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

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Pre-Clinical Screening

Pre-Clinical Toxicology

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Clinical Phase 1

↓

Phase 2

↓

Phase 3

↓

Phase 4

Flow Chart

Traditional **Clinical**

IND NDA

Pre-Clinical → **Phase 1 →2→3→** **Phase 4**

In vitro Post-Approval

Subcellular Clinical testing

Cellular ← and Non-Clinical

In Vivo

Rodents

Non-Rodents

Copy of the homepage of the website //nihroadmap.nih.gov

Title at top of website reads as follows: NIH Roadmap. Accelerating medical discovery to improve health

The following is highlighted on this page: Re-engineering the Clinical Research Enterprise

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

Ratio: Human Dose/Mouse LD10

First dose (entry) in human is 1/10 of mouse LD10. The second dose is 2/10 of mouse LD10. Dose escalation then proceeds cautiously at smaller increments (67%, 50%, 40%, 30%).

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

Two bar charts. The first shows dose ratio from 0.1 to >4 by frequency. The second bar chart shows AUC ratio from 0.1 to >4 by frequency.

Most cases are grouped in the 0.6 – 1.2 range for dose ratio.

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

Chromatography tracing for metabolites in rats and humans.

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®

Chemical structure for terfenadine/Seldane®

Chemical structure for fexofenadine/ALLERGRA®

Target-Guided Dose Escalation

Preclinical Pharm/Tox **Clinical Phase 1 Trials**
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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	**PD**	**PK**	~~**Toxicity, Activity**~~
Phase Zero			**(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!)

ABT-888 Phase Zero Plasma PK

Plot showing plasma concentration (uM) of 10mg (N=3), 25 mg (N=3), 50 mg (N= 7), and 0.21 μM target (horizontal line on graph) over time (hours).

The 10 mg dose resulted in plasma concentrations above target for almost 12 hours.

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

Bar chart that shows percent of baseline over baseline and post-dose in tumor biopsies 3-6 hours post dose. Post-dose shows percent of baseline at greatly reduced levels for Pt 4, Pt 5, Pt 6, Pt 7, and Pt 10. Pt 11 shows a lower percent of baseline but not a greatly reduced level as with the others.

S.Kummar, T.A.T. 2008

First NCI Phase Zero Project
PARP enzyme inhibitor

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

Four brain scans are shown. One is at baseline, the second is at 25 mg bid, the third is 50 mg bid, and the fourth is 36 hrs later. The brain scan at 25 mg bid shows partial MAO-B inhibition whereas the brain scan at 50 mg bid shows almost complete inhibition. The brain scan at 36 hrs later looks much like the baseline scan showing that Lazabamide has passed out of the system.

First-In-Human Trials Identity Crisis?

What is Inherent in First-In-Human Trials?

<surprise!>

Translational Research

Graphic illustration of a man on the left side of the page with a light bulb over his head showing that he has an idea. There is an arrow from the man to the graphic illustration on the right side of the paper of a young girl in a hospital bed with a physician attending to her. There is another arrow from the drawing on the right to the drawing on the left completing the circular motion of this drawing.

A map of the Bethesda/Rockville area and surrounding area showing where NIH and the FDA are located. Also, around the edges of the map are the names of some of the remote sites for the "Principles of Clinical Pharmacology" course in the direction where they are located.