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

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Pre-Clinical Screening

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Pre-Clinical Toxicology

⇓

Clinical Phase 1

⇓

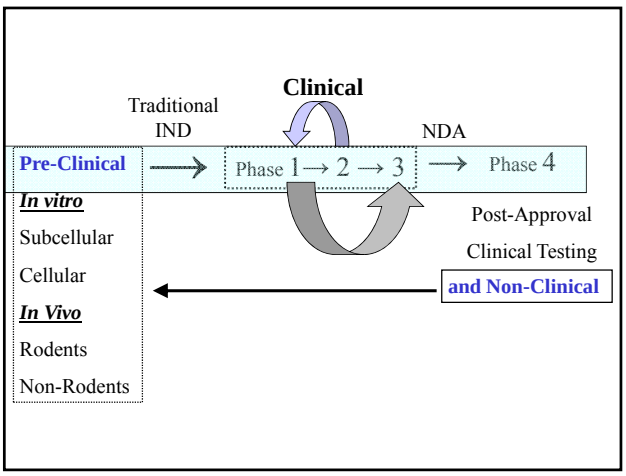
Phase 2

⇓

Phase 3

⇓

Phase 4



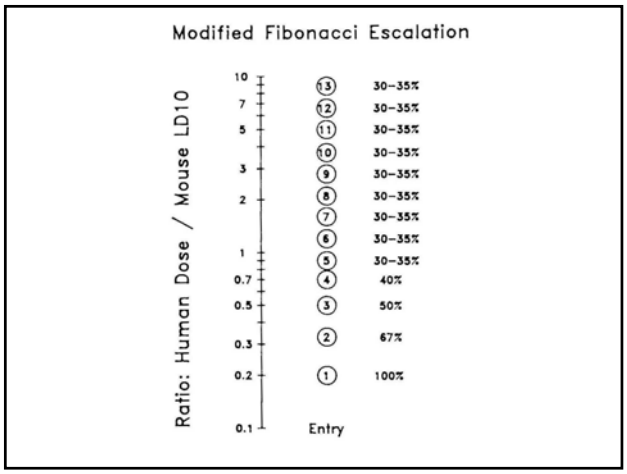
Re-Engineering Phase I (FIH) Trials

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



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

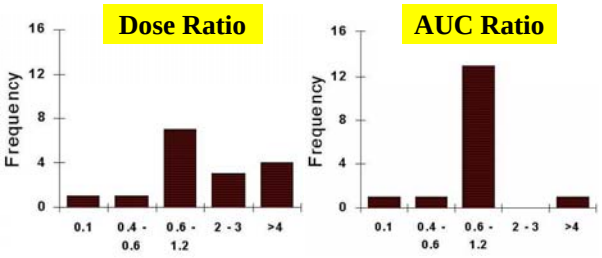
Concentration of Drug as a Biomarker or Endpoint

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>

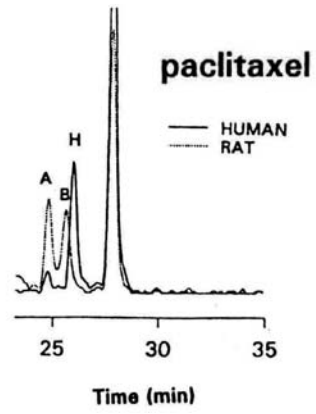
Additional Effects on Drug Metabolism

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

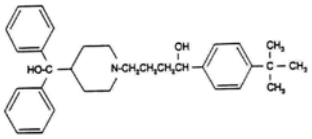
Metabolism as the Principal Confounding Factor for First-in-Human Trials

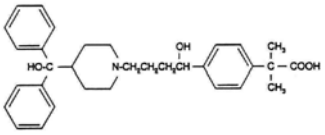


In Addition to Explaining Interspecies Differences, Other Applications for Metabolism Studies in Phase 1:

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

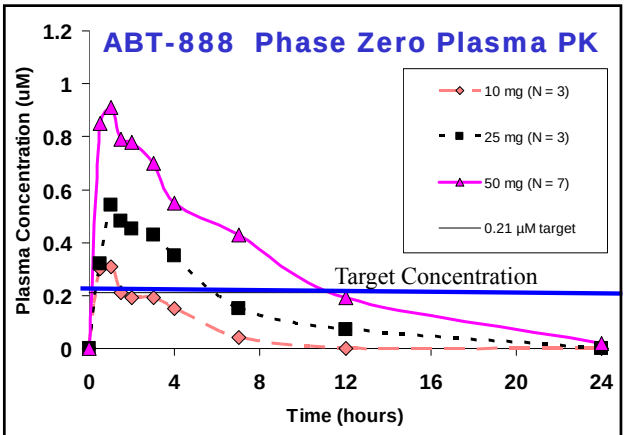
Key question can be as simple as whether drug candidate is absorbed from GI tract

⇒ Readily Answered

Key Question for Phase Zero PARP Project:

Can DNA Repair Enzyme Be Inhibited?

(Need Tumor Sample and Suitable Assay!)



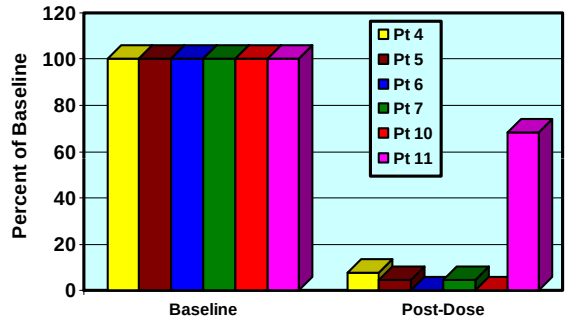
S.Kummar, ASCO 2007

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

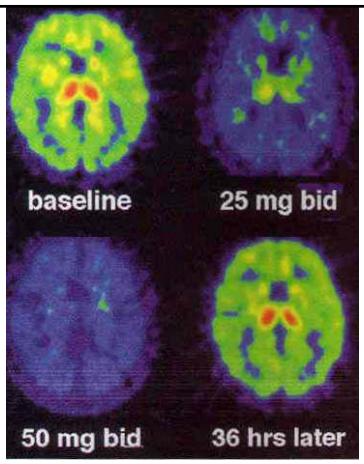
Functional Imaging via PET: Biomarkers for Treatment Evaluation

- **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