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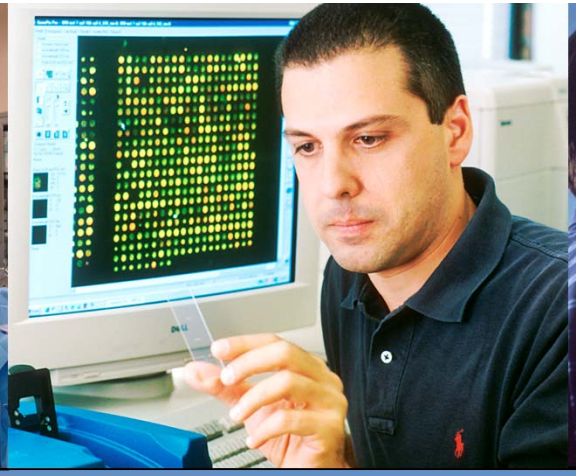


Preclinical Pharmacokinetic and Pharmacologic Studies with Anti-tumor and Other Therapeutic Agents

Preclinical Toxicology of Drugs Developed for Cancer & Other Diseases

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

NCI Board of Scientific Advisors

November 2, 2009

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

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Concepts for Review: Presentation Outline

Preclinical Pharmacokinetic and Pharmacological Studies with Anti-tumor and Other Therapeutic Agents

Preclinical Toxicology of Drugs Developed for Cancer and Other Diseases

Overview

- What do the pharmacology and toxicology contracts support and why do we need them?
- How are these contracts used (compounds prioritized) within a unified NCI drug development program: Overview of previous and current (new) pipeline management processes
- Review of the productivity of both contracts

Pharmacology

- Specific examples of projects supported by the Pharmacology contract
- Review of the Pharmacology contract budget request

Questions

Toxicology

- Productivity of toxicology contract with specific examples of completed projects
- Review of Toxicology contract budget request
- Summary

Questions

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Preclinical Pharmacology and Toxicology Contracts

Why does NCI need preclinical pharmacology and toxicology contracts and what do they provide?

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2004 NIH Summit Workshop

"A major reason for the tremendous cost of drug development is the high rate of drug candidate failure during clinical testing…….. It is recognized that failure to detect drug toxicities in preclinical testing contributes significantly to drug candidate failure during clinical phase testing."

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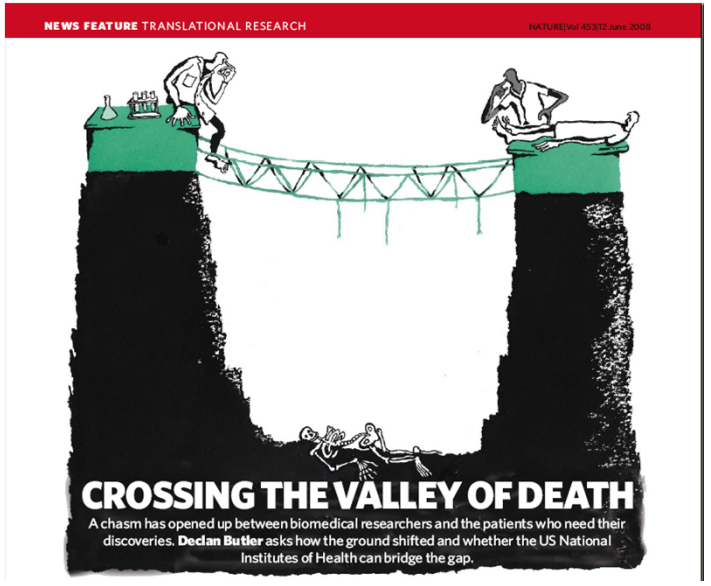
Role of Preclinical Pharmacology & Toxicology at NCI

- Toxicology and pharmacology studies not simply about proving the efficacy & safety of a molecule; intended to characterize the sequence and extent of adverse effects as they relate to drug exposure—pharmacology and toxicology studies tightly linked

- With appropriate characterization, in most cases, safe operating parameters can be established for human clinical trials

- BUT, most difficult (costly) resources for academic and small biotech investigators to access: Important for NCI to make them available to extramural community



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FDA Preclinical Pharmacology & Toxicology Requirements

Small Molecules

- Two Species - Rodent & Non-rodent
- Clinical Route & Schedule
- Pharmacokinetics/Dynamics – Optional
- Identity, stability, >98% purity

Biologicals

- Most Relevant Species
- Clinical Route & Schedule
- Biodistribution

Study designs are agent-directed & IND-Enabling.

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NCI Preclinical Pharmacology/ Toxicology Studies

Agent-Directed Design:

- Studies Guided by Pharmacokinetics/ Dynamics (PK/PD)
- Correlate PK/PD to Efficacy
- Correlate PK/PD to Safety & Toxicity
- Incorporate *In Vitro* Toxicity Data/Studies As Appropriate and Available
- Correlate PK/PD with Toxicity and Safety Across Species
- Ameliorate Toxicity by Change in Route and/or Schedule
- Compare Toxicity with Accepted Clinical Agents as Necessary

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Preclinical Therapeutics Stage Gates

Exploratory Screen Development

- Prepare a product profile
- Conduct a technology overview
- Develop a screening strategy
- Identify potential biomarkers (efficacy/surrogate)
- Develop a strategy for "clinical readiness"
- Prepare medical needs assessment
- Prepare project operational plan

Screening/ Designed Synthesis

- Run screen(s)
- Assess mechanism of action for link to disease
- Determine desirable potency
- Determine evidence of structure–activity relationship
- Evaluate functional activity in vitro
- Determine selectivity for target
- Evaluate PK, PD, and physiochemistry using best available tools/in silico modeling
- Assess amenability to synthesis
- Evaluate stability

Lead Development

- Establish laboratory objectives for clinical efficacy
- Resolve IP issues
- Evaluate activity in validated disease models
- Evaluate physiochemistry
- Differentiate Leads from current therapies
- Evaluate preliminary safety issues
- Develop PD and toxicology biomarker assays(s)
- Assess achievability of human PK/PD profile
- Assess feasibility of scale-up and bulk synthesis

Candidate Seeking

- Evaluate synthesis and proposed clinical formulation
- Evaluate biopharmaceutical properties
- Assess potency against clinical efficacy
- Evaluate biodistribution
- Evaluate clinical readiness of PK/PD assay(s) and specimen handling SOPs
- Assess amenability to imaging
- Evaluate safety issues (most sensitive species) in range finding toxicology studies

Clinical Candidate

- Manufacture GMP-grade bulk drug
- Conduct IND-directed toxicology studies
- Define / toxicokinetics
- Determine preclinical MTD and DLTs
- Validate PK/PD assay(s) and specimen handling SOPs
- Develop and validate product characterization and release assays
- Characterize clinical product
- Prepare CMC package and toxicology summary report
- Prepare and review clinical protocol
- Prepare and file IND

Preclinical Toxicology and Pharmacology are required for decision-making throughout drug discovery and development and for IND filing for clinical trials

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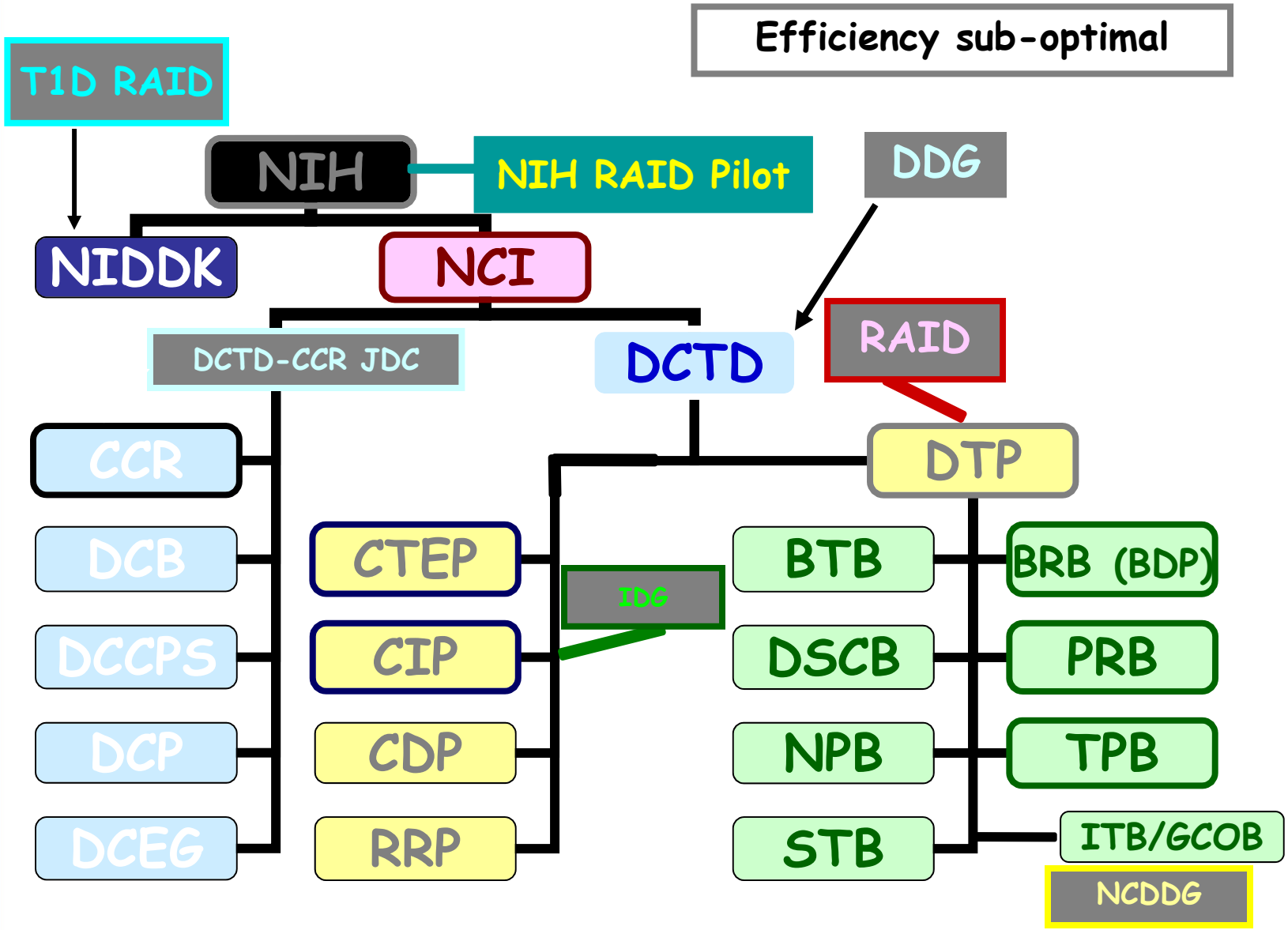
Drug Development Programs: NCI & NIH



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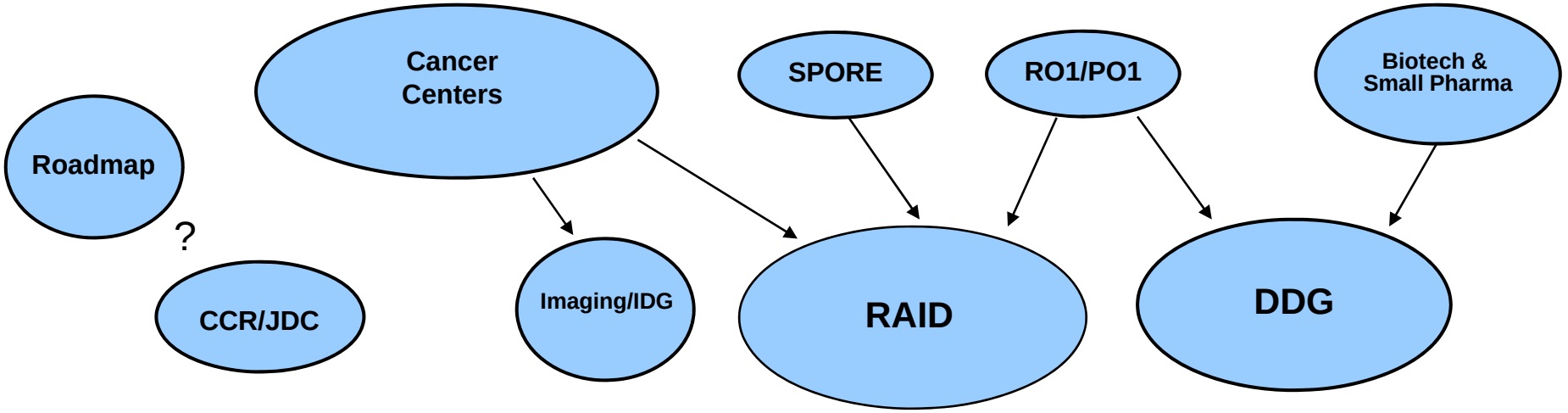
Decentralized NCI Drug Development

- **Created inefficiencies** (duplication of experimental work and/or mission)
- **Fostered resource silos** (staff with expertise in an area could be unintentionally excluded from a project)
- **Confused collaborators** (which mechanisms most appropriate for entry of agent into the program? What resources available?)
- **Confused staff** (What projects had priority? What resources could be accessed? Who had decision making authority?)

Transformation of the NCI Therapeutics Pipeline



CBC Created

The NCI Experimental Therapeutics (NExT) Pipeline:

Target discovery through early stage clinical trials

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Goals of the NCI's Therapeutics Platform

- Pursue the development of treatments for unmet medical needs (e.g, rare cancers and pediatric tumors); provide resources for natural product development and the development of high risk targets; allow a sufficient time line to move new developments in functional biology and TCGA into drug discovery
- The success of the program measured by IND filings (first in human studies); licensing of novel therapeutics; an improved cancer therapeutics success rate; and, ultimately, approved NDA's made possible by support of academic and small biotech investigators

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How Does An Extramural Investigator Access NCI's Drug Discovery and Development Resources?

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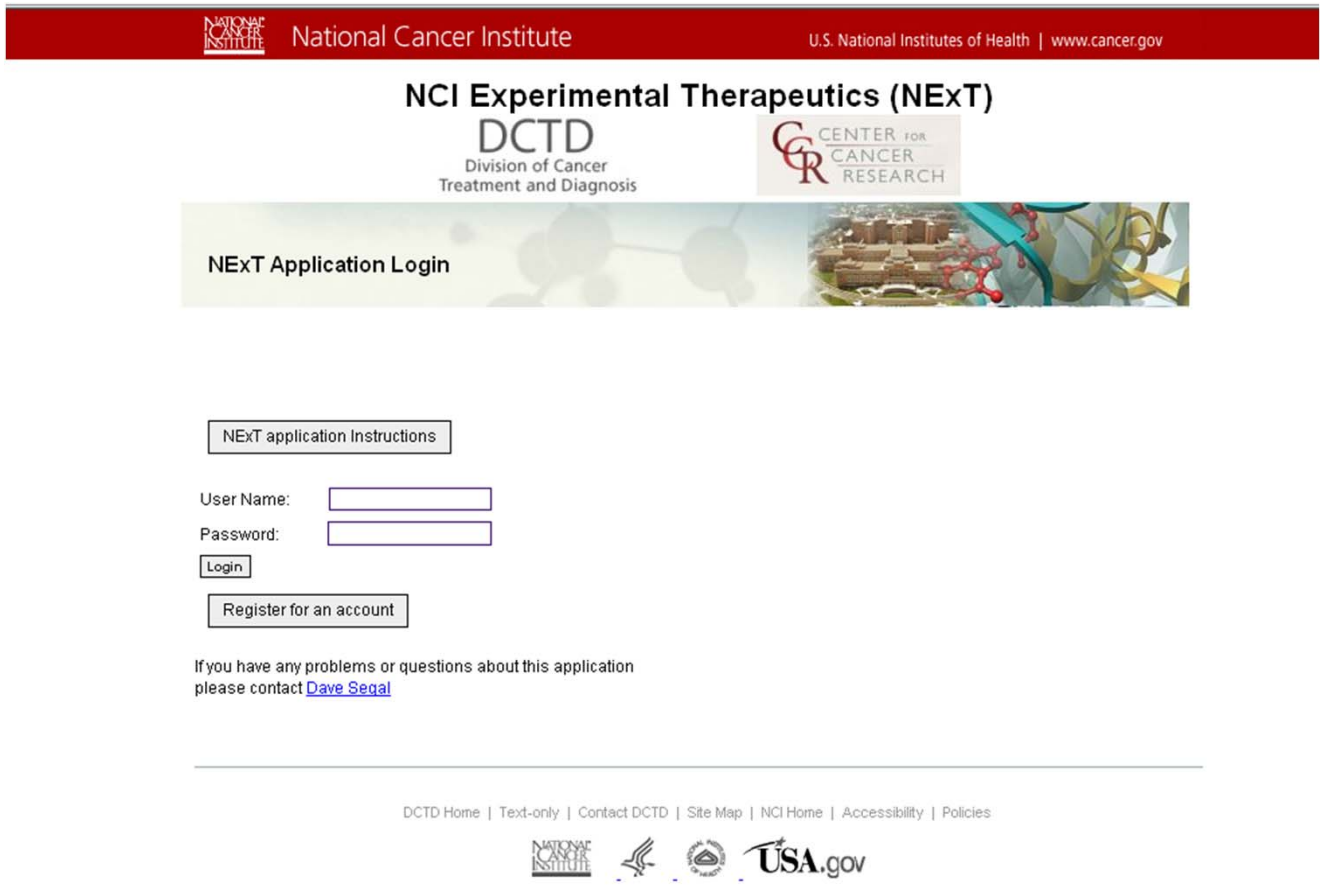
NExT Application Process

Extramural scientists may propose targets, screens, or molecules for entry into the NExT pipeline
https://dctd.cancer.gov/nextapp or
https://dctd.cancer.gov/nextregistration



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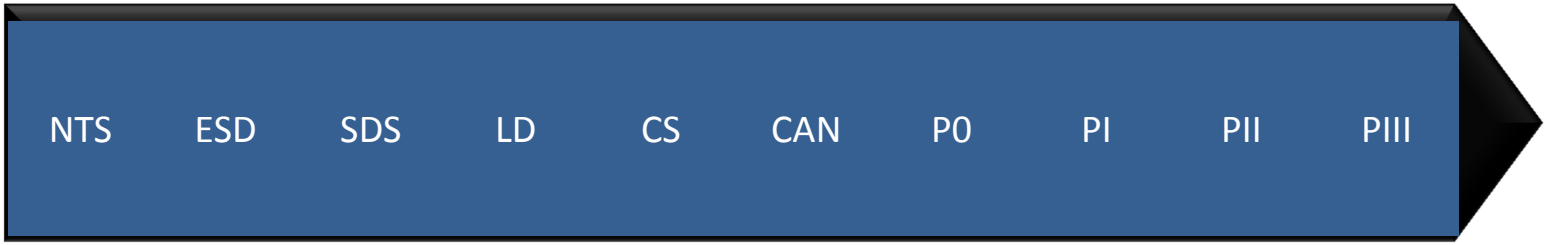
NExT Applications: Cycle 1 (9/15/09)

Cycle 1: Total of 52 NExT proposals for cycle 1 received



Number of proposals:

NTS	ESD	SDS	LD	CS	CAN	P0	PI	PII	PIII
0	17	11	13	3	2	0	6	0	0

Discovery Definitions:

NTS = New Target Substrate
ESD = Exploratory Screen Development
SDS = Screening/Designed Synthesis
LD = Lead Development
CS = Candidate Seeking

Development Definitions:

CAN = Clinical Candidate
P0 = Phase 0
PI = Phase I
PII = Phase II
PIII = Phase III

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Therapeutics Discovery & Development Support Provided by NCI (NExT)

- Medicinal chemistry, HTS, lead optimization
- Synthesis of oligonucleotides
- Chemical synthesis of small molecules and peptides
- Scale-up production of small molecules and biologicals
- Development of analytical methods
- Isolation and purification of naturally occurring substances
- Exploratory toxicology studies and pharmacokinetic evaluation
- PK/efficacy/ADME studies (bioanalytical method development)
- Development of suitable formulations
- Range-finding initial toxicology and IND-directed toxicology
- Product development planning and advice in IND preparation
- Later-stage preclinical development of monoclonal antibodies, recombinant proteins, and gene therapy agents
- Manufacture of drug supplies, including biological agents
- Analytical methods development for bulk material
- Formulation studies
- Production of clinical dosage forms
- Stability testing of clinical dosage forms
- Regulatory support

Toxicology & Pharm

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NCI Chemical Biology Consortium (CBC)

- ***Mission:*** **Dramatically increase flow of early stage drug candidates into NCI therapeutics pipeline**

- ***Vision:***
- **Develop integrated network of chemists, biologists, and molecular oncologists, with synthetic chemistry support**
  - ✓ **Active management by NCI and external advisory boards**
  - ✓ **Unify discovery with NCI pre-clinical and clinical development**
  - ✓ **Linked to other NCI initiatives; CCR chemistry integral partner**
- **Focus on unmet needs in therapeutics: "undruggable" targets, under-represented malignancies**
- **Enable a clear, robust pipeline all the way from target discovery through clinical trials for academic, small biotech, and pharma investigators**

NExT FRONT END

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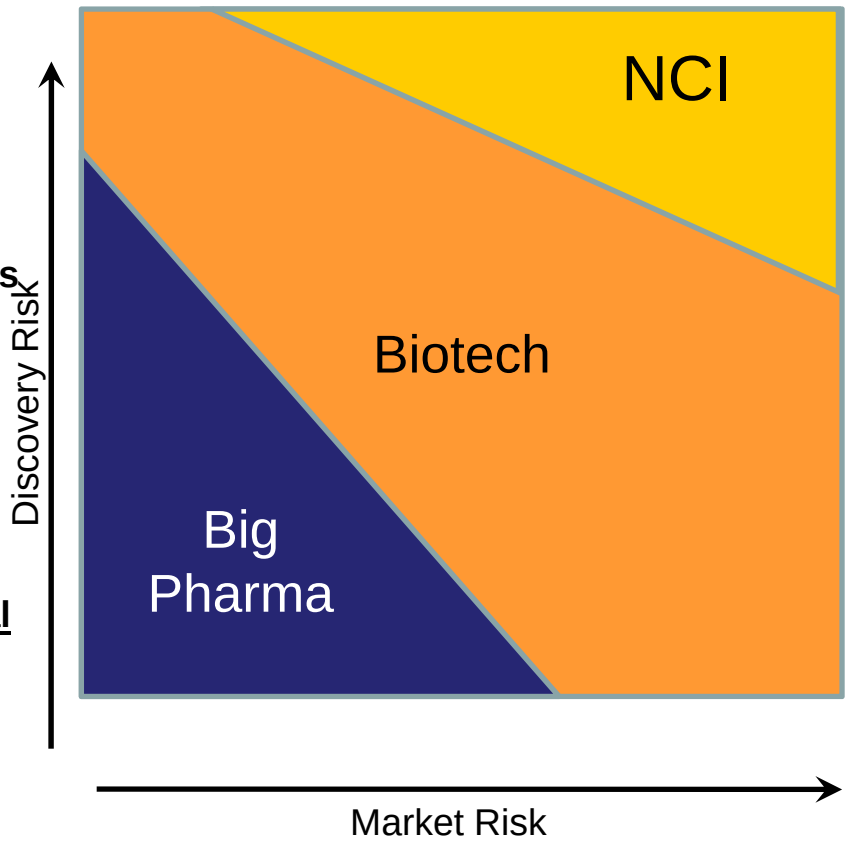
Chemical Biology Consortium

Why is CBC different?

- Builds on >50 yrs of NCI experience in cancer drug development
- Not intended to replicate Pharma
- CBC members will submit own projects and take on those of other investigators
- Focus on bringing academic targets and molecules to patients
- Will not shy away from difficult targets
- Longer time horizon
- NCI committed to supporting CBC projects from inception through proof-of-concept, PD-driven clinical trials if milestones achieved: Only NCI could do this
- Inclusive involvement of CBC members in shared projects developed in parallel across consortium



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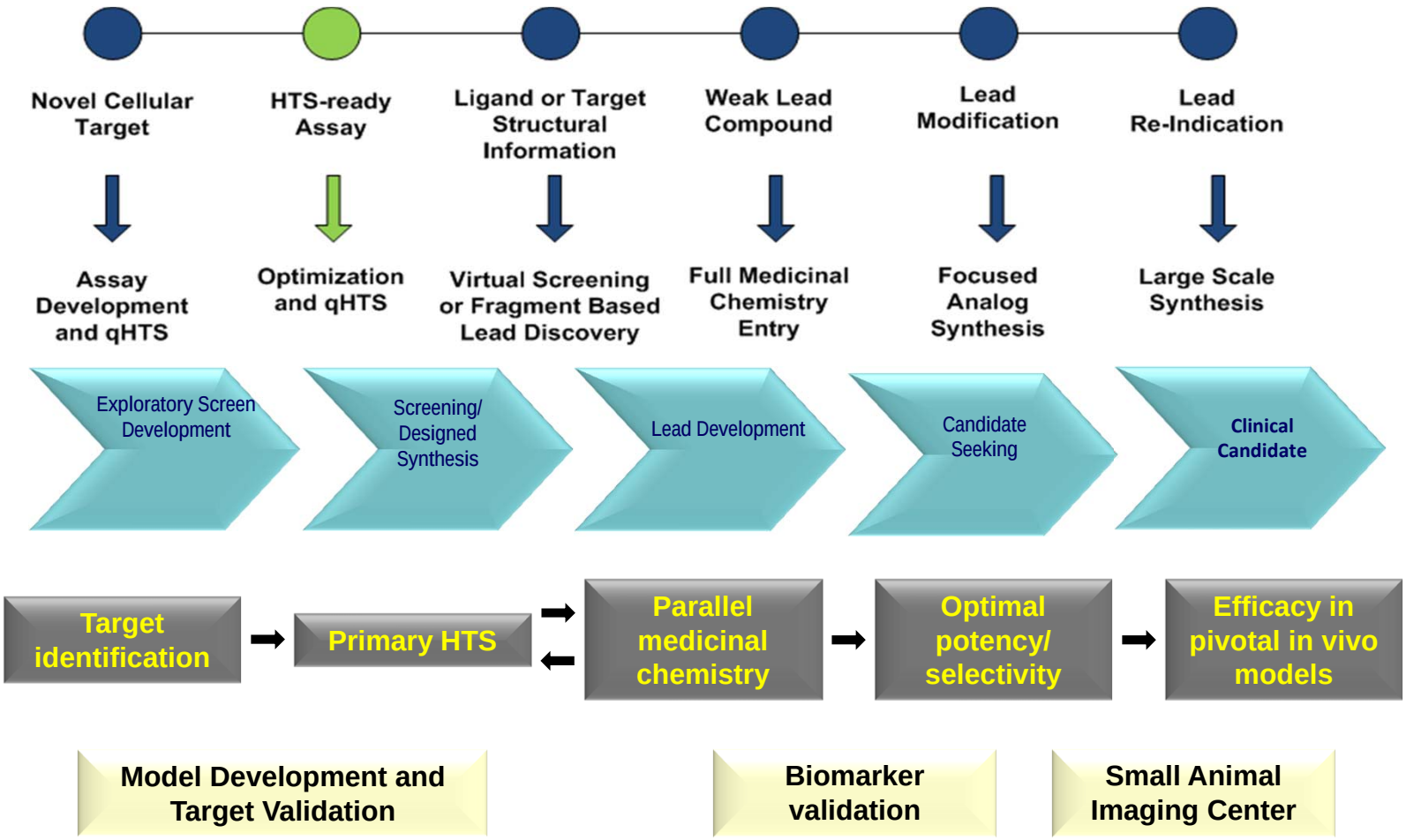
Multiple Entry Points into the CBC



Adapted with permission from the NIH Chemical Genomics Center

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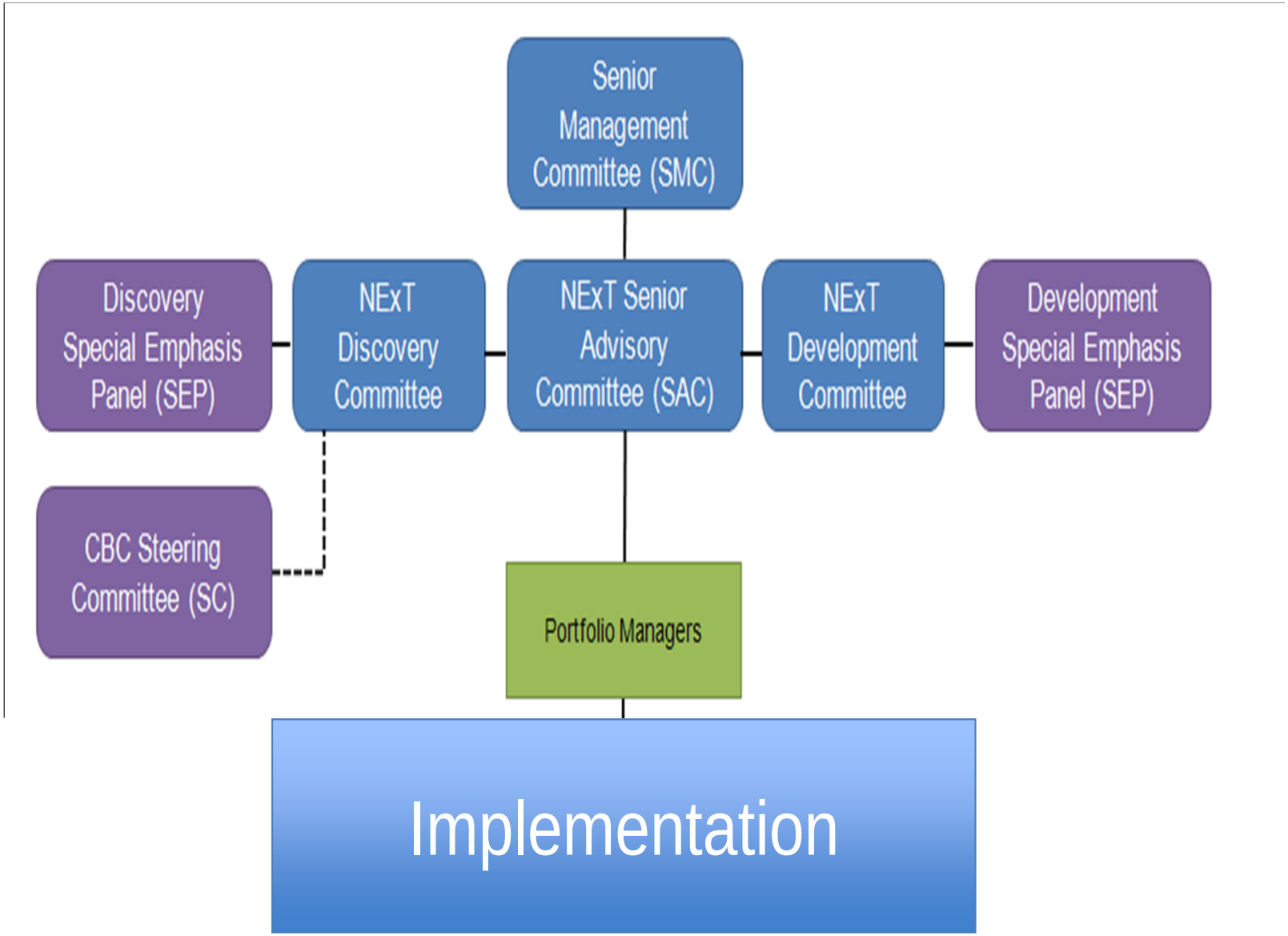
How Are Projects/Compounds Selected?



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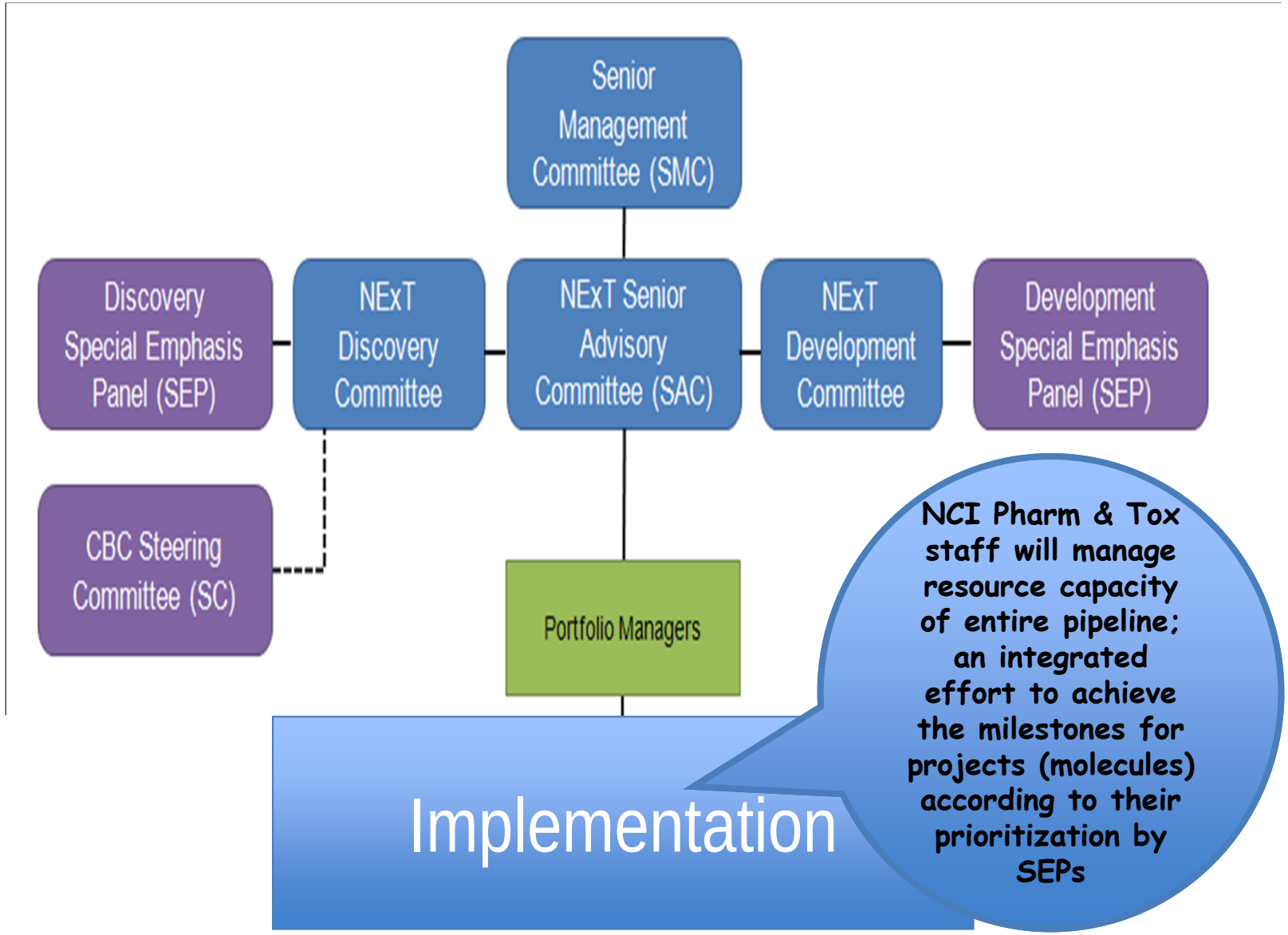

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Which Compounds Will Actually Move Forward?

- Selection and ongoing prioritization is based on the following criteria:
  - ✓ Scientific Merit
  - ✓ Feasibility
  - ✓ NCI Mission
  - ✓ Novelty
  - ✓ Clinical Need

Scoring:

1 = Exceptional

3 = Excellent

6 = Satisfactory

9 = Poor

- A Stage Gate evaluation process to benchmark the progress and priority of projects within the portfolio
- Evaluation process will also provide guidance about the priority utilization of the capacity – based resources provided to NCI by these contracts

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Productivity Overview

NCI Drug Discovery and Development Accomplishments *via* Preclinical Pharmacology and Toxicology Contracts During Current Funding Cycle

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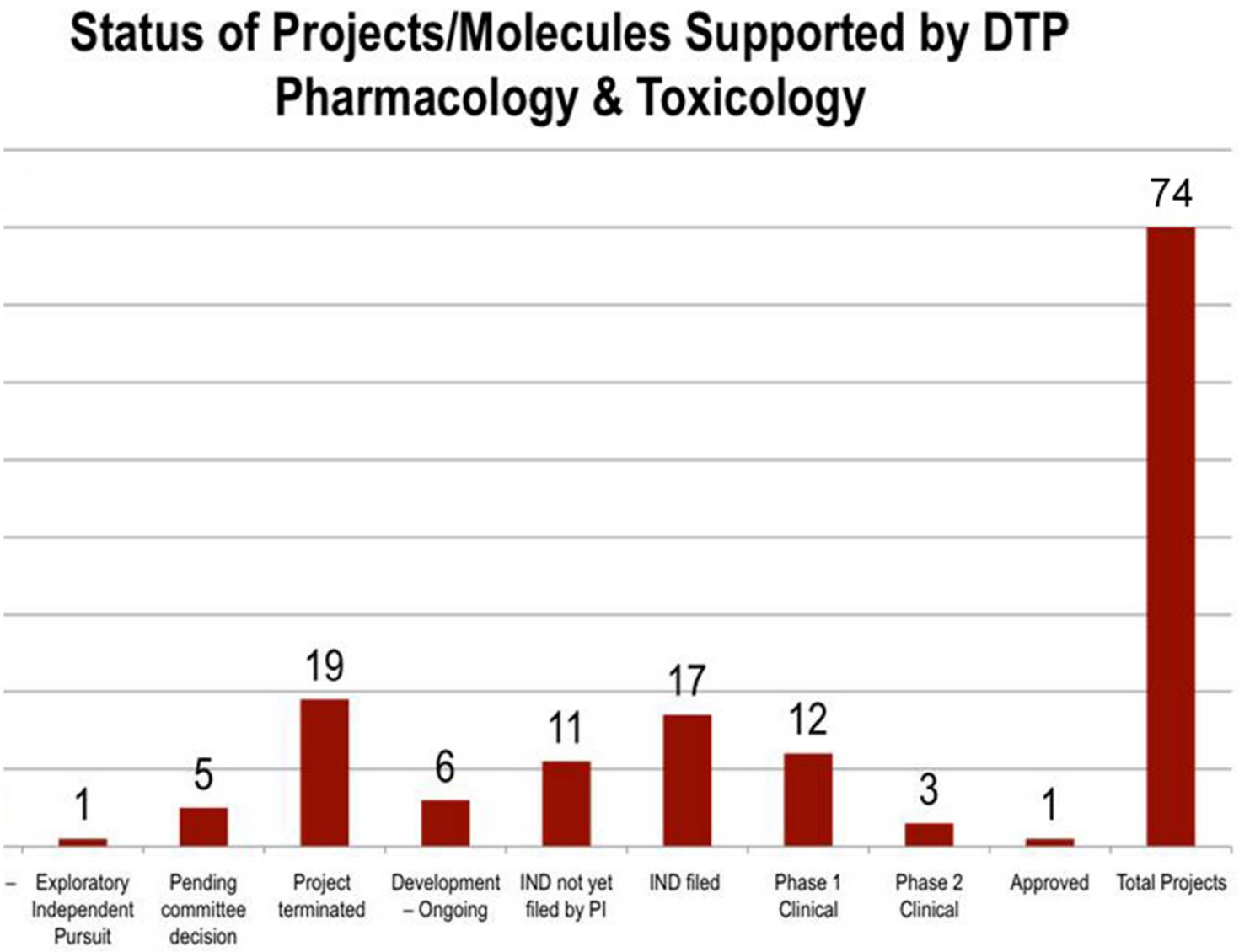
What Did We Get For Our Toxicology and Pharmacology Investment?



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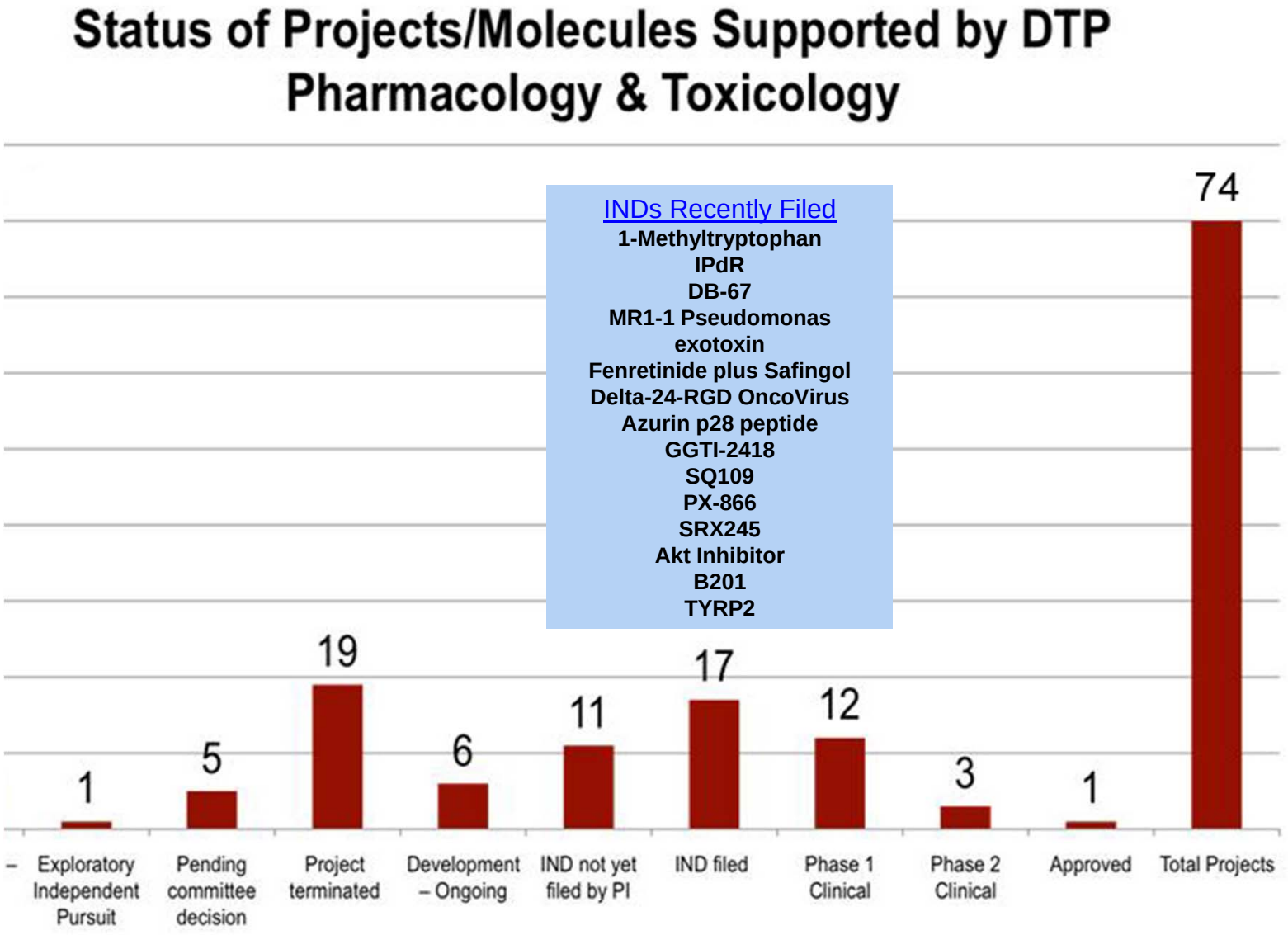

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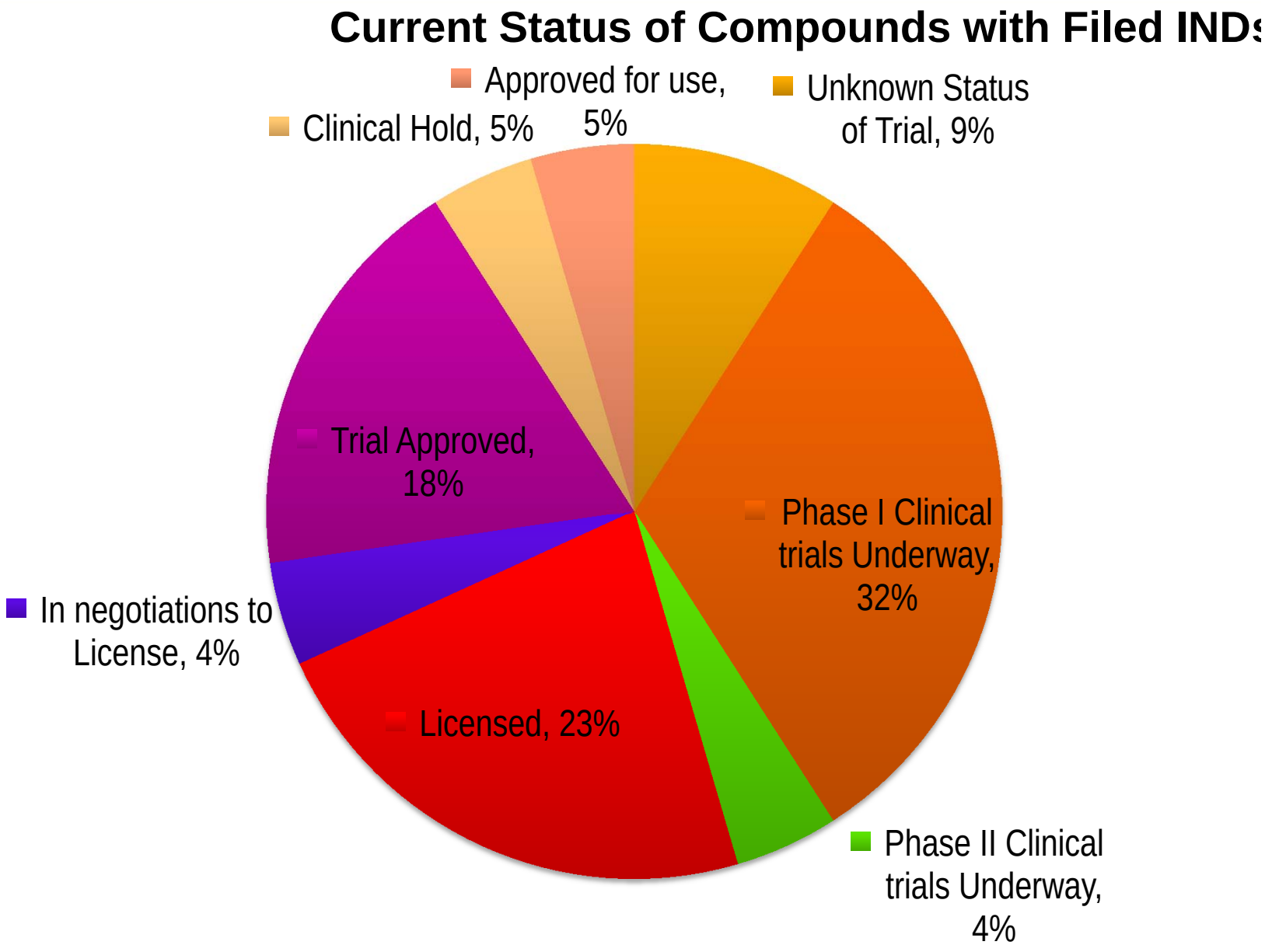
Status of Compounds with Filed INDs Supported by These Contracts That Have Entered the Clinic



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Compounds with Filed INDs Supported by Pharmacology & Toxicology Contracts That Have Entered the Clinic

Phase I

Fenretinide (IV)
FAU
Dimethane sulfonate
PS-341+17-AAG
CDDO
Indenoisoquinolines
STAT3 Decoy
Ad5/3-delta 24-Ovarian
MV-NIS Virus (Myeloma)
EPI-A0001
AdVhAFP AdenoviralVector
Chimeric 11-1F4 monoclonal
Replication-Competent
Herpes Simplex Viral Mutants

Phase II

17-DMAG
Fluorodeoxcytidine/THU

Approved by ODAC

Depsipeptide

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FDA Advisory Committee Recommends Gloucester Pharmaceuticals' Romidepsin (Depsipeptide) for Approval for Cutaneous T-cell Lymphoma

- Cambridge, MA - September 2, 2009 - Gloucester Pharmaceuticals announced today that the FDA's Oncologic Drug Advisory Committee (ODAC) voted 10 in favor with one abstention to recommend approval of romidepsin to treat patients with cutaneous T-cell lymphoma (CTCL).

- A New Drug Application (NDA) for romidepsin in CTCL is under review with the FDA and a Prescription Drug User Fee Act (PDUFA) date of November 12, 2009 has been set.

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Pre-Clinical Imaging Drugs and Technologies

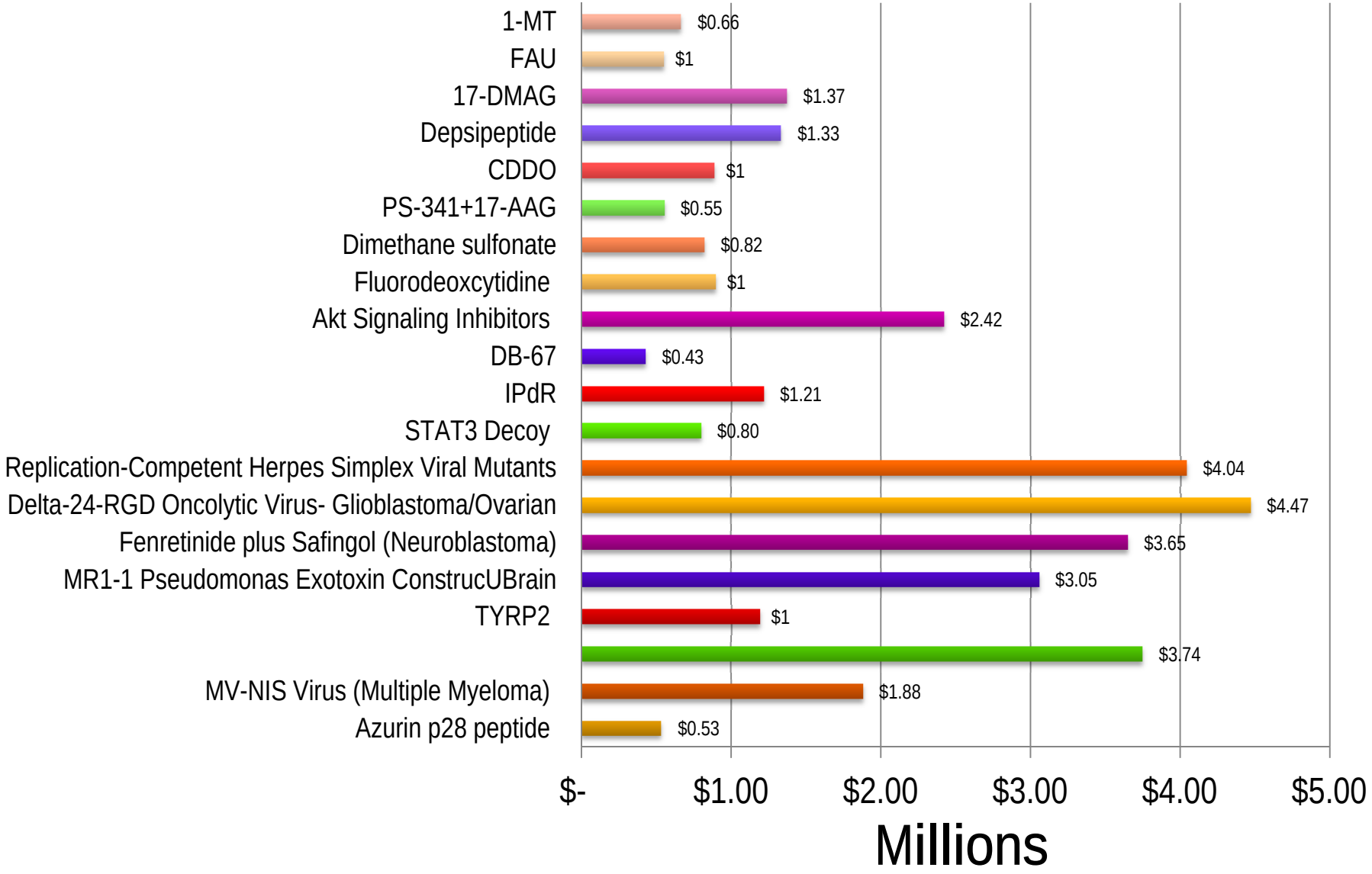
Agents in development

- ^{18}F-d-cytidine
- ^{13}N-gemcitabine
- ^{11}C-SN-38
- ^{11}C-AMT
- ^{18}F-paclitaxel
- ^{18}F-DCFBC
- ^{18}F Her2 Affibody
- ^{18}F-FES
- ^{11}C-acetate
- ^{18}F-FLT
- ^{18}F-MISO
- ^{18}F-Galacto-RGD
- ^{111}In-Herscan
- Gd-chelated albumin

Pre-clinical development (pharmacology and toxicology)

Synthesis and GMP Scale up (including radiolabeling)

NCI Development Costs for Projects to IND Filing



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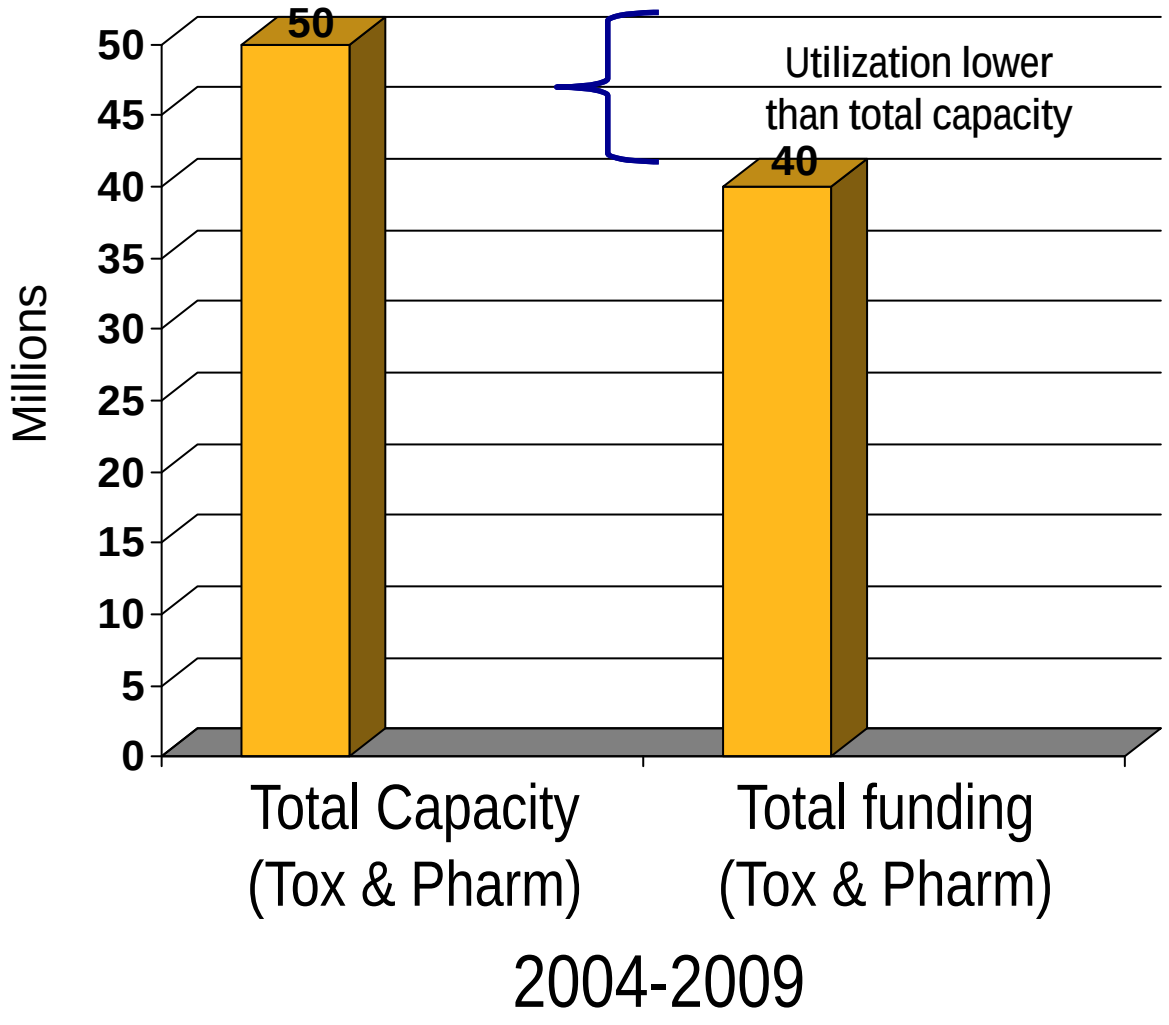
Total Utilization of Contracts is Driven by Portfolio Needs/Capacity and Available Funds



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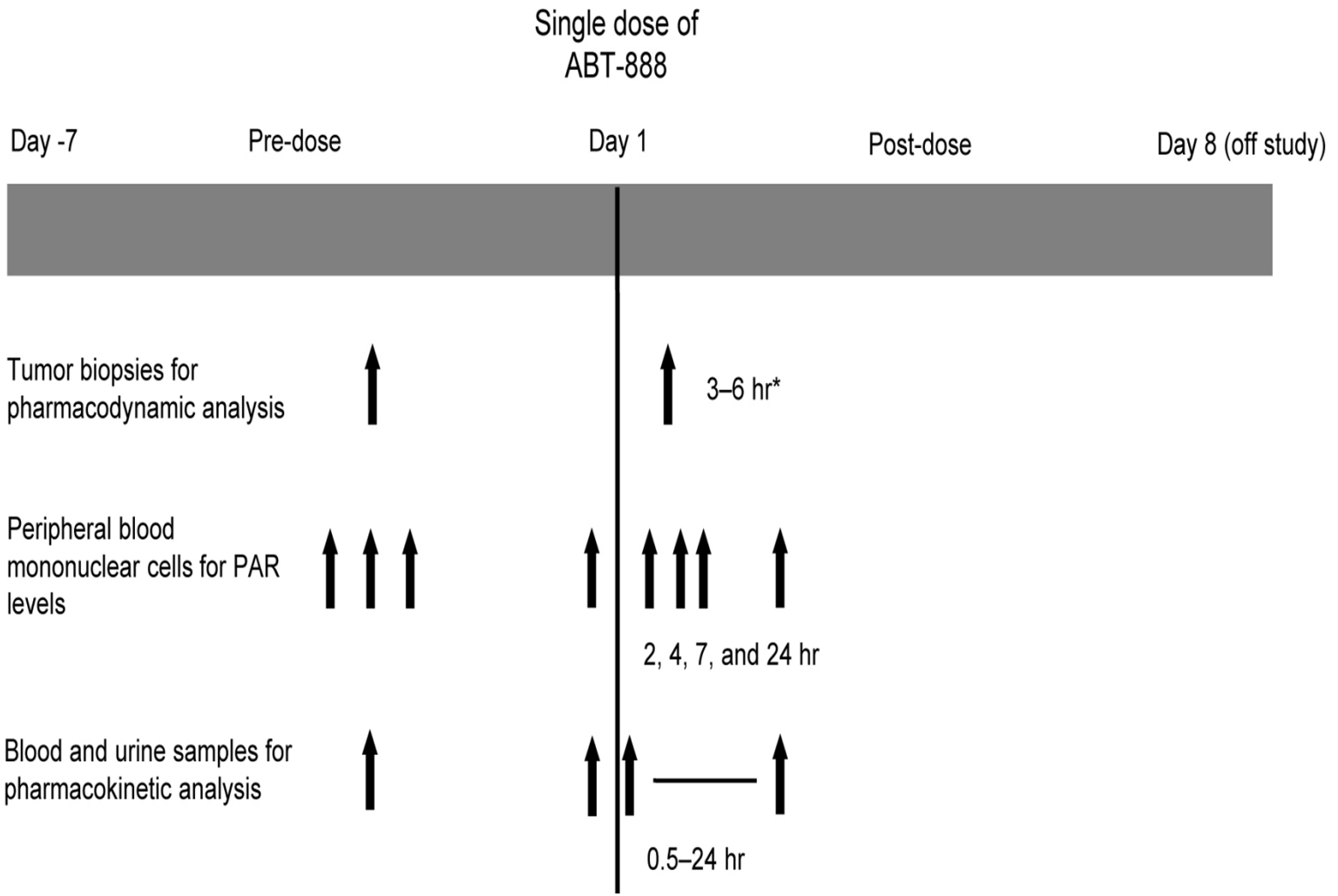
ABT-888 Phase 0 Trial Schema



**Tumor biopsies only if:*

- *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*

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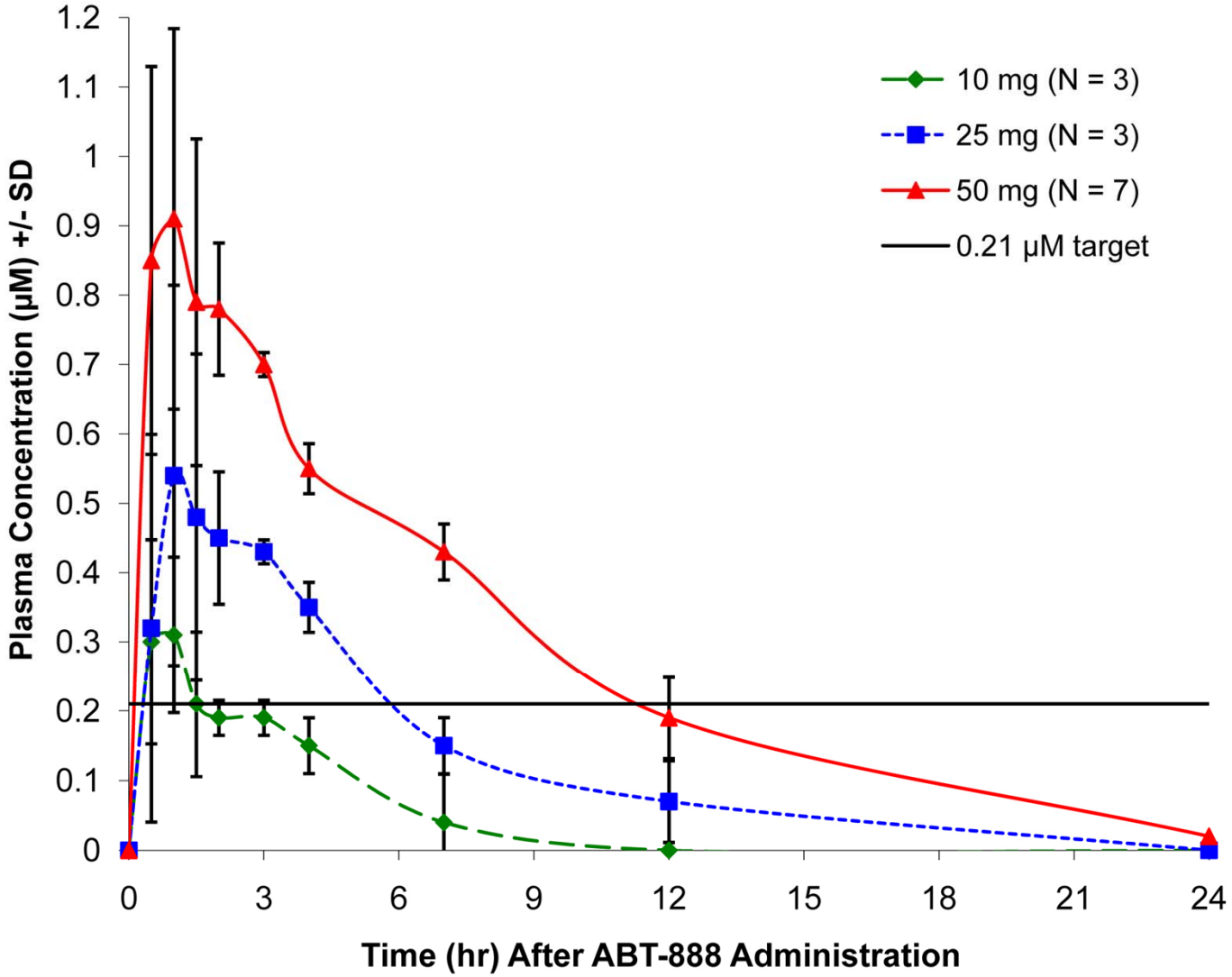
Pharmacokinetics of Single Oral Dose of ABT-888



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Assessment Points for PK and PD studies

- PK/PD modeling used to help optimize dosing regimens, thereby decreasing risk of failure at the final stage.
- TPB Staff will be responsible for providing PK data, PD data (e.g. protein post-translational modifications, RNA expression) and modeling expertise to teams and use these tools for the purpose of assessing exposure effect relationships *in vivo.*
- A variety of PK/PD modeling tools are available to our drug development researchers, and one of these is WinNonlin.

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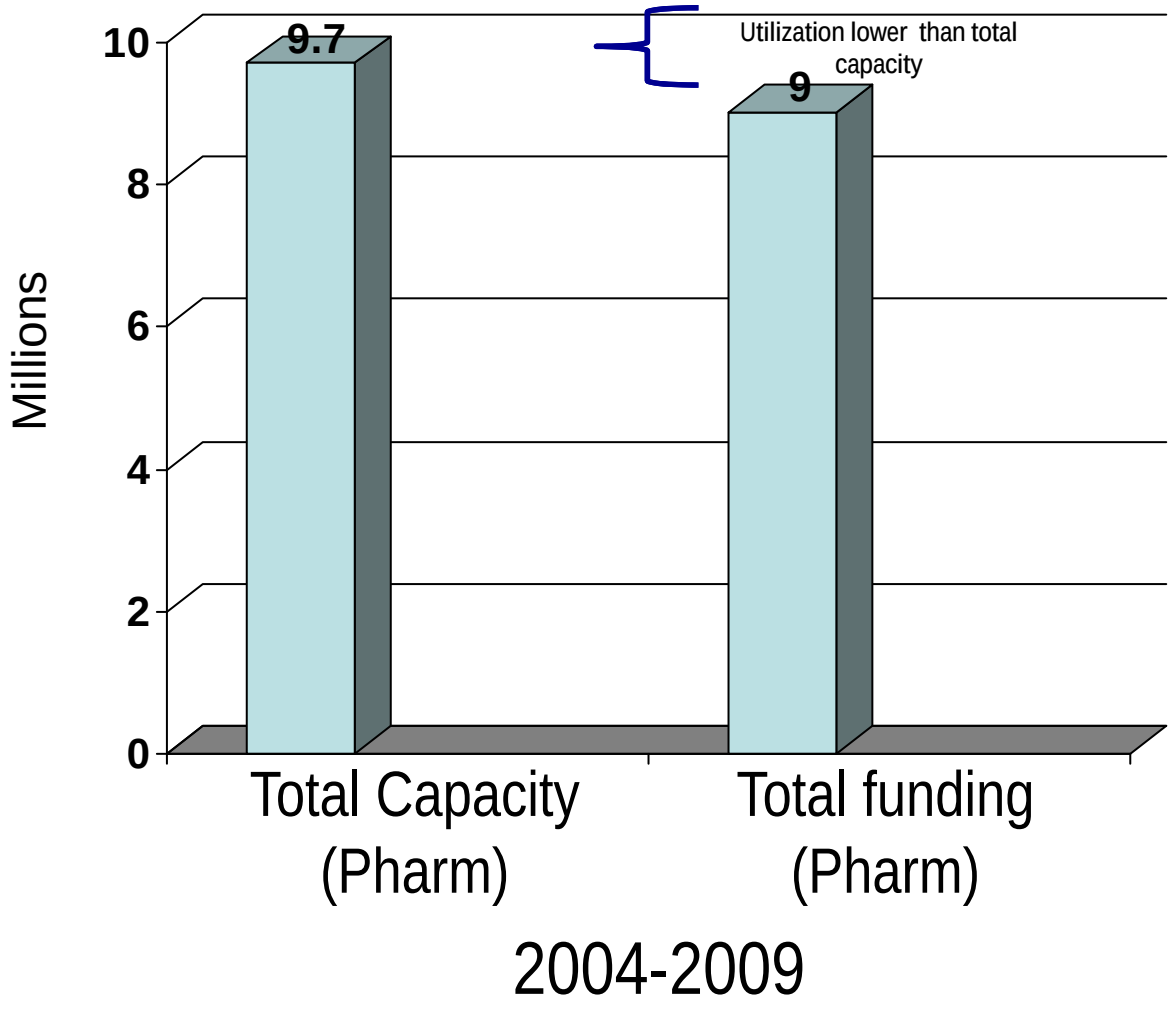
Total Utilization of Contracts is Driven by Portfolio Needs/Capacity and Available Funds



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PROPOSED BUDGET FOR PHARMACOLOGY CONTRACT
Summary of Budget Request and Justification

- Year 1 funding request: $3,364,900
  - ✓Increase over current FY 11 negotiated amount; similar total labor hours
- Total (5-year) funding request: $18,225,384 (estimated 7 awards)
  - ✓*Previous Average yearly total $ 2,679,779*
  - ✓*Requested Average yearly total $ 3,645,077*
- Additional capacity projected to cover the increase in work expected [NExT and NIH], but actual funding per year will depend on portfolio need and available budget

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Questions?

- Overview of Pharmacology and Toxicology Program
- Pharmacology Contract

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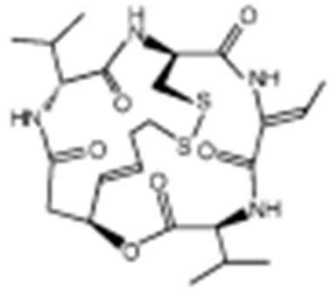
Depsipeptide (Romidepsin)



- Isolated from *Chromobacterium violaceum*
- Induced morphological reversion of H-ras transformed NIH3T3 Cells
- Inhibits proliferation; causes G1 and G2/M arrest
- HDAC inhibitor (HDAC1 and HDAC2)
- Dropped by Fujisawa due to cardiotoxicity in the dog
- NCI was able to separate efficacy from cardiotoxicity so that the drug could move forward in the clinic

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Depsipeptide Efficacy/Cardiotoxicity Study in Mice

- Antitumor Activity (Lox Melanoma sc):
  - ✓ iv Q4D x 3 (20/20 CR) > iv Dx5 (6/20 CR) > iv Dx5 ip Q4D x 3 (2/10 CR) > ip Q3H x 8 Q4D x 3 (None)
- Lethality:
  - ✓ ip Q3H x 8 Q4D x 3 (10/10 2 Dose Levels) >> iv Dx5 (1/10, I Dose Level); None in iv Q4Dx3 and ip Q4Dx3
- Myelotoxicity:
  - ✓ iv Dx5 > iv Q4D x 3 ~ ip Q3H x 8 Q4D x 3 > iv Q4D x 3; ip Q4Dx3 - None
- Cardiotoxicity:
  - ✓ iv Dx5 >> iv Q4D x 3 > ip Q4D x 3

Intermittent Schedule More Active, Less Toxic in the Mouse; also Less Cardiotoxic in the Dog; Permitted FDA Approval of NCI-Sponsored Trials

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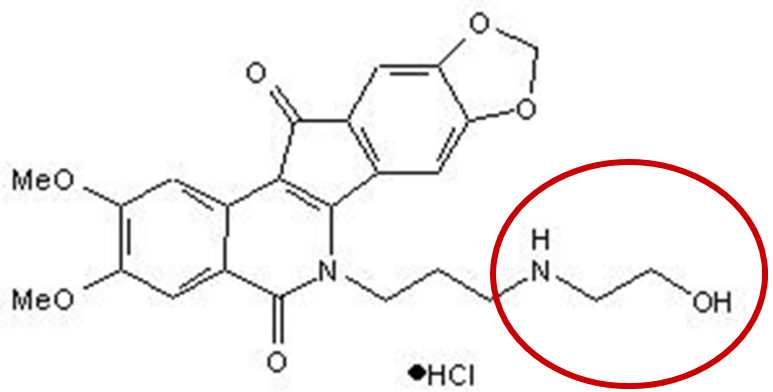
Indenoisoquinolines (Topoisomerase I Inhibitors)

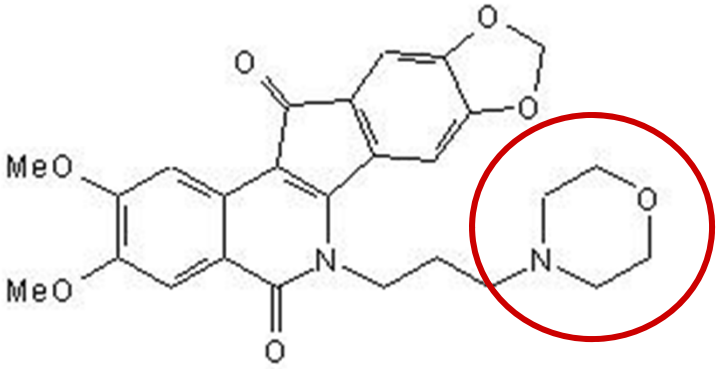
Non-camptothecin Topo I inhibitors with potentially improved pharmaceutical properties over those of clinically available camptothecins.

Phase I Candidates

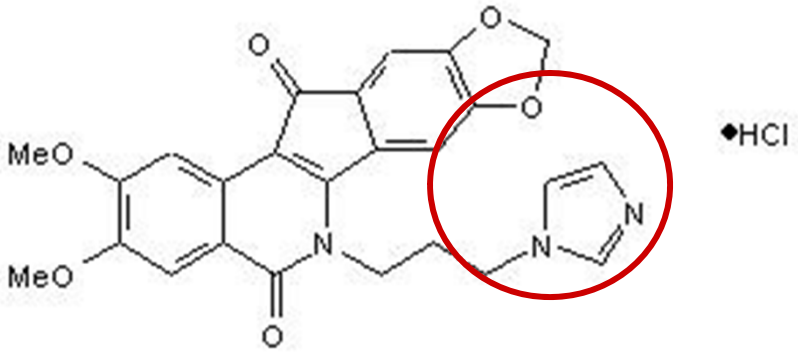
Pommier and Cushman



NSC 706744



NSC 724998; 743400 (HCl Salt)



NSC 725776

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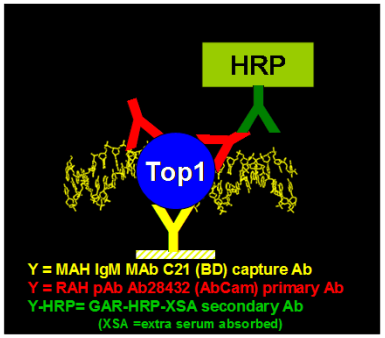
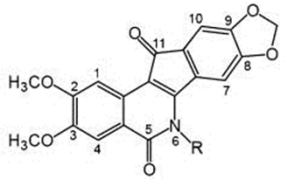
Indenoisoquinoline Proof of Mechanism Randomized Phase I Trial

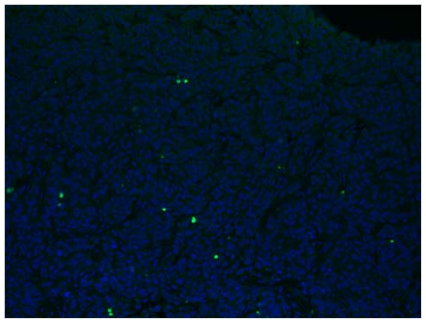




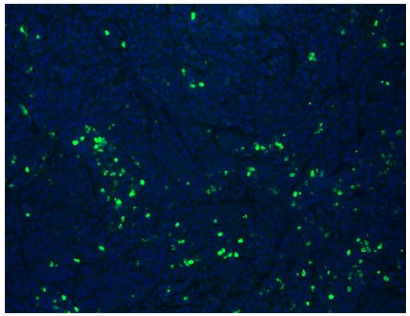
R =

$-CH_3$	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

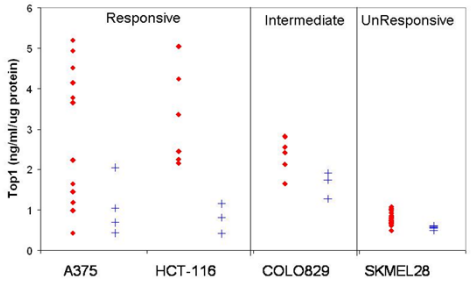
Vehicle



25 mg/kg iv
NSC 724998

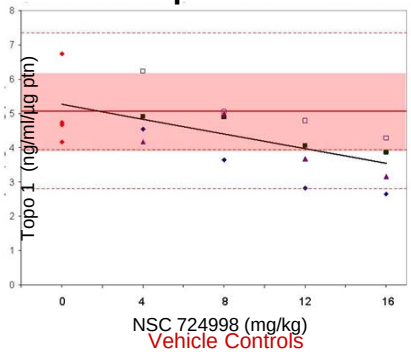


Topoisomerase I Levels in Xenograft Extracts
AAXR2-18, YKR2-39, YPR2-2, AAYR2-17



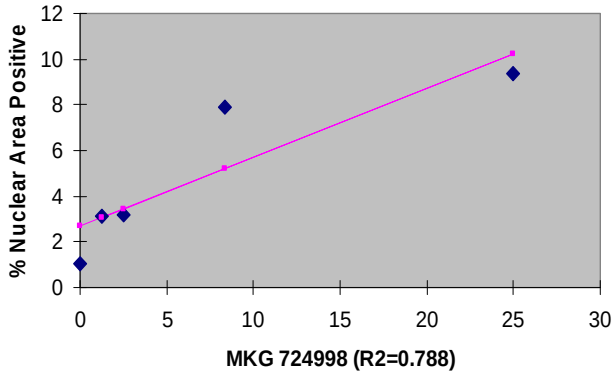
Vehicle Control - ♦
4h Topotecan
(15 MG/KG) treated +

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

Dose Response of gH2Ax to 724998 at +2 Hours A375 Xenograft



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

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Topotecan vs. New Top1 Inhibitors (Indenoisoquinolines) Human vs. Mouse Bone Marrow

Drug	Mouse IC90 (nM) ± SD (range)	Human IC90 (nM) ± SD (range)	Ratio Mouse/Human
Topotecan HCl (Hycamptin)	120 ± 50 (64 - 160)	5.9 ± 5.1 (1.7 - 15)	20.3
NSC 724998	29 ± 12 (18 - 41)	27 ± 14 (7.1 - 45)	**1.1**
NSC 706744	47 ± 6 (47 - 48)	8.1 ± 2.9 (4.4 - 11)	5.8

FDA IND approved 10/20/09

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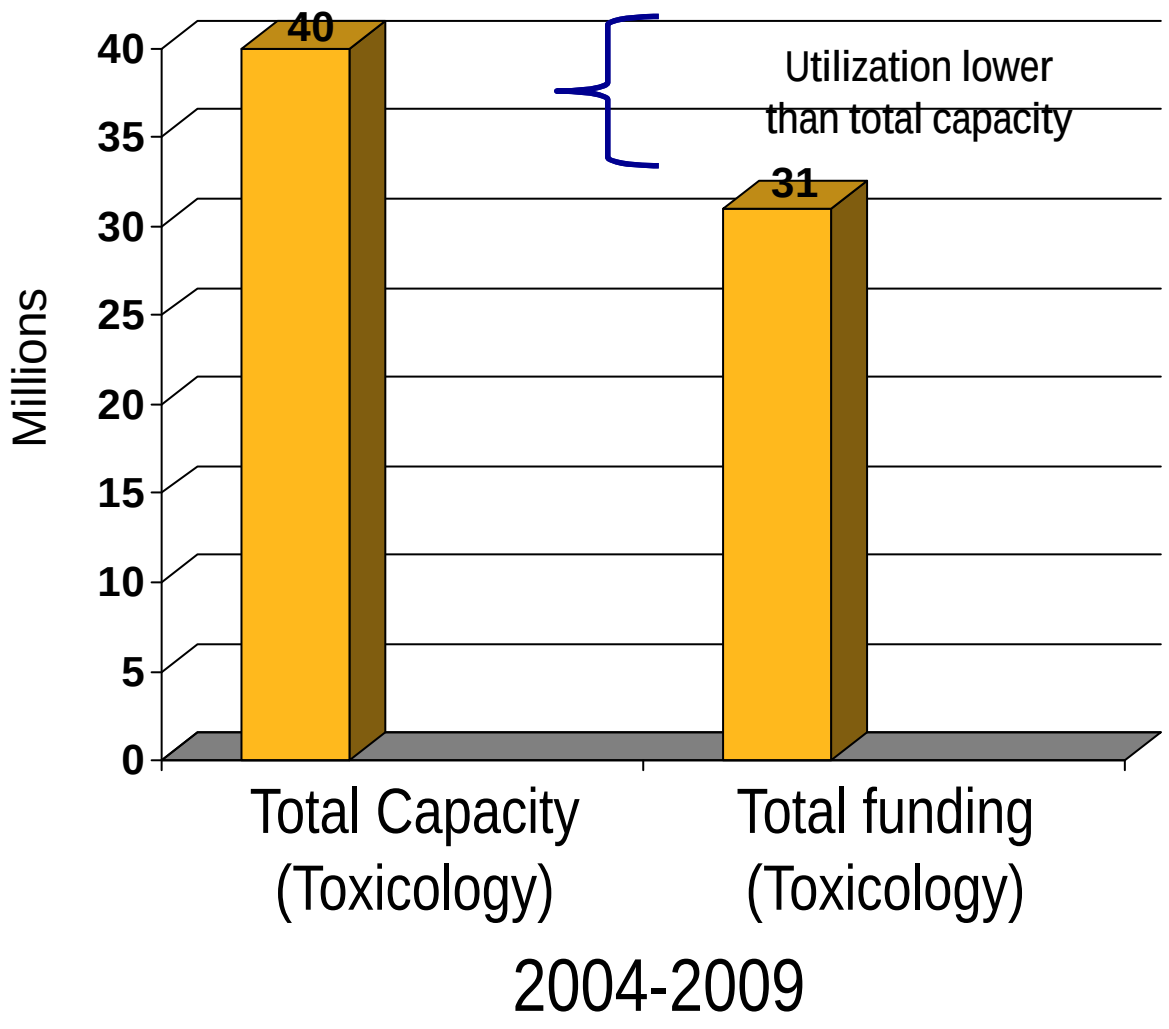
Total Utilization of Contracts Driven by Portfolio Needs/Capacity and Available Funds



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PROPOSED BUDGET FOR TOXICOLOGY

Summary of Budget Request and Justification

- Year 1 funding request: $9,255,189
- Total (5-year) funding request: $ 52,134,254
  - ✓ **Previous Concept negotiated total =** $58,676,230 **(**7 year base)
  - ✓ **There is an increase in the average yearly total requested**
    - ➢ **Previous-** $8,382,319 **average requested per year**
    - ➢ **Current -** $13,033,543 **average requested per year: Increase in costs and anticipated number of NEXT projects**
- Additional capacity needed to cover the increase in work expected [NExT—including imaging drug development--and NIH], but actual funding per year will depend on portfolio needs and available budget

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Summary

- **Pharmacology and Toxicology contracts support an integrated program of PK, PD, efficacy, and safety studies that bridge the gap between target and NME discovery and the development of agents for human clinical trials by academic investigators**
- **Essential part of a newly-unified NCI pipeline for small molecules and biologics**
- **Successful track record of bringing molecules to the clinic, and most importantly to the FDA (depsipeptide—this cycle; pralatrexate—last cycle)**
- **Prioritization of usage by extramural scientists as part of formal Discovery and Development Special Emphasis Panels**
- **Usage expected to increase from ~10-15 to ~15-20 projects per year based on new chemical biology effort; however, usage will depend on available funding**

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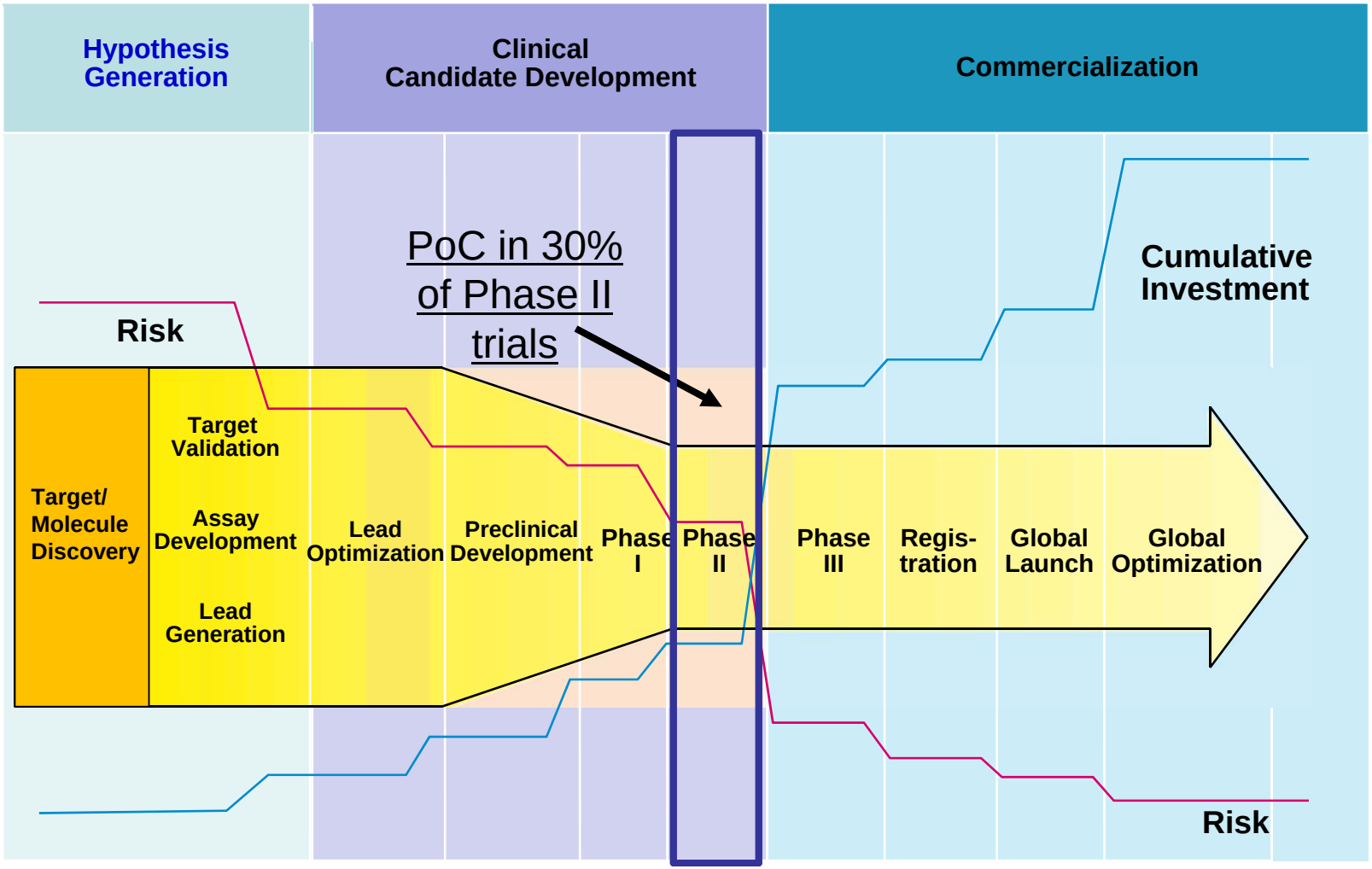
Success: What Will it Look Like?

Transparent, Accountable, Inclusive, & Unified



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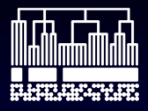
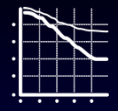
DCTD Division of Cancer Treatment and Diagnosis






Accelerating Cancer Diagnosis and Drug Development

- **Developmental Therapeutics**

Jerry Collins
Joe Tomaszewski
Myrtle Davis
Melinda Hollingshead
Ralph Parchment
Robert Kinders
Giovanni Mellilo
Steve Creekmore

- **Center for Cancer Research**

Yves Pommier
Lee Helman
Bob Wiltrout
Shivaani Kummar

- **DCTD**

Jason Cristofaro
Barbara Mrochowski

- **CTEP**

Jamie Zweibel
Jeff Abrams

- **Cancer Imaging**

Jim Tatum
Paula Jacobs

- **Cancer Diagnosis**

Jim Jacobson
Sheila Taube

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Questions?

- Toxicology Program
- Integrated Drug Development Effort

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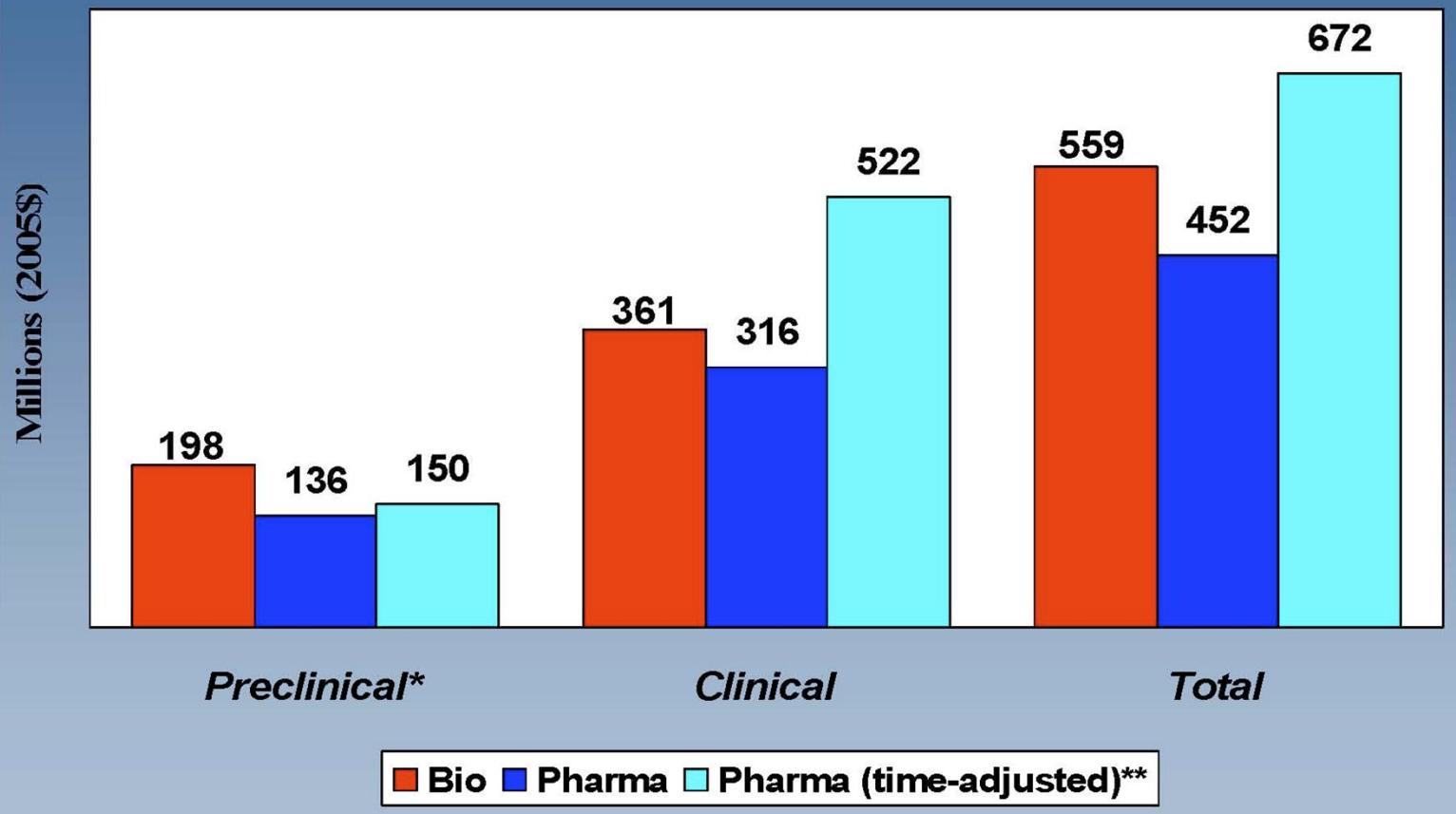
Comparing Development Costs: NCI vs. Pharma

Biopharmaceutical Pre-Approval Out-of-Pocket Cost per Approved New Molecule



* All R&D costs (basic research and preclinical development) prior to initiation of clinical testing

** Based on a 5-year shift and prior growth rates for the preclinical and clinical periods

Source: DiMasi and Grabowski, *Managerial and Dec Econ* 2006, in press

Tufts Center for the Study of Drug Development