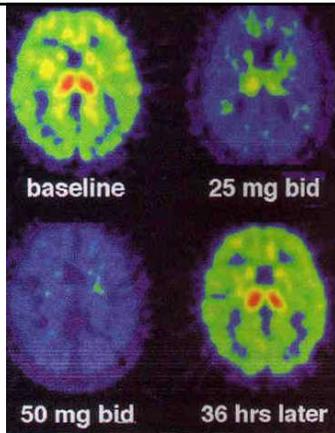
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**MAO-B  
Inhibition by  
Lazabamide**

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



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## **First-In-Human Trials Identity Crisis?**

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

**<surprise!>**

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