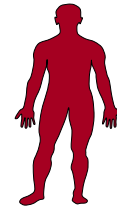
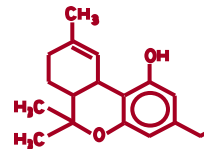
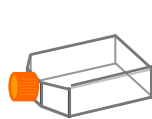
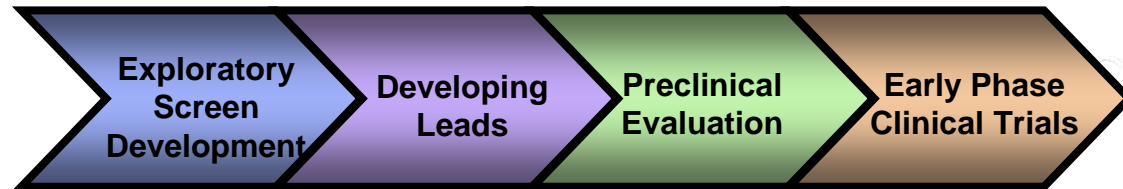


Early Phase Cancer Clinical Trial Design: Changing the Model

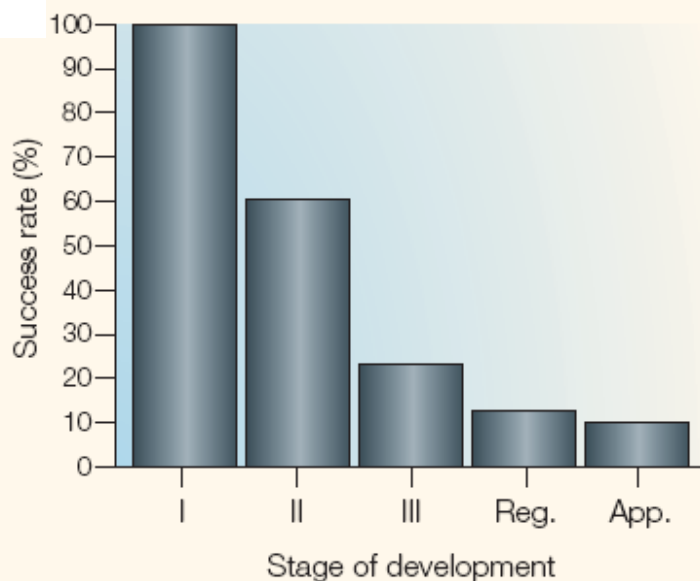
James H. Doroshow, M.D.

Division of Cancer Treatment and Diagnosis
National Cancer Institute



Most Drugs Fail in Late Stages of Development- Particularly in Oncology

Rates of success for compounds entering first
in man that progress to subsequent phase



- 70% of oncology drugs that enter Phase 2 fail to enter Phase 3

- 59% of oncology drugs that enter Phase 3 fail

- Late stage failure leads to enormous risk

Kola & Landis; Nature Reviews Drug Discovery 2004



Technology and PK: Practical Matters (Or Time Marches On In Merrill Egorin's Lab)

10-500 μ M 1960-70



1-10 μ M 1975



0.2-1 μ M 1980-95



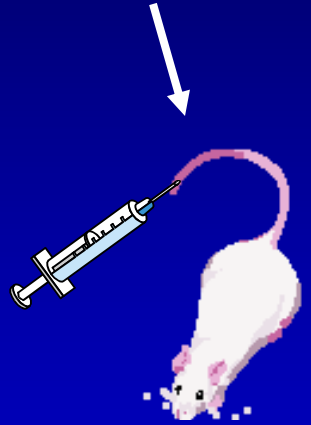
pM-nM 2000



**CHANGE
MODELS**



Stages of Therapeutics Development: Current



N=30

Phase I

N=300

Phase II

N=3000

Phase III

FDA

FDA's Exploratory IND

**Guidance for Industry,
Investigators, and Reviewers**

Exploratory IND Studies

CAM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2006
Pharmacology/Toxicology

Toxicology evaluation is more limited than for traditional IND application because of reduced dosing and limited exposure in Exploratory IND study; Phase 0 (pre-Phase 1) trials can begin earlier than traditional Phase 1 studies



What Are the Characteristics of a Phase 0 Trial Performed Under an xIND?

First-In-Human, single agent or combination:

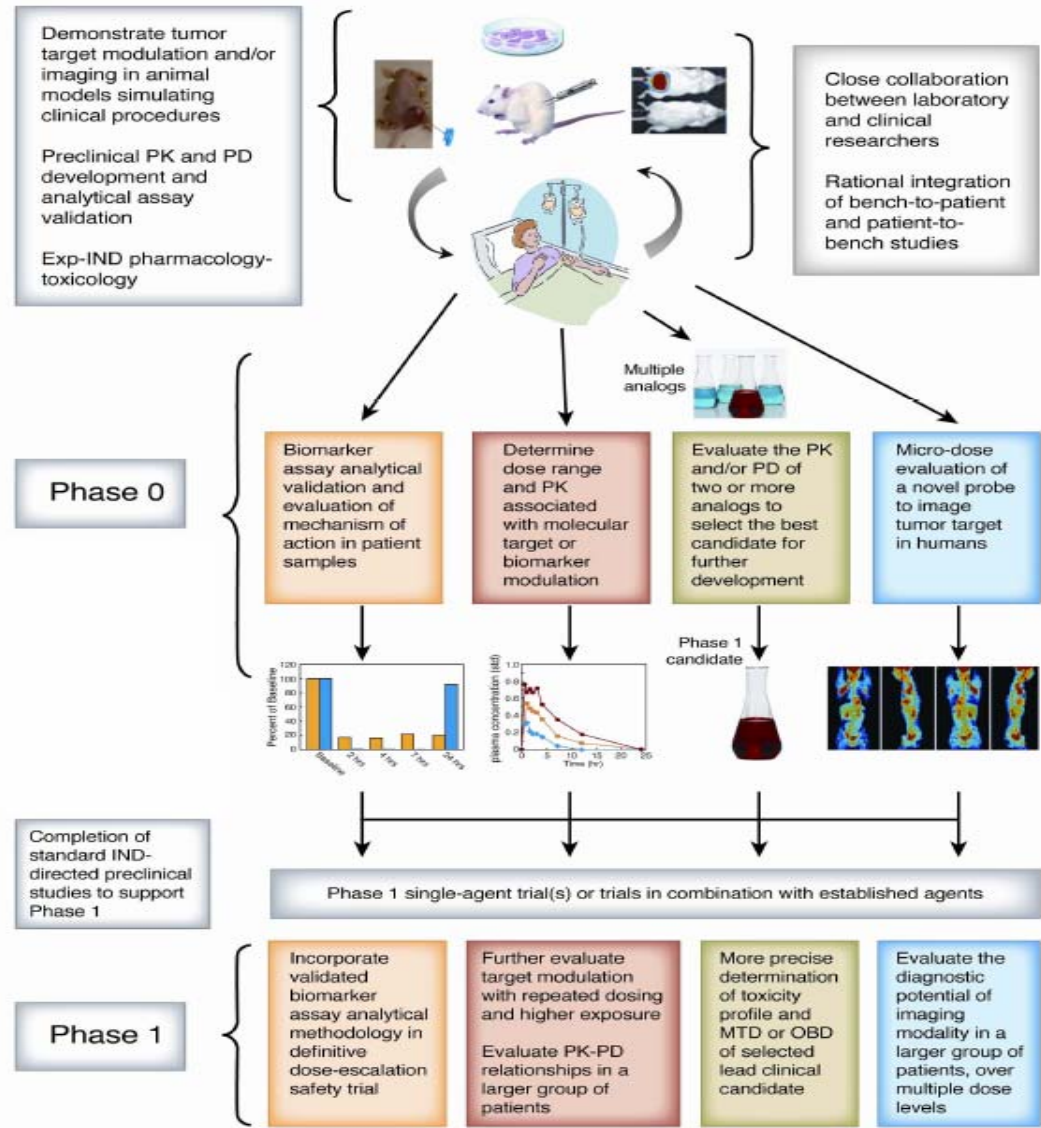
- Limited number of subjects ($\approx 10-12$)
- Very limited drug exposure (≤ 7 days; non-toxic dose; 1 cycle)
- No therapeutic (or diagnostic) intent
- Conducted prior to traditional Phase 1 dose escalation, safety, and tolerance studies that initiate a development program
- Can be initiated with a less extensive pre-clinical data package than traditional Phase 1 trials
- Provide PK/PD data to support rapid future dose escalation and inform subsequent Phase 1 and 2 trials
- Initial target assay development; drug/target assessments in primary and surrogate tissue for imaging and expression

OVERALL GOAL IS TARGET DEVELOPMENT:

Provide initial rationale and guiding principles for further agent development based on studies in humans (rather than xenografts)



Target Development Early Phase Trials



CAM

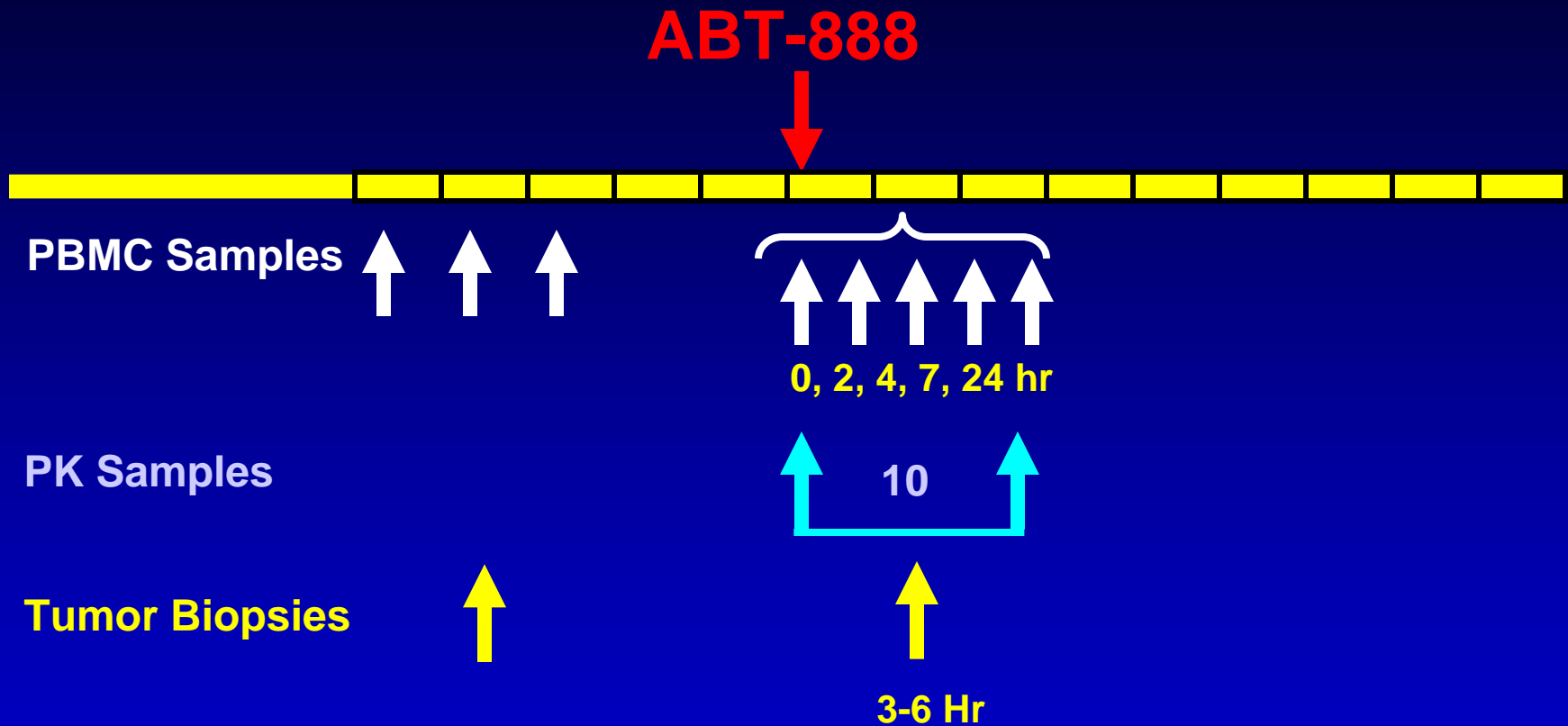


How Can Phase 0 Trials Improve Efficiency and Success of Subsequent Trials?

- Eliminating an agent very early in clinical development because of poor PD or PK properties
 - E.g., lack of target effect, poor bioavail., rapid clearance
 - “Fail Fast, Fail Early”
- By informing subsequent trials
 - Validating a PD assay for assessing target modulation
 - Developing a reliable SOP for tissue acquisition, handling, processing
 - Determining dose and time course that yields a required target effect
 - Intensively evaluating PK, providing a closer approximation to a safe, but potentially effective starting dose and support for limited sampling in subsequent trials
 - Eliminate full single agent Phase I prior to Phase I combination studies

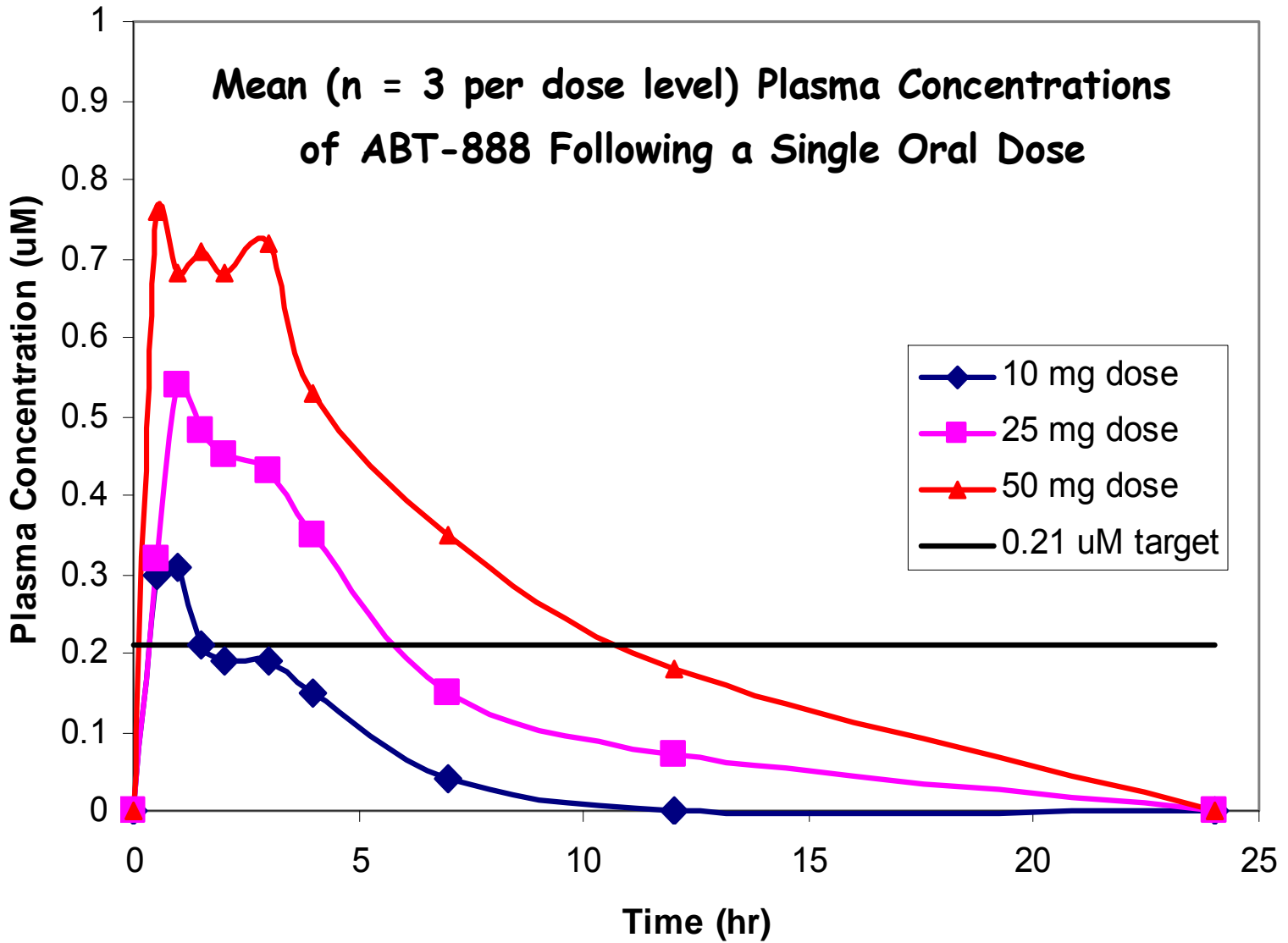


First Oncology Phase 0 Trial NCI Study Schema

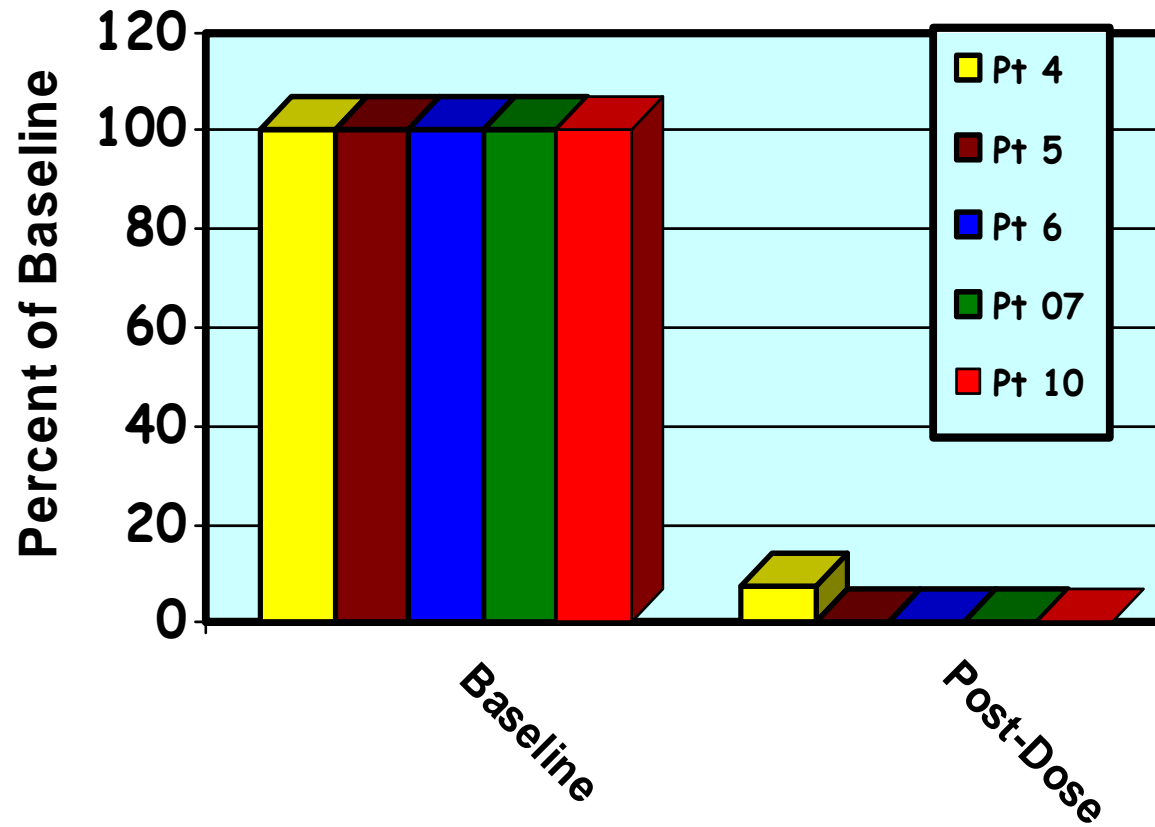


Tumor biopsies planned:

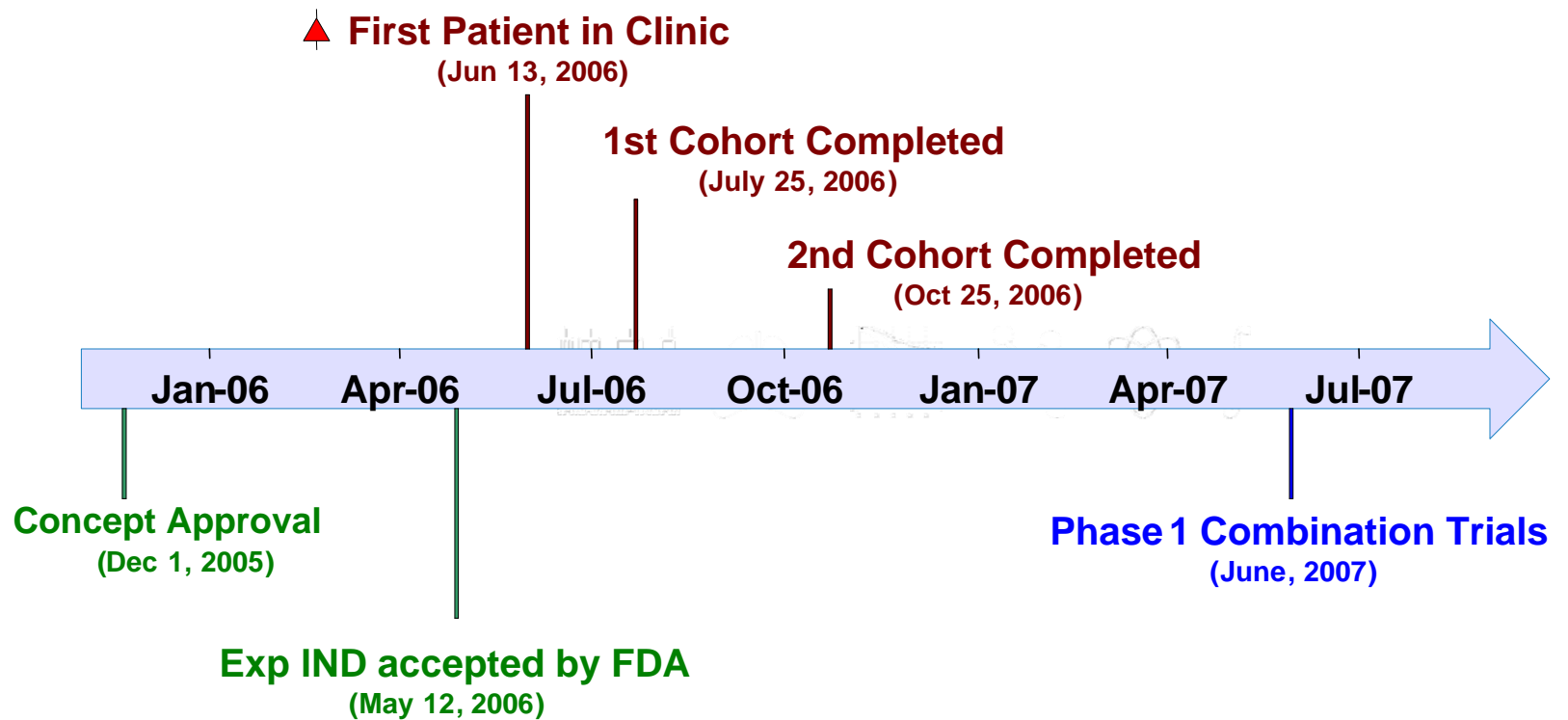
- Significant PARP inhibition in PBMCs from at least 1 of the 3 participants at a given dose level, OR
- Plasma C_{Max} of 210 nM was achieved in at least 1 participant



PAR Inhibition in Tumor Biopsies

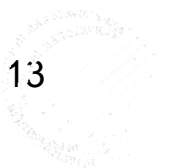


First Phase 0 Trial - Timeline



Phase II Trials:

Focus on Predictive Power and Target Assessment



Characteristics of Current Phase II Oncologic Drug Trials

- **Estimate clinical activity of a new drug in a defined patient population, usually disease specific**
- **Characterize the safety and toxicity of a specific dose and schedule**
- **Identify late-onset or cumulative toxicity**
- **Early stopping rules avoid exposing pts to inactive drugs**
- **“Objective response” most frequent endpoint:**
 - **CR, PR, PD most frequently determined with radiographic techniques**
 - **Demonstrates “antitumor activity”**
 - **Not always useful for assessing “patient benefit”, survival, quality of life improvement, or for agents that slow rate of growth but do not cause size regression**
- **Time to progression: May capture biological effects better than response rate**



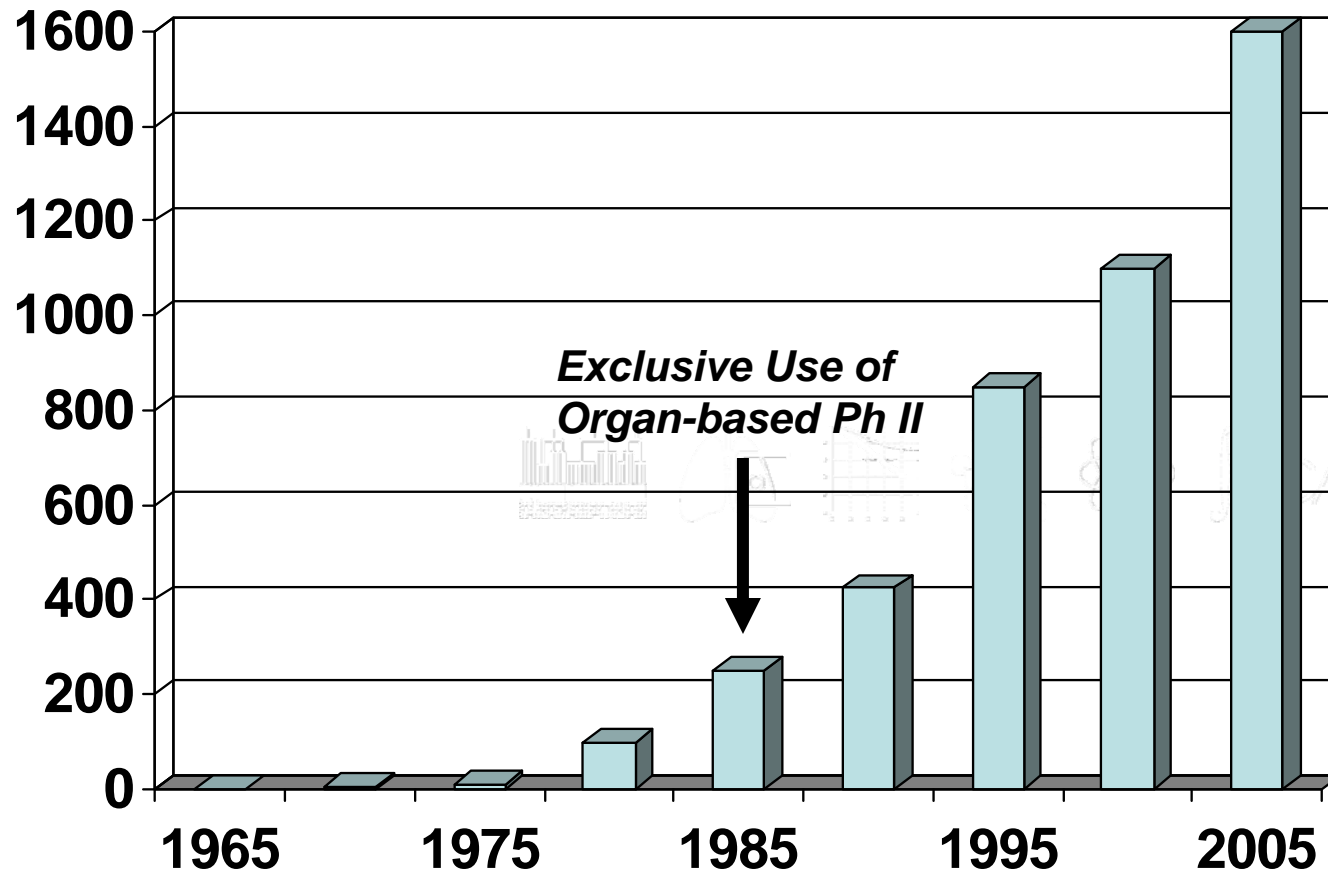
Current Phase II Trial Design Issues

- **Classically:** performed just after “standard” therapy
 - Now: broad range of effective 2nd and 3rd line therapies
 - Are patients who have been exposed to more prior Rx less likely to respond, and thus harder to assess?
 - Role of improving sensitivity of imaging modalities
- **Usually single agents:** better to define efficacy, although unlikely to see objective tumor shrinkage; however, real question is integration into multimodality programs
- **Current practice of developing a broad range of organ-site- or histology-based trials—began ~1980**
 - Very expensive in time and resources
 - Major regulatory and administrative burden
 - Does not necessarily reflect current cancer biology
 - Not based on effective pre-clinical model systems
 - Does not incorporate effects of agents on targets





Published Phase II Cancer Treatment Trials: Missing the Forrest for the Trees



Improving Predictive Power in Phase II

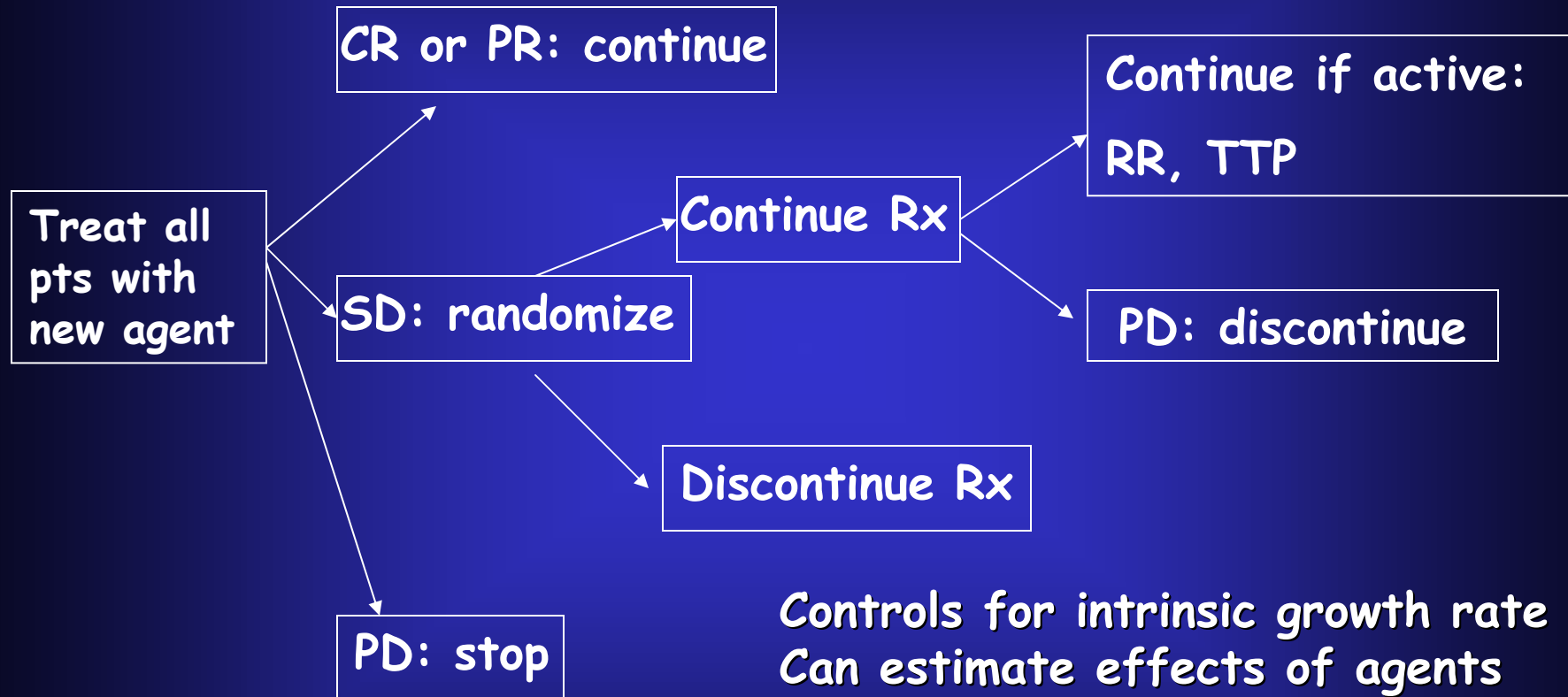
- Large, continuously updated historical control databases
- Randomized Phase II trials—need for concurrent controls
- Randomized discontinuation trials
- Adaptive designs
- “Window of Opportunity”
- “Broad Phase II” multiple diseases

GET TISSUE TO ASSESS THE TARGET



Current Phase II Trial Designs

Randomized Discontinuation Study



Controls for intrinsic growth rate
Can estimate effects of agents
that slow growth and do not cause
regression
But: large sample size; how long to
give before randomize

Phase II Trials: Time for a Change Or, Back to the Future

***A single SWOG phase II trial conducted within
two years of the drug's first-in-human study . . .***

- **Accrued over 400 patients and was submitted for publication 24 months after initiation!**
- **Defined activity in multiple diseases:**
 - ✓ Breast cancer
 - ✓ Lymphoma
 - ✓ Sarcoma
 - ✓ SCLC
 - ✓ Prostate
 - ✓ Bladder
 - ✓ Endometrium
- **Defined appropriate schedule—from three**
- **Defined critical toxicities**



“Broad” Phase II Trial of Doxorubicin

PHASE II EVALUATION OF ADRIAMYCIN IN HUMAN NEOPLASIA

ROBERT M. O'BRYAN, MD,* JAMES K. LUCE, MD,† ROBERT W. TALLEY, MD,‡
JEFFREY A. GOTTLIEB, MD,§ LAURENCE H. BAKER, DO,¶
AND GIANNI BONADONNA, MD**

Four hundred and seventy-two patients with disseminated neoplasia were treated with two or more doses of adriamycin. The initial dose for “good risk” patients was 75 mg/m² every 3 weeks, and for “poor risk” patients was 60 mg/m² every 3 weeks. Objective remissions were seen in 118/472 patients, with best results noted in lymphomas (21/48), sarcomas (21/64), and carcinoma of the breast (16/50). Eighty-nine per cent of remissions occurred within three courses. Hematopoietic toxic effects were seen in 73% of patients; nausea, vomiting, and/or stomatitis were observed in 43%. Changes in electrocardiograms were seen in 42/472 patients after cumulative doses of adriamycin ranging from 45 mg/m² to 600+mg/m². Irreversible congestive heart failure occurred in two patients after cumulative doses of 555 mg/m² and 825 mg/m², respectively. It is concluded that adriamycin is an active agent, most remissions occur promptly, and significant cardio-toxic reactions appear to be cumulative.

Cancer 32: 1-8, 1973



Molecular Target Assessment in Phase II Trials

Goals:

- Improve eligibility for subsequent trials: enrich pt selection for target of interest
- Measure biological effect of new agent
- Predict clinical response or futility
- Enhance trial efficiency

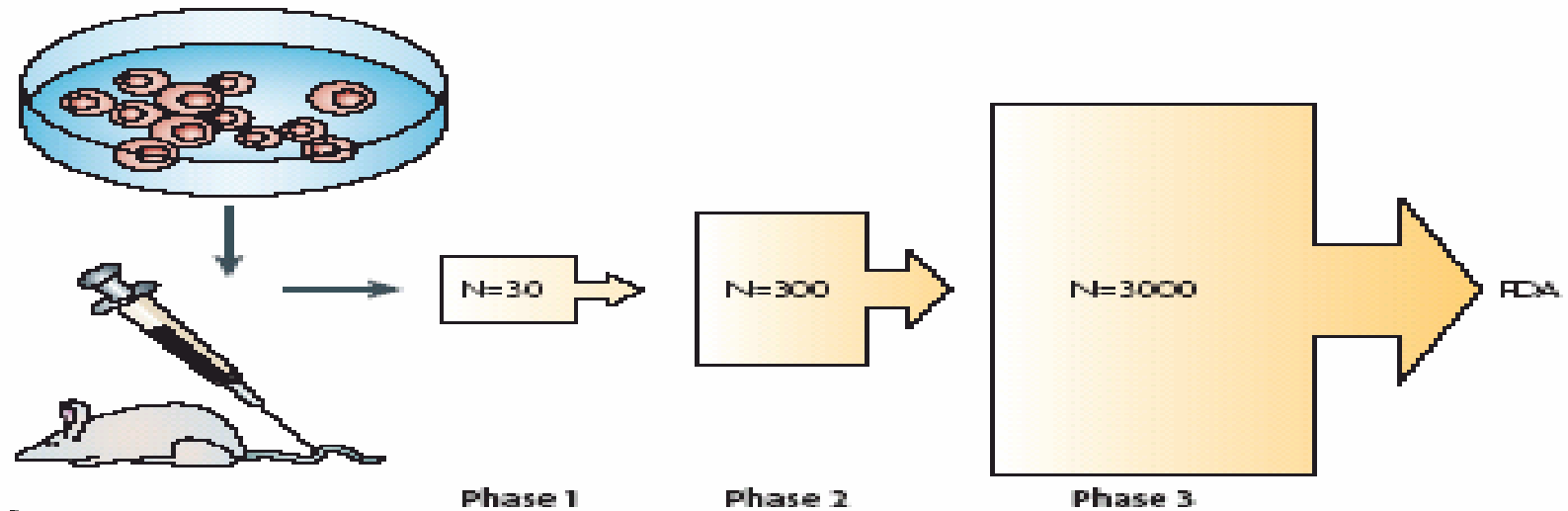
Challenges:

- Tissue acquisition: timing, risk
- Compliance and pt participation
- Biological effect \neq clinical effect
- Unknown or “off-target” effects

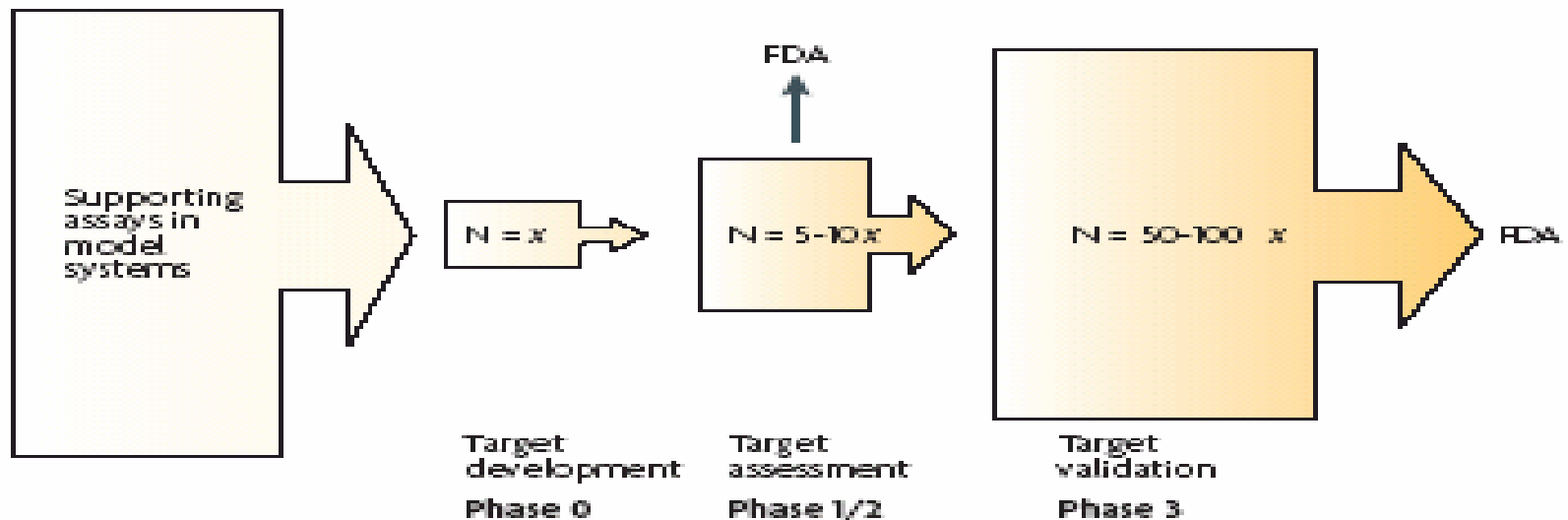


Models of Cancer Drug Development: Present and Future

a



b



NCI Early Phase Therapeutics Team

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