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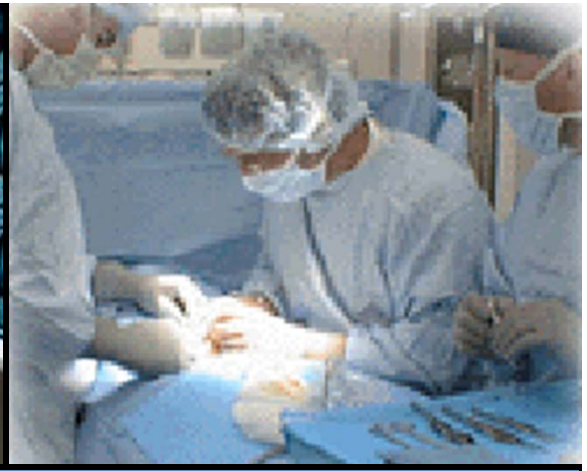


NCI's Roadmap to Personalized Cancer Treatment

James H. Doroshow, M.D.
Director, Division of Cancer Treatment and Diagnosis

National Cancer Advisory Board

Bethesda, MD

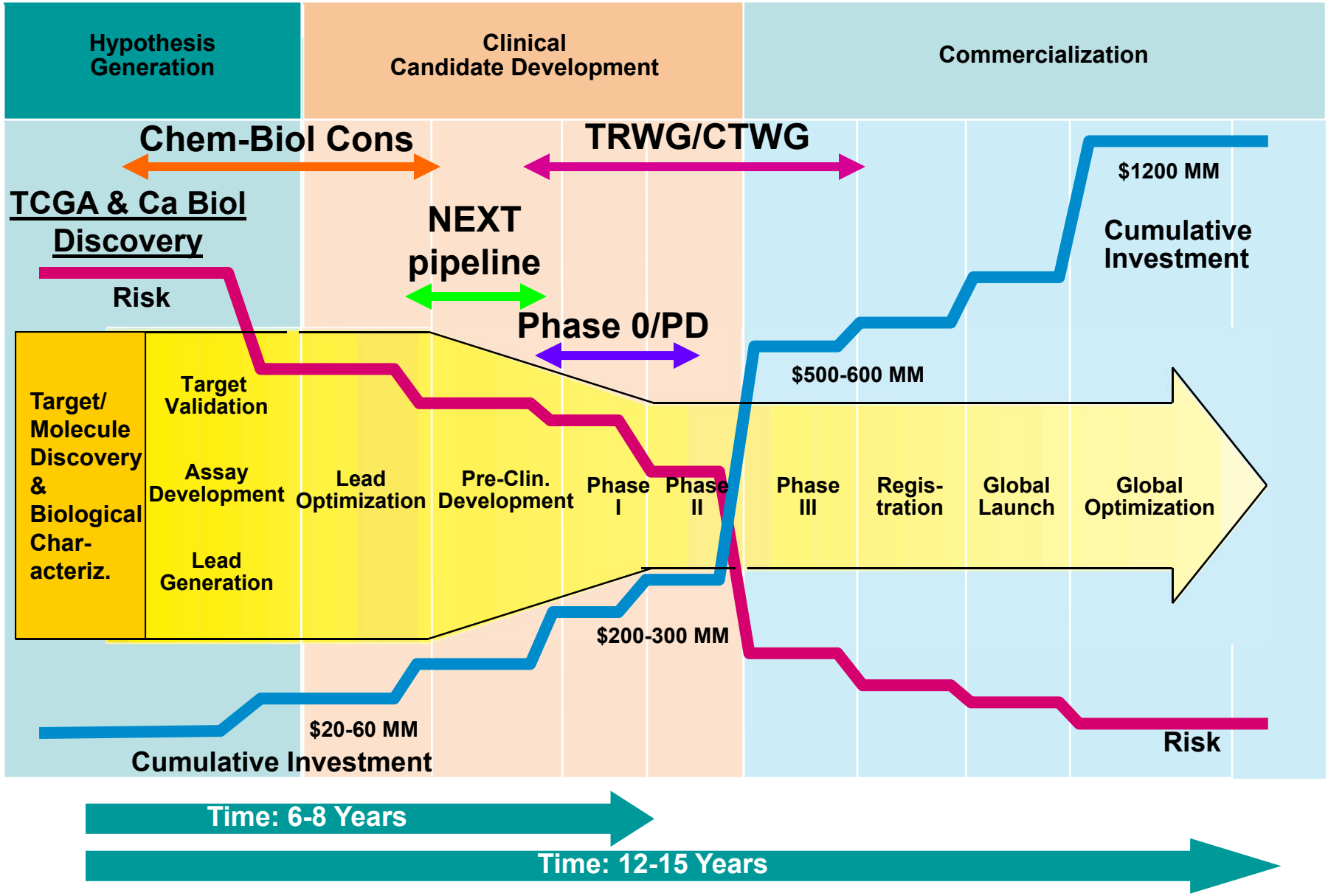
June 11, 2009

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Top Biotech Patent Applicants 2002-06 (Marks & Clerk Esqs.)

Rank	Assignee	Number of Patents
1	Japan Sci and Tech Agency	1022
2	Univ. of California	543
3	Genentech*	421
4	United States Gov. (NIH)	334
5	Univ. of Texas	277
6	Millenium Pharmaceuticals*	272
7	Mass. General Hospital	201
8	Applera*	195
9	Novozymes*	162
10	Zymogenetics*	161
11	Johns Hopkins	154
12	Stanford	148
13	Human Genome Science*	141
14	Columbia	137
15	Univ. of Pennsylvania	133

Therapeutics Development Timeline



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Critical Requirements for the Development of Personalized Cancer Treatment: Phase I-III Transition

- Timely prioritization & dedicated resources for essential biomarker validation studies, utilizing standardized laboratory practices
- Accelerate prioritized translational research initiatives in the area of personalized therapy
- Support for the coordination of hypothesis-driven biomarker studies across the entire clinical/translational science continuum

Focus: Improve the specificity of treatment while reducing the high rate of failure (and cost) during the Phase I to III transition

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Contributions of CTWG/TRWG Implementation to Personalized Therapeutics

- Biomarker, Imaging, and QOL Studies Funding Program
- Development of Special Translational Research Acceleration Program (STRAPs)
- Grand Opportunity: Coordination of Clinical/Translational Research Across the NCI

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Biomarker, Imaging and QOL Studies Funding Program (BIQSFP)

- Purpose
  - Ensure that the most important correlative science and quality of life studies can be initiated in a timely manner in association with clinical trials
  - Intent is to fund studies conducted in association with Phase 2/3 trials when cost is too high to be covered by Cooperative Group or other mechanisms
- Prioritization Criteria
  - Correlative science (essential marker and imaging)

    Developed by the Task Force of the Program for the Assessment of Clinical Cancer Tests (PACCT) and approved by CTAC in July 2007
  - Quality of Life and Symptom Management

    Developed by the Symptom Management and Health-Related QOL (SxQOL) Steering Committee and approved by CTAC in November 2007

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Prioritization: Integral and Integrated Studies

1st Integral studies: a test that must be performed in order for the trial to proceed

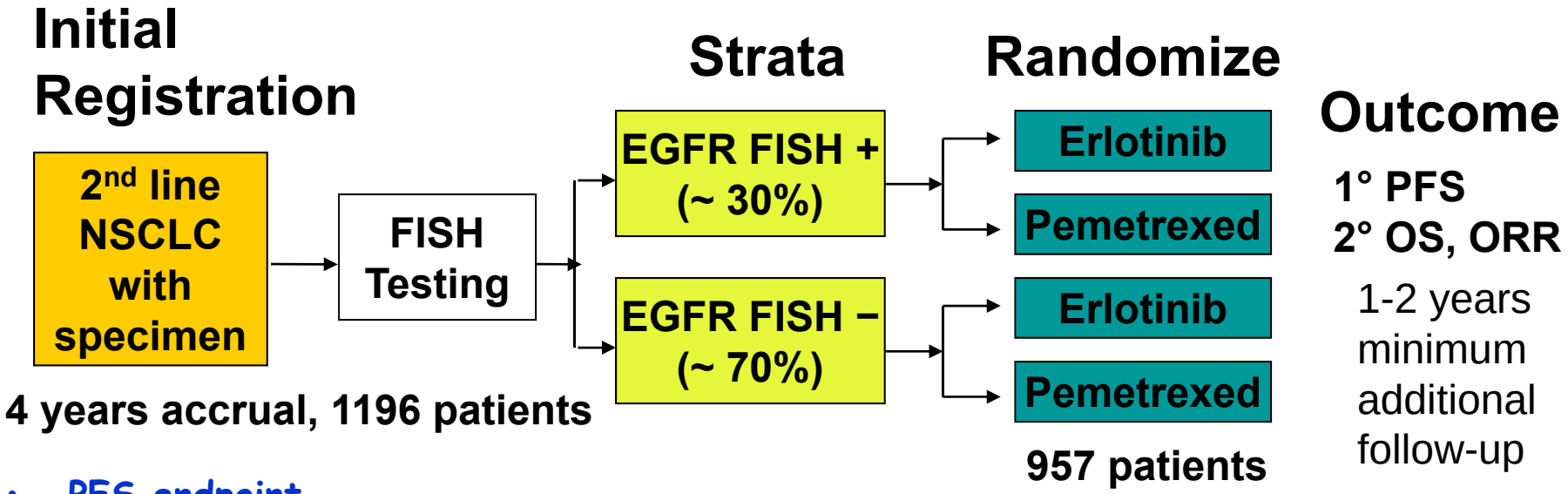
- Test to establish patient eligibility
- Test for patient stratification
- Test to assign patient to treatment arm, including early response endpoints for assignment of treatment during a trial

2nd Integrated studies: studies that are intended to identify or validate markers and imaging tests or QOL instruments that might be used in future trials

- Study plans clearly described in trial protocol
- Tests performed on all cases although results not used to guide decisions in current trial

N0723: Predictive Marker Study Design

NCCTG (Study Chair: Alex Adjei) + CALGB, ECOG, SWOG, NCIC
Others: C-Path & industry partners, Pharma, FDA



- PFS endpoint
  - Less influenced by treatment crossover
  - Will require synchronized treatment schedules, independent blinded imaging review
- Power
  - 90% to detect 50% PFS improvement favoring erlotinib in FISH+, 2.5---3.75m
  - 90% to detect 30% PFS improvement favoring pemetrexed in FISH–, 1.92--2.5m
  - > 90% to detect interaction
- IHC, mutational analysis, PGN evaluation in addition to FISH

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Contributions of CTWG/TRWG Implementation to Personalized Therapeutics

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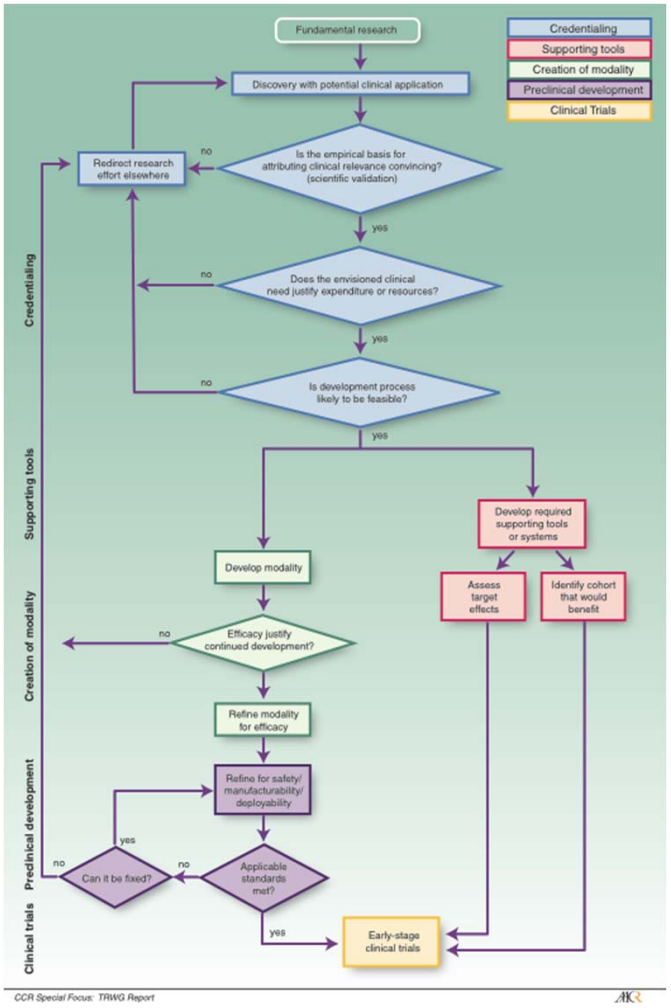
The Challenge of Early Translation



How can we best assure that:

- The most promising concepts enter the developmental pathways?
- Concepts that do enter advance to the clinic or to productive failure?
- Progress is as rapid, efficient and effective as possible?

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Translational Research Acceleration Initiative

Select several projects/year that are "ripe" for translation

- **Translational Research Acceleration Process Will:**
  - Gather information on translational opportunities
  - Prioritize translational research opportunities
  - Develop a funding & project management plan to accelerate prioritized opportunities

- **Translational Research Acceleration Process Will NOT:**
  - Impact Discovery research
  - Replace existing infrastructure or mechanisms for clinical or translational research

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Critical Elements for a Process to Prioritize Translational Research Opportunities

Intra-pathway Prioritization

Pathway-specific criteria determined and weighted; prioritization performed by extramural content experts

Inter-pathway Prioritization

Performed by the Clinical and Translational Research Advisory Committee (CTAC) of the NCI

Executive Decisions

NCI leadership

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Proposed Funding Strategy

Special Translational Research Acceleration Project (STRAP)

- Requirements:
  - Goal of completing early stage human studies
  - Project management plan
  - Specific development milestones and timelines
  - Development/commercialization strategy
- Funds for new and/or expanded projects
- Project management would link new or existing teams and projects and facilitate hand-offs between groups
- Opportunities to include industry/foundation funding or participation

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TRWG Implementation
Next steps & Timeline

RFI for Translational Research Opportunities Pilot
Immune Response Modifier Pathway — Late summer ‘09

↓

Prioritize — Fall ‘09

↓

Fund & Manage — 2010

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Contributions of CTWG/TRWG Implementation to Personalized Therapeutics

- Biomarker, Imaging, and QOL Studies Funding Program
- Development of Special Translational Research Acceleration Program (STRAPs)
- Grand Opportunity: Coordination of Clinical/Translational Research Across the NCI (RFA-OD-09-004)

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Contributions of CTWG/TRWG Implementation to Personalized Therapeutics: Coordination GO Grants

- Facilitate high impact translational research by rewarding collaborative team science
- Studies associated with multi-institutional clinical trials, conducted by consortia of SPORES, Cancer Centers, Cooperative Groups, PO1s, or other partners that, for example:
  - Validate therapeutic biomarkers
  - Correlate immunological signaling pathways with outcome from immunotherapy
  - Perform pharmacogenomic profiles to understand therapeutic efficacy or toxicity
- Due May 27, 2009; supported by ARRA initiative; funding start date: September 30, 2009

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Critical Requirements to "Personalize" Early Phase Trials

- Increase focus on proof-of-mechanism early phase clinical trials
  - Consider the first-in-human study as the culmination of pre-clinical development
  - Demand evidence that personalized therapies affect relevant pathways in tumor tissue (associated with efficacy)
  - Employ surrogate tissues only when there is a clear relationship between effect on the target in surrogate and in tumor
- "Clinical readiness" of pharmacodynamic assays
  - Pharmacodynamic assay development with validated analytical performance
  - Tissue acquisition and handling in the clinical setting
  - Storage transferability
  - Stability of analyte
  - Inter-, intratumoral variability

Novel Approaches to Early Phase Personalized Trials

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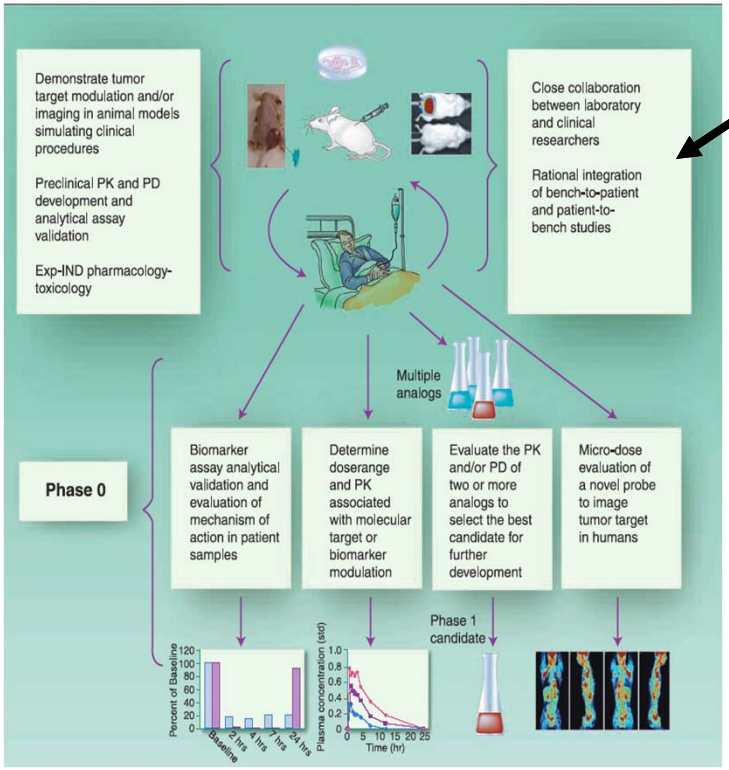
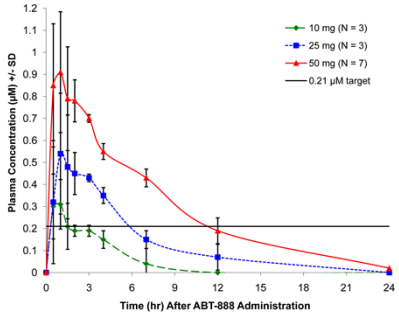
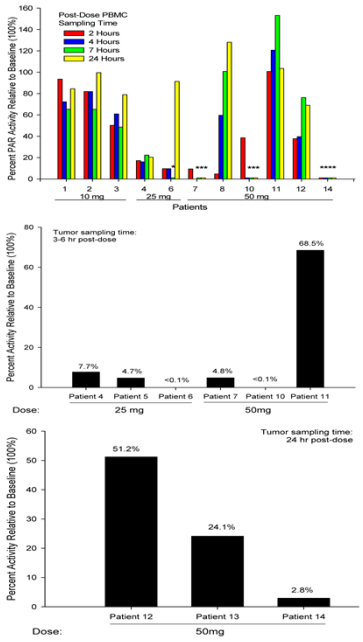
"Clinical" Approach to Mouse Models



Phase 0 Trial of ABT-888





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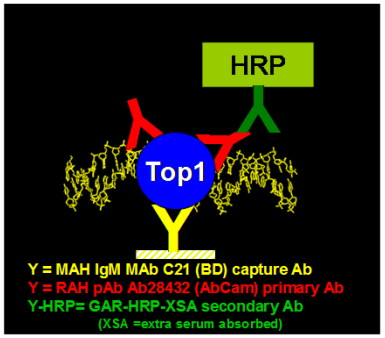
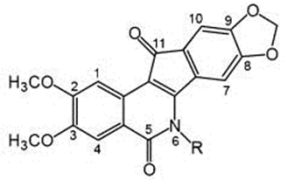
Indenoisoquinoline Proof of Mechanism Randomized Phase I Trial

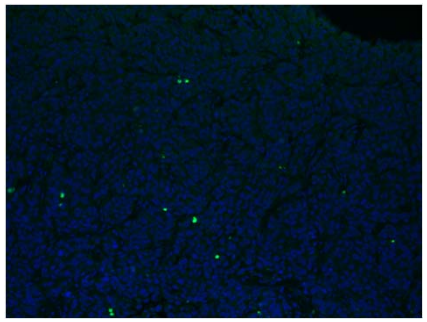




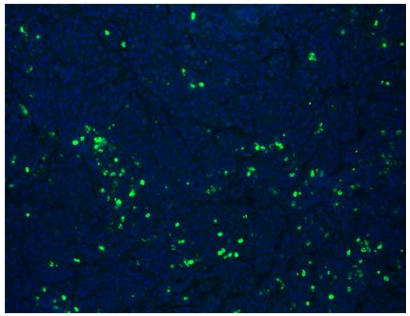
R =

$-CH_3$	NSC 314622
$-(CH_2)_3-NH-(CH_2)_2OH$	NSC 706744 (MJ-III-65)
$-(CH_2)_3-$ 	NSC 725776
$-(CH_2)_3-N$ 	NSC 724998

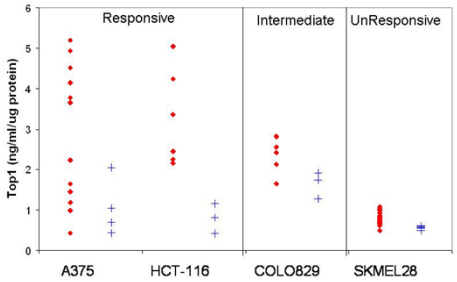
Vehicle



25 mg/kg iv
NSC 724998

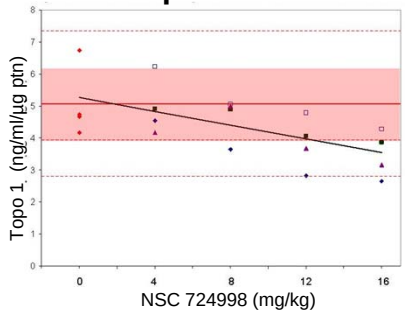


Topoisomerase I Levels in Xenograft Extracts
AAXR2-18, YKR2-39, YPR2-2, AAYR2-17

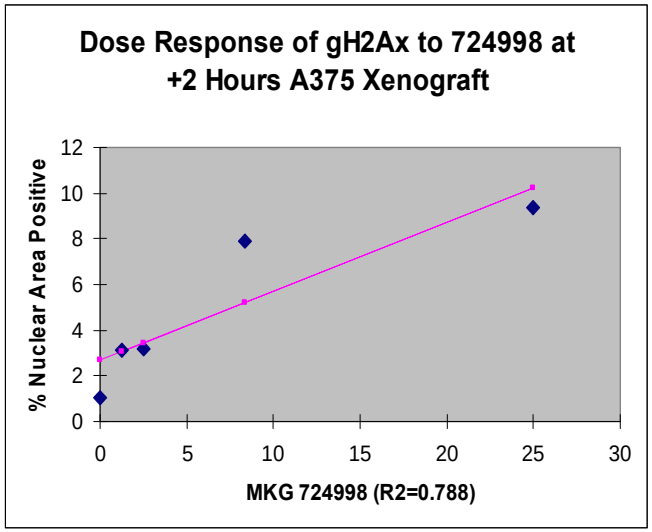


Vehicle Control - ♦
4h Topotecan
(15 MG/KG) treated ✚

Dose Response: Indenoisoquinoline Treated A375 Xenografts



Vehicle Controls
Solid red line = Avg vehicle control Dashed red line = Avg ± 1 and 2 SD
Black line = Dose Response



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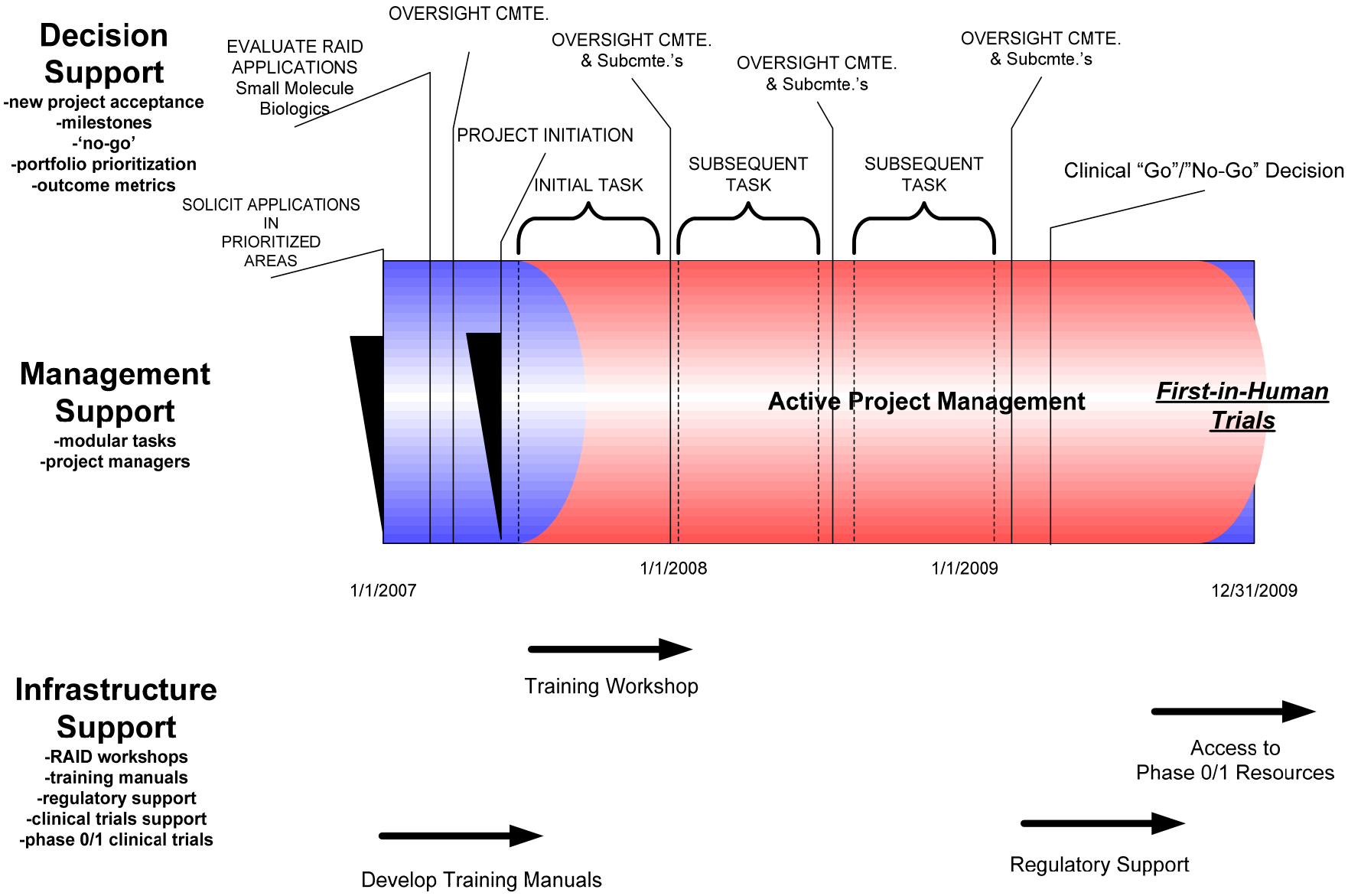
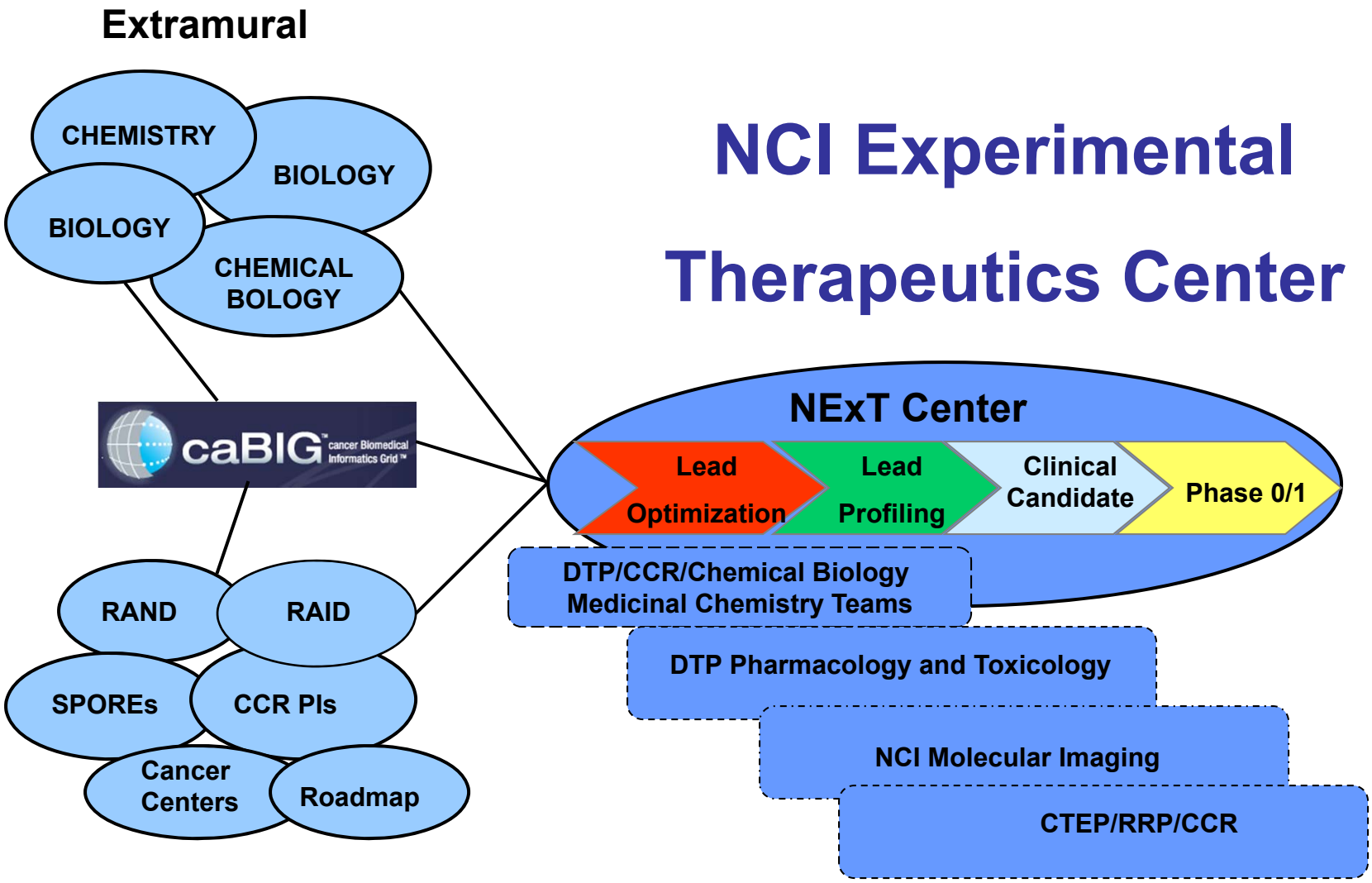
NCI Experimental Therapeutics (NEXT) Pipeline
Critical Issues in the Development of Personalized Therapies

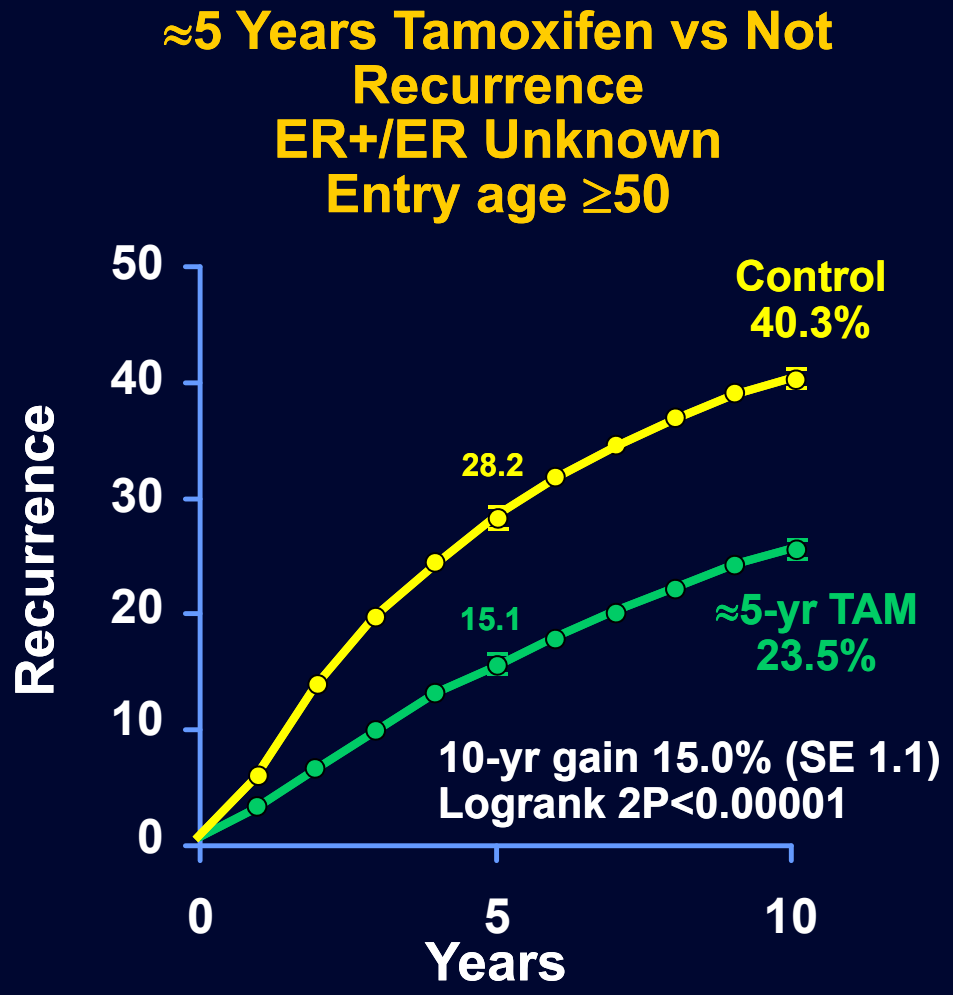
- How best to support academic investigators who wish to move from target or molecule discovery to clinical trials (preclinical testing, toxicology, GMP production, and regulatory support)
- Addressing the “pharmacogenomics divide” (courtesy of Drs. Ames and Goetz, Mayo Clinic)
- Establishing a scientific rationale for combinations of targeted therapies

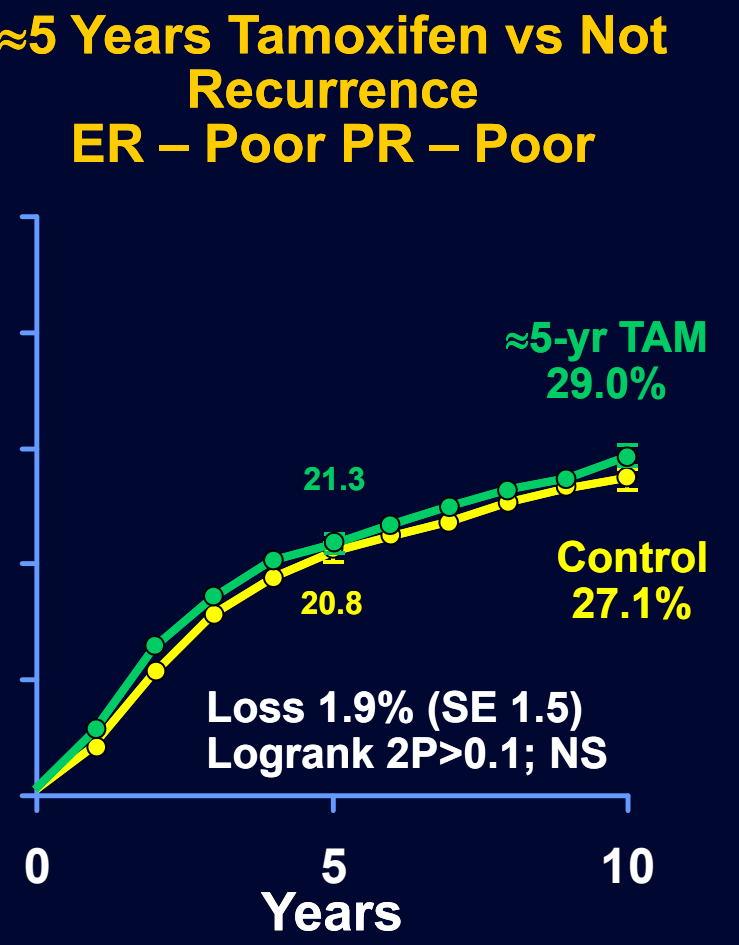
Reorganization of RAID Drug Development




Extramural
CHEMISTRY
BIOLOGY
BIOLOGY
CHEMICAL BOLOGY
caBIG cancer Biomedical Informatics Grid
RAND
RAID
SPOREs
CCR PIs
Cancer Centers
Roadmap
NCI Experimental Therapeutics Center
NExT Center
Lead Optimization
Lead Profiling
Clinical Candidate
Phase 0/1
DTP/CCR/Chemical Biology Medicinal Chemistry Teams
DTP Pharmacology and Toxicology
NCI Molecular Imaging
CTEP/RRP/CCR
Discovery
Development
Clinical Investigation

Oxford Overview: 5 Years of Tamoxifen vs Not
ER Positive vs ER Negative





Classical Understanding of Tamoxifen Pharmacology (1975-2005)

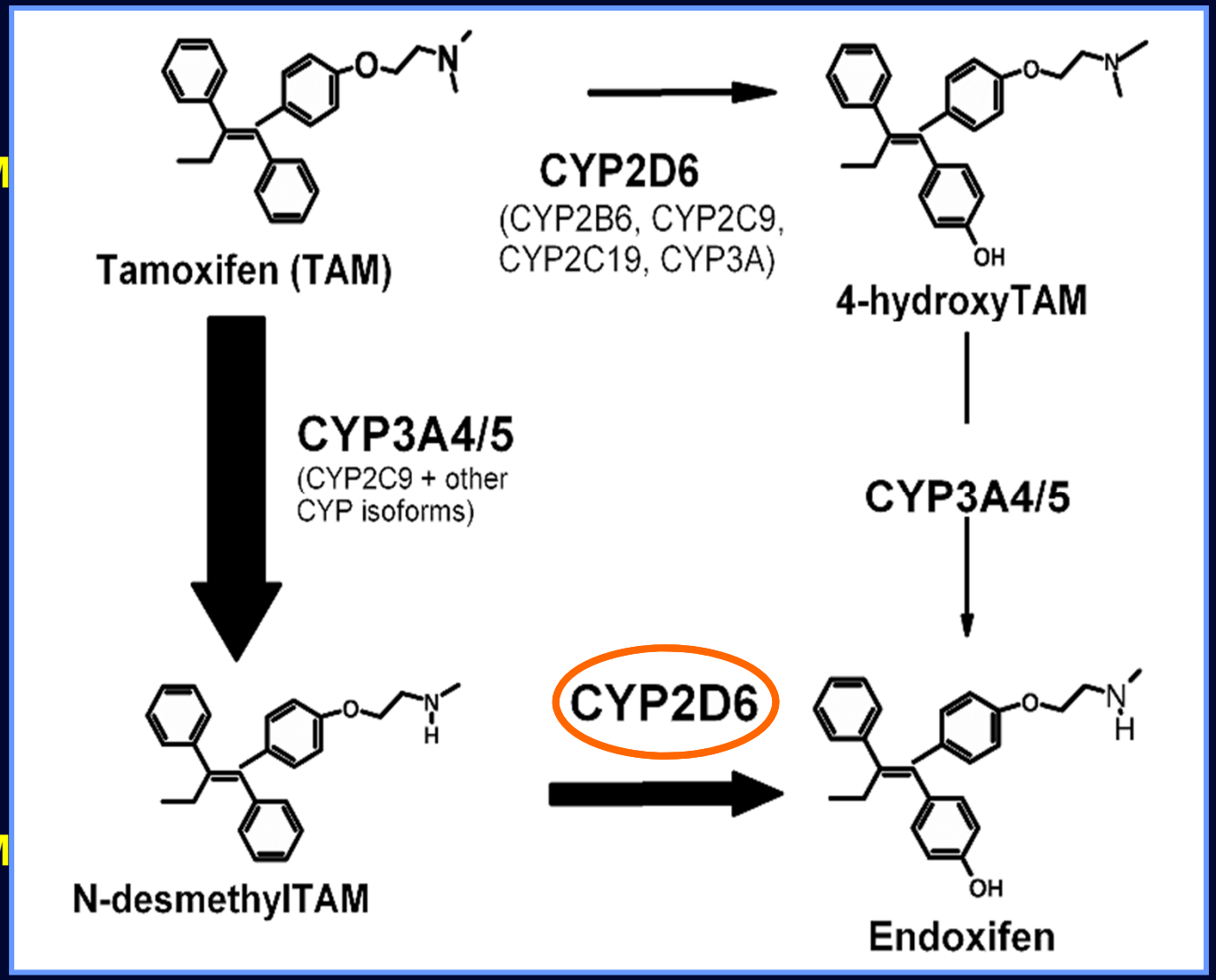
- Selective Estrogen Receptor Modulator
- Disrupts ER activity by stabilizing ER protein, blocking estrogen binding to the receptor
- Partial anti-estrogenic effects in the breast
- Estrogenic effects in uterus and bone
- Wide variability in the concentrations of tam and its metabolites without any association with drug response or toxicity

Tamoxifen Pharmacology (2009)

- Not all tamoxifen metabolites are created equal
- Tamoxifen metabolites exhibit marked differences in
  1) ER binding
  2) Inhibition of cell proliferation

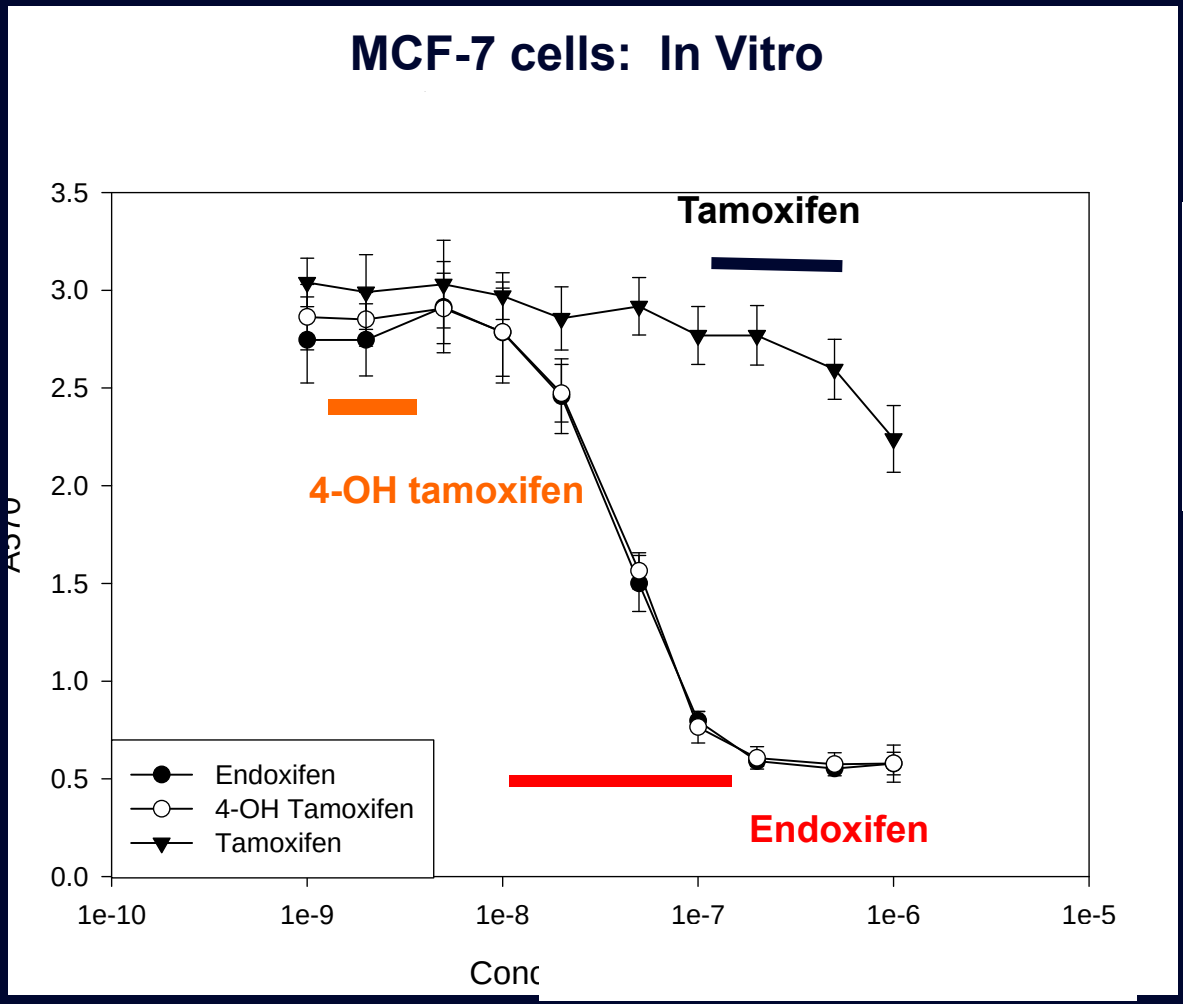
Stearns et al. JNCI 2003

Tamoxifen Metabolic Pathway (Humans)



Jin Y et al: J Natl Cancer Inst 97:30, 2005

Endoxifen and 4-OH-Tamoxifen are Equipotent as Inhibitors of Estrogen Stimulated Cell Proliferation



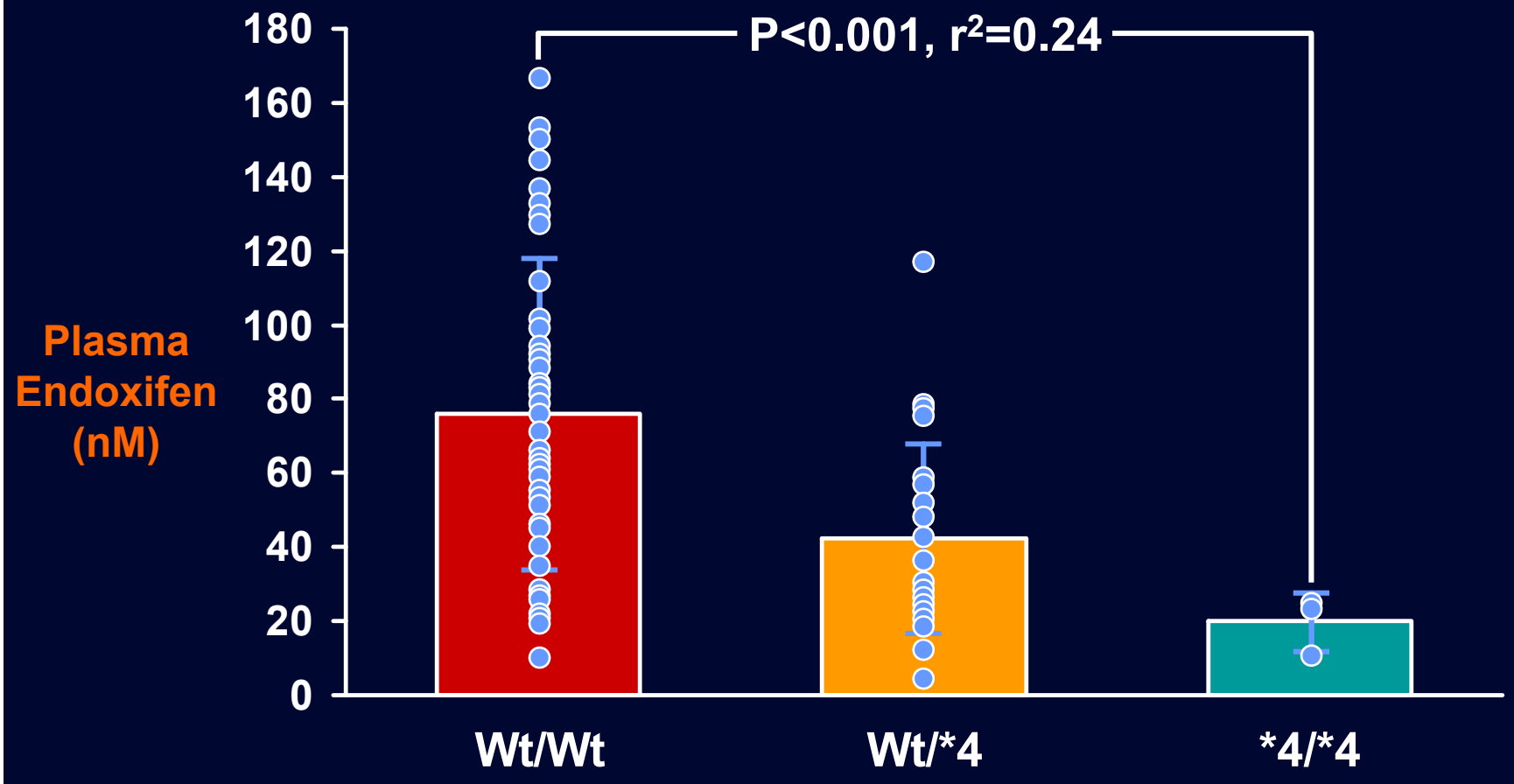
Concentrations in humans

- Tam (300-500 nM)
- 4HT (5-10 nM)
- Endoxifen (20-180 nM)

Concentration

Johnson MD, et al: Breast Cancer Res Treat 85:151-9, 2004

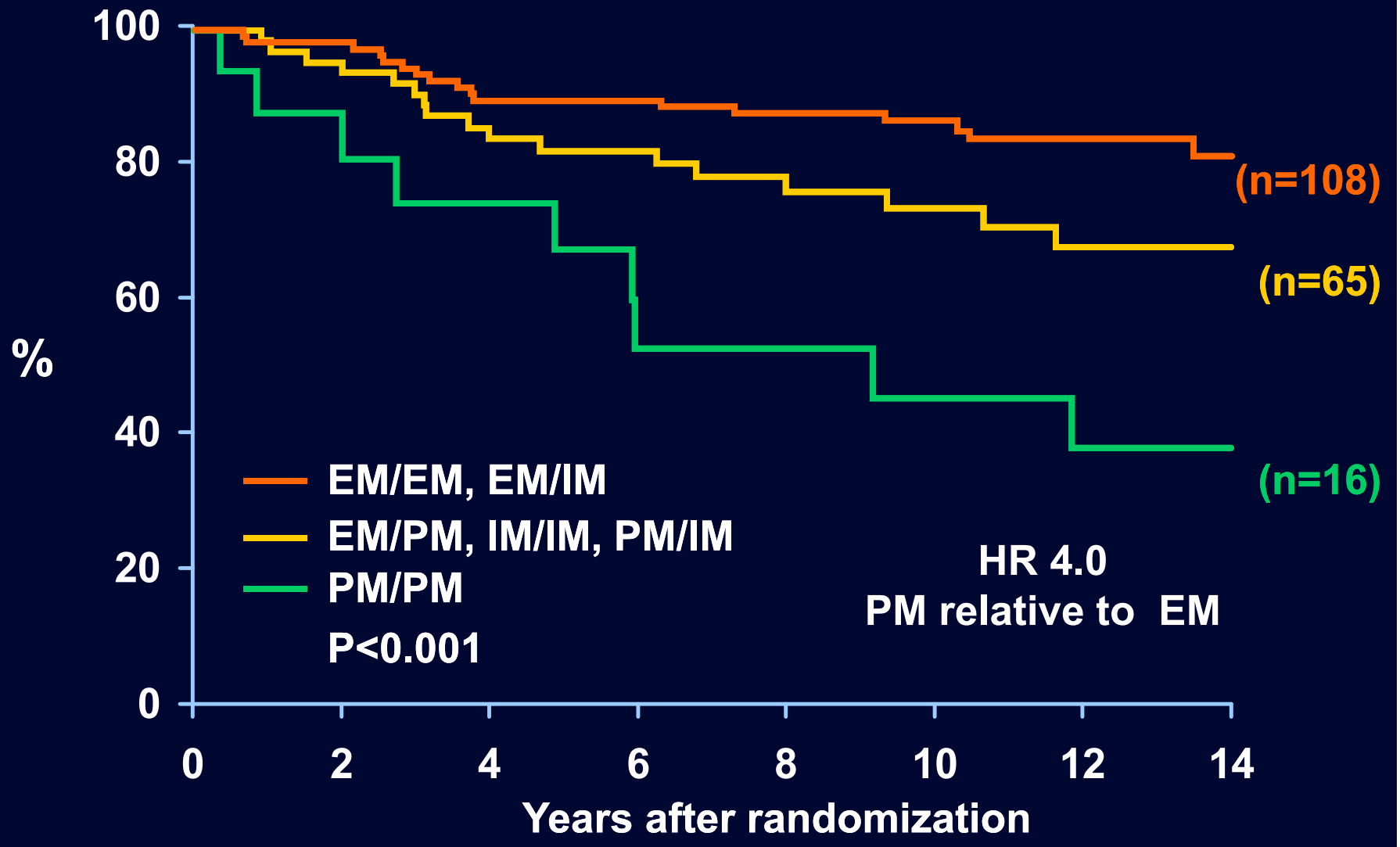
CYP2D6 Genotype and Endoxifen



CYP2D6*4 (most common genetic variant associated with the CYP2D6 poor metabolizer state)

Jin Y et al: J Natl Cancer Inst 97:30, 2005

Time to Recurrence According to CYP2D6 Metabolizer Status* in Women Receiving Adjuvant Tamoxifen



Goetz et al., Updated NCCTG 89-30-52, SABCS 2008

CP1173022-1

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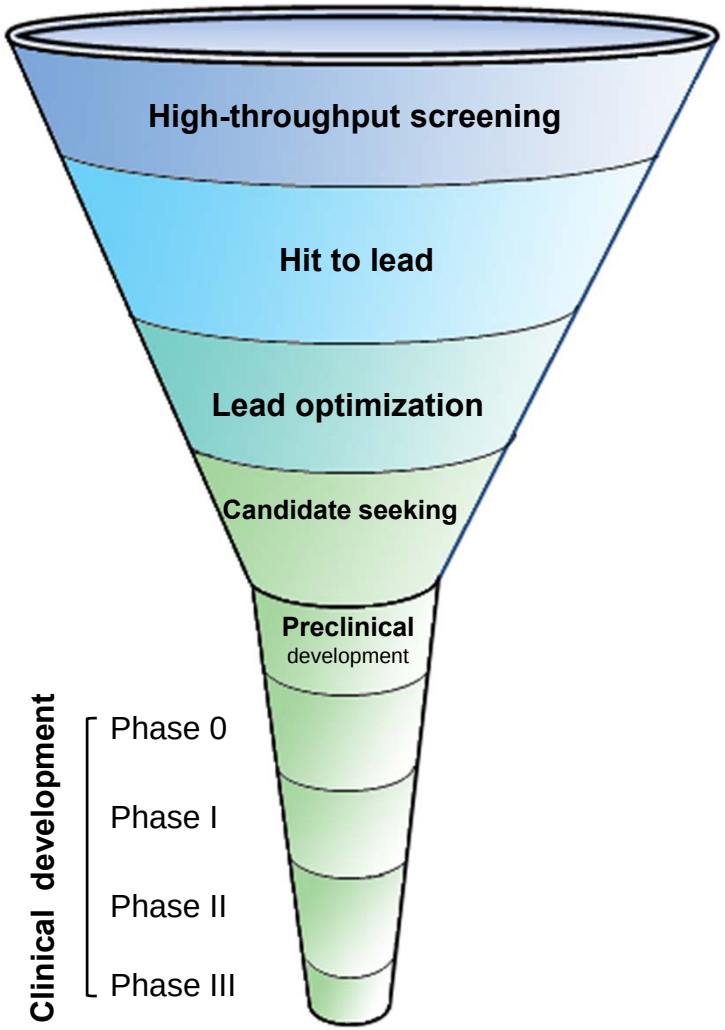
Crossing the Pharmacogenetic Divide

- CYP2D6 critical for endoxifen exposure and, thus, tamoxifen drug effect; endoxifen potently inhibits ERα as well as other traditional mechanisms
  - Metabolic activation of tamoxifen limits drug activity
  - Administration of endoxifen would bypass pharmacogenetic limitations of tamoxifen

- However, no IP possible for 30-year old metabolite, even though it is a new "drug"
  - Preclinical pharmacology, toxicology
  - Drug formulation and GMP production
  - IND submission
  - Phase I clinical trial

NCI has undertaken to produce clinical grade drug to begin the development process leading to a phase I study of endoxifen

Chemical Biology Consortium (CBC)

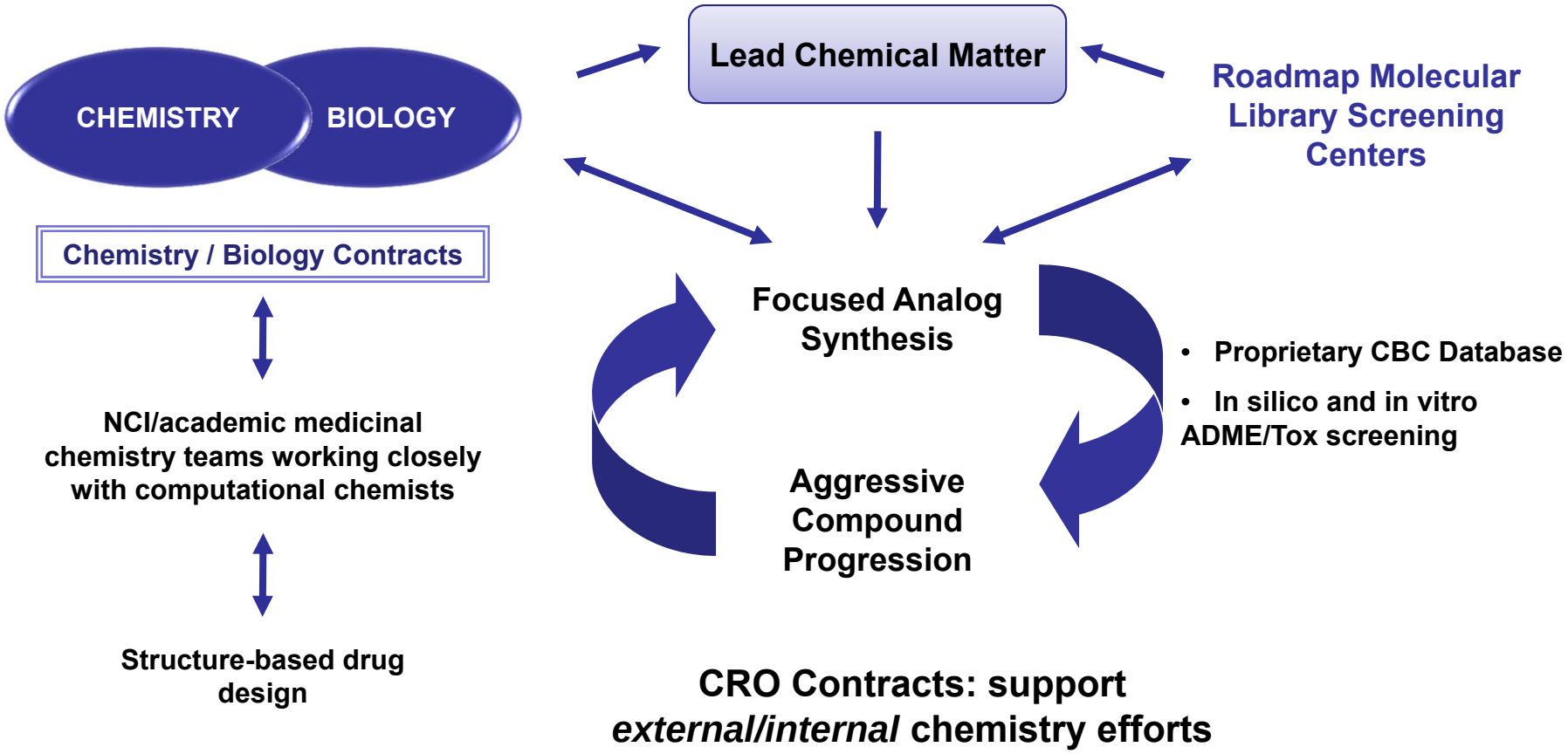


Vision

- Develop an integrated network of chemists, biologists, and molecular oncologists, with synthetic chemistry support.
  - Unify discovery with NCI preclinical and clinical development.
  - Link to other NCI initiatives with CCR as an integral partner.
  - Active mining of grant pool.

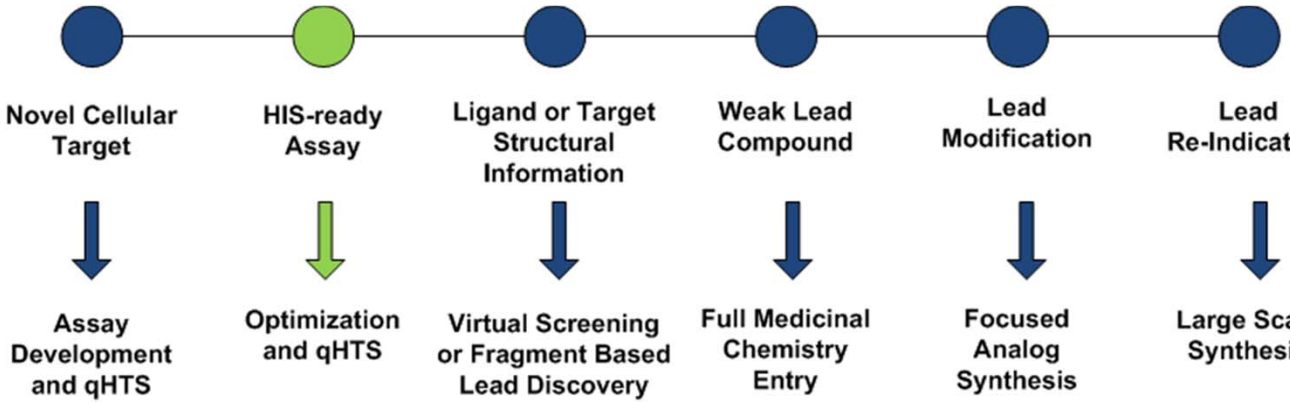
- Focus on unmet needs in therapeutics such as “undruggable” targets and under-represented “orphan” malignancies.
- Enable a clear, robust pipeline from target discovery through clinical trials for academic, small biotech, and pharma investigators.

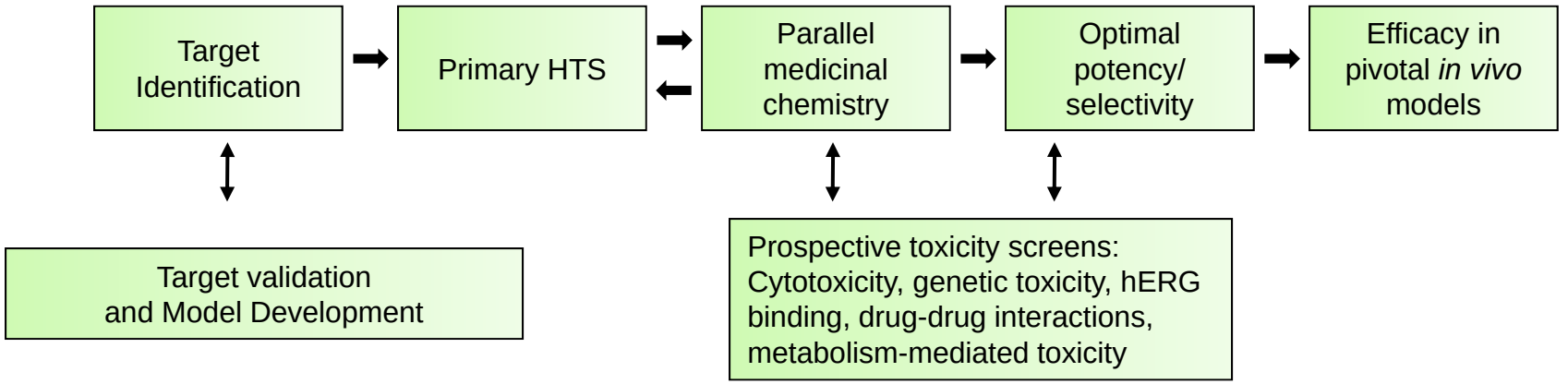
CBC: Enabling Hit-to-Lead and Lead Discovery



Program Focus: Cross-site medicinal chemists (*academia, NIH, contractors*) working on high-risk, high-impact targets in a team setting

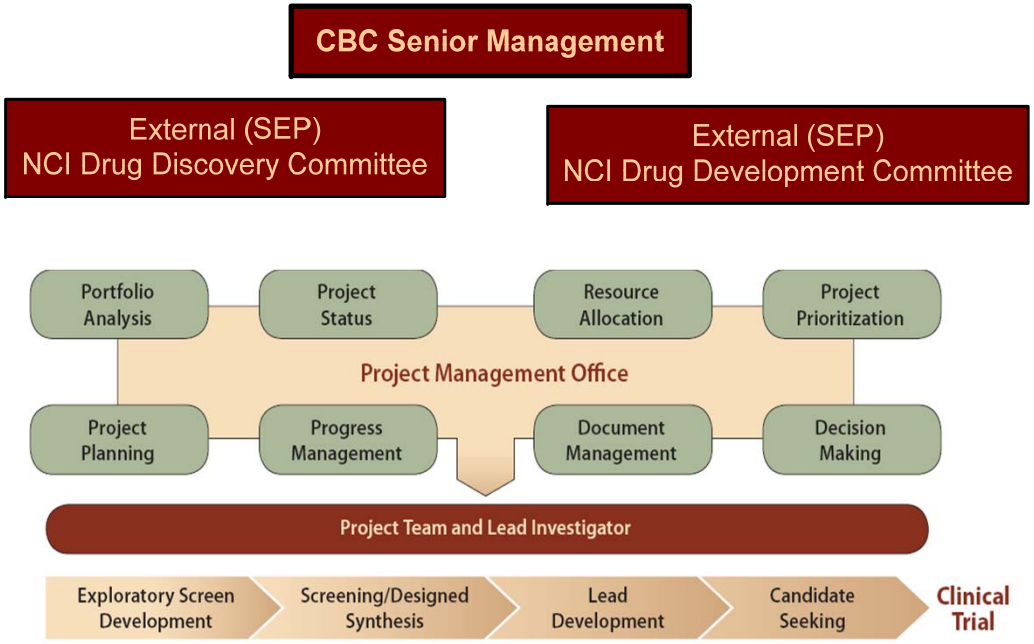
Entry Points into NCI Drug Discovery and Development Platform





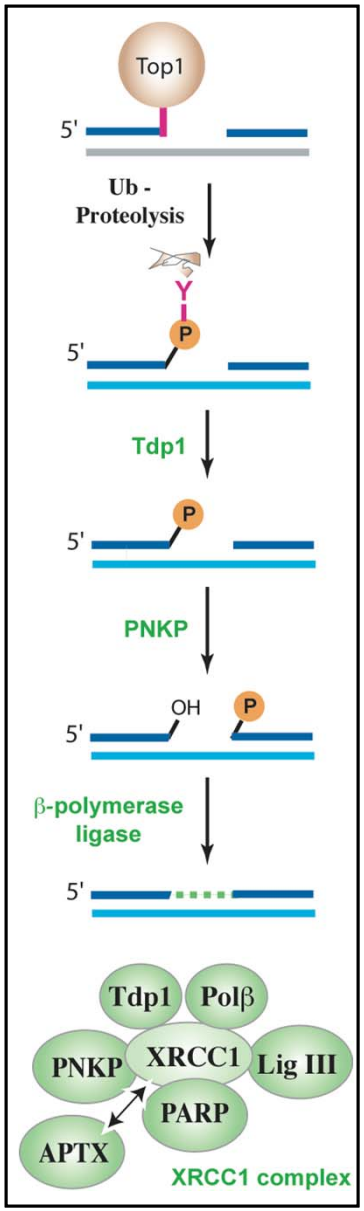
2009 and Beyond: Working towards Success

- **New Drug Discovery and Development Platform**
  - New Stage Gate process: agreed milestones
  - Projects are driven by a Project Team led by a Project Leader and Project Manager
  - Specific criteria (i.e., milestones) must be met to progress through each stage gate
- **New Governance**
  - External Special Evaluation Panels and Internal Review Committees will work together to approve and prioritize new projects and review stage-gate progression



  - A standard, defined drug development process will provide metrics for informed portfolio analysis
  - **Launch of Chemical Biology Consortium to "jump start" NCI pipeline**
- **New Infrastructure**
  - Adding Contract Research organizations (CROs) and increasing in house capacity to invigorate early phase drug discovery at the NCI

Tdp1 is a Rational Anticancer Target



- Tdp1 repairs DNA lesions created by Top1 trapping
- No Tdp1 specific inhibitors
- Tdp1-deficient cells are hypersensitive to Top1 inhibitors
- In Tdp1-knockout yeast, this hypersensitivity appears only when cells are also defective for checkpoints and repair pathways

CBC Early Discovery Activities-Tdp1 Pilot with Pommier Laboratory

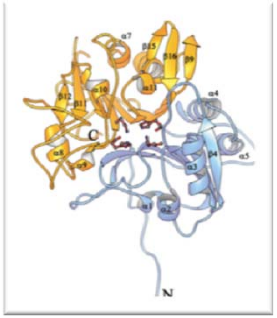
Joint collaboration between CCR/DCTD/NCGC

Screen development and high-throughput screening → **Hit to Lead** → **Lead Optimization** → **Candidate Seeking**

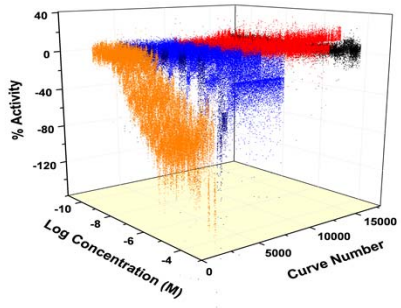
Target Identification *Pommier Laboratory* → Primary uHTS ⇄ Parallel medicinal chemistry → Optimal potency/ selectivity → Efficacy in pivotal *in vivo* models

NIH Chemical Genomics Center

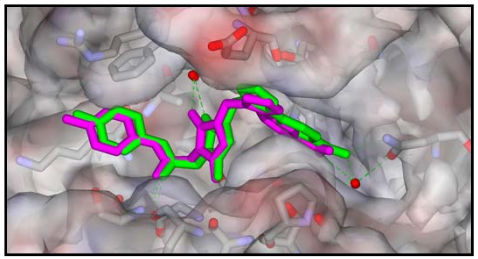
Secondary biochemical and cell-based screens *-Pommier Laboratory*



Co-crystallization with HTS "Hits"



Biacore: compound-enzyme affinity constants



Computational Docking

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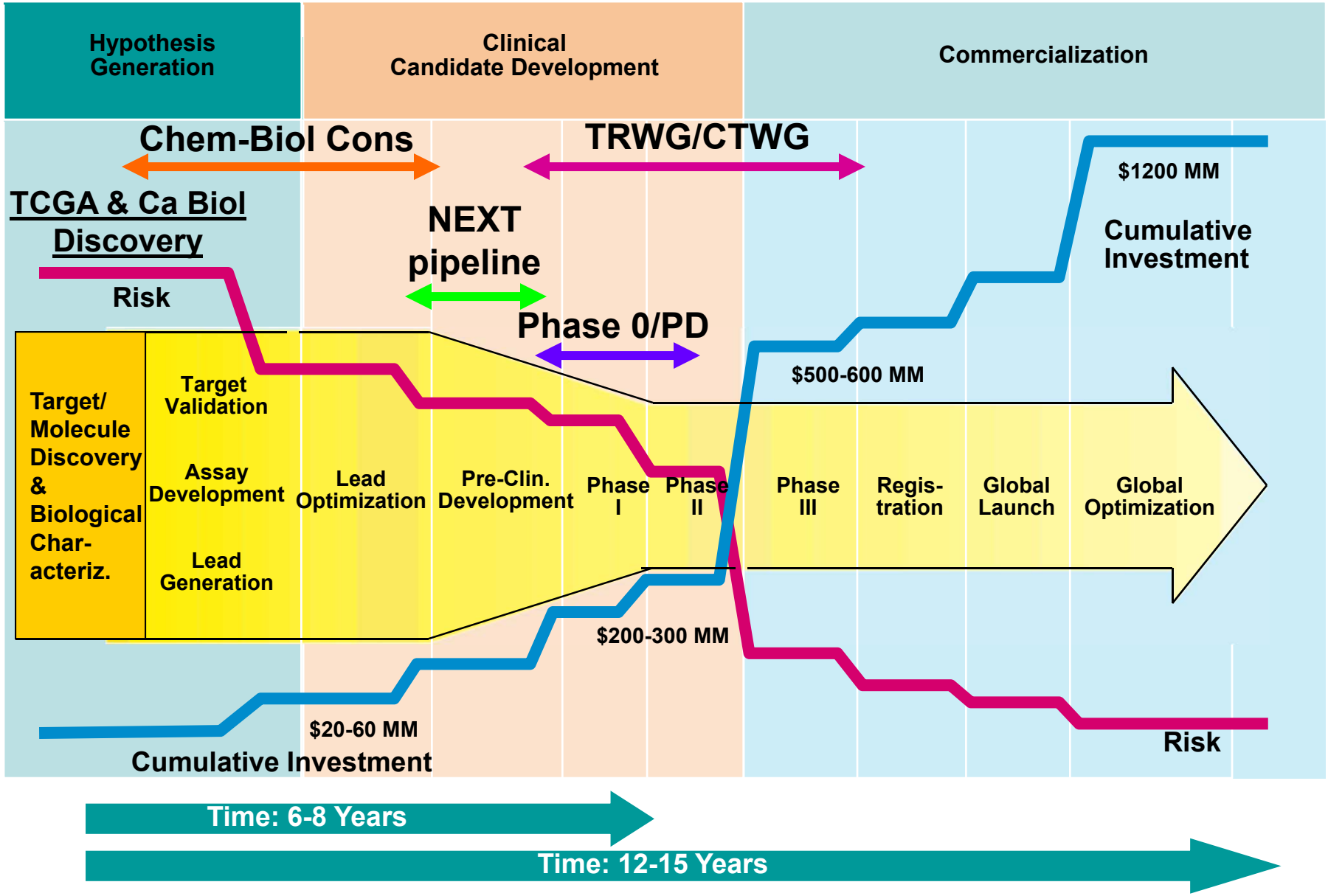
Initial CBC Participants

- Burnham
- Southern Research
- SRI International
- Vanderbilt
- Emory
- UCSF
- Univ. No. Carolina
- Pittsburgh
- Univ. of Minnesota
- Georgetown
- NCI Intramural Chemical Biology
- Affiliate Investigators

Therapeutics Development Timeline



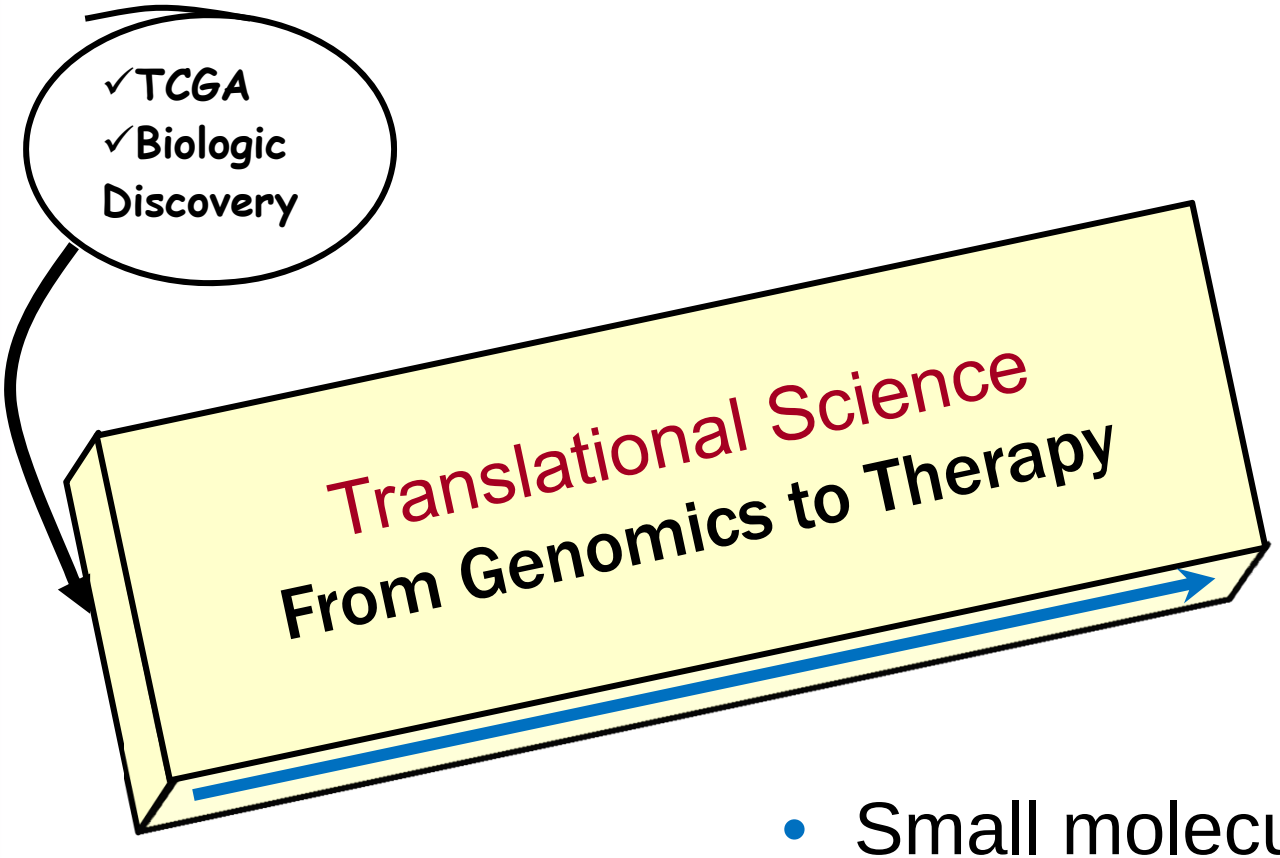
National Cancer Institute

The Cancer Genome Atlas

- Pilot includes glioblastoma, ovarian and lung cancers
- Glioblastoma (80 percent tumor purity, with matched normal controls)
  - Genomic analysis of 214 patient cases; 168 patient cases sequenced
  - Identified NF1, Erbb2, and PIK3R1 as highly associated with GBM (EGFR, p53)
  - At least 4 subtypes emerging
- New data integration and analysis underway

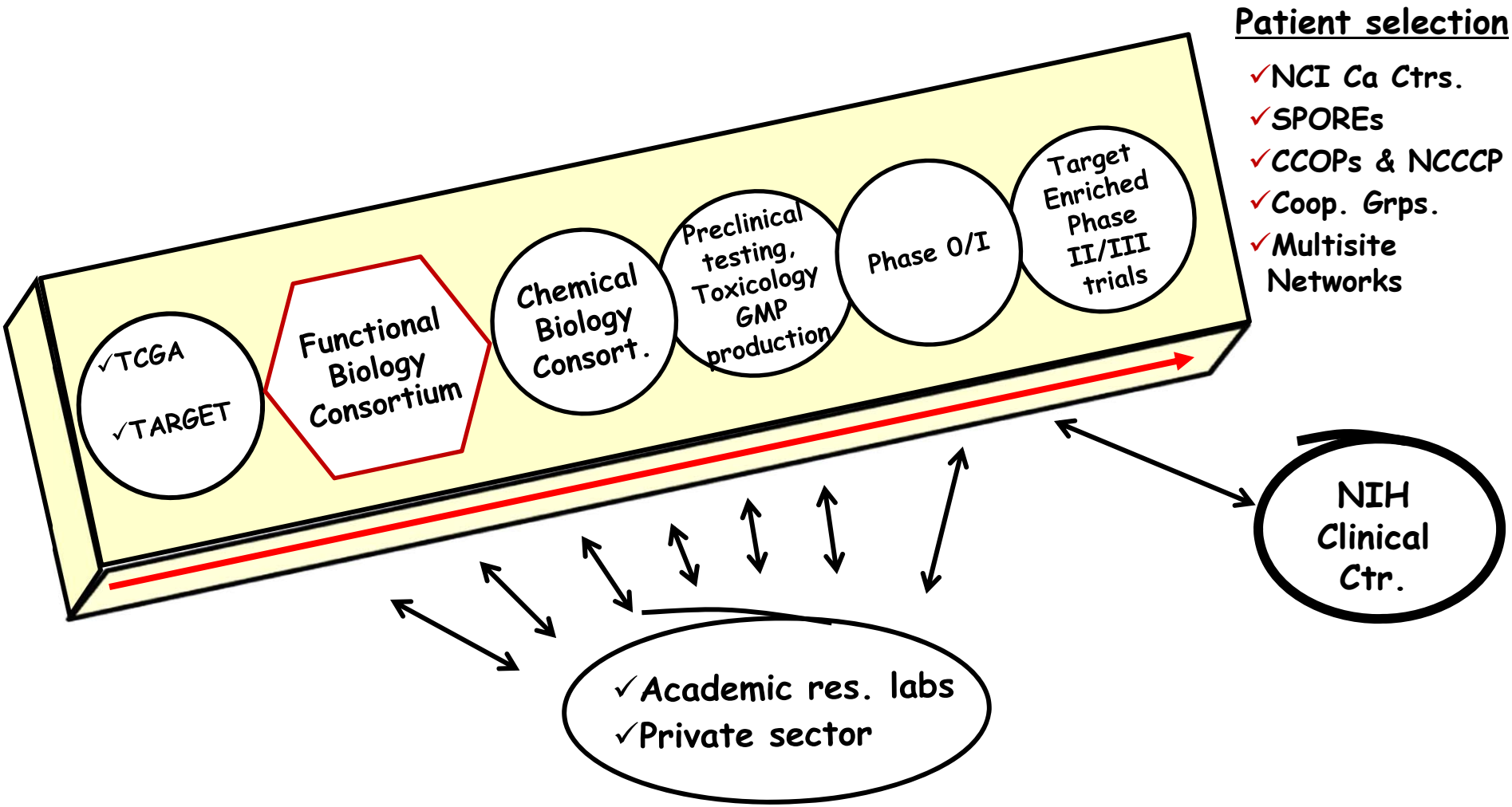
National Cancer Institute

Personalized Cancer Medicine



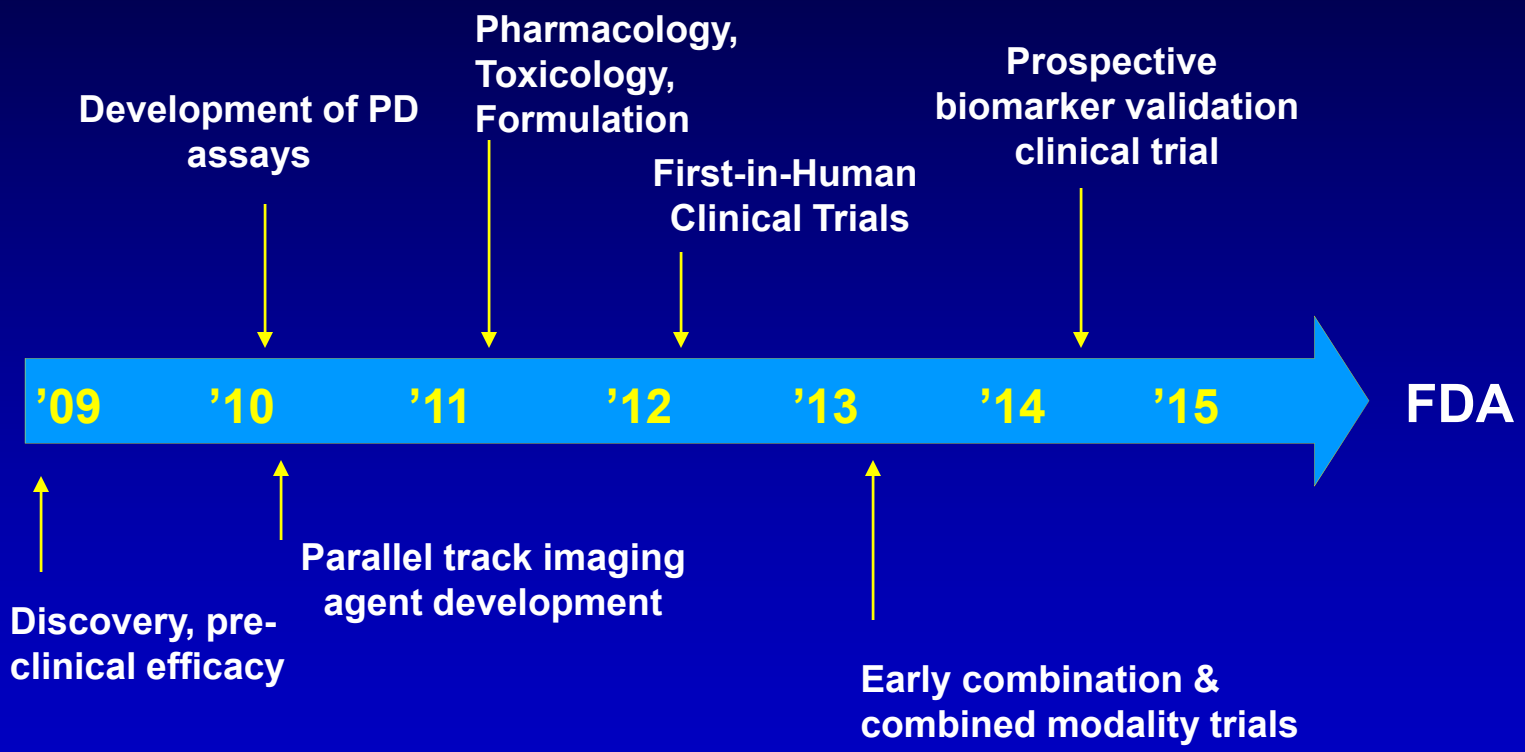
- Small molecules
- Biologics
- Biomarkers

NCI's Roadmap to Personalized Cancer Treatment



National Cancer Institute

NCI's Timeline to Personalized Medicine in Cancer Treatment



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NCI's Roadmap to Personalized Medicine in Cancer Treatment

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National Cancer Institute

Personalized Cancer Treatment: Questions for the NCAB

- How should NCI support a coordinated approach to characterizing the functional biology of the output of its TCGA program in the context of personalized therapeutics?
  - How can we add value beyond that of the genomic discovery effort itself and ongoing investigator-initiated studies that will follow from TCGA?
  - What approaches would be most appropriate?
- What are the major **continuing or new** roadblocks to the development of personalized cancer medicines in the academic and biotech arena in 2009?
- What new/enhanced resources should the NCI consider developing to accelerate progress in the field of “personalized” cancer therapeutics?