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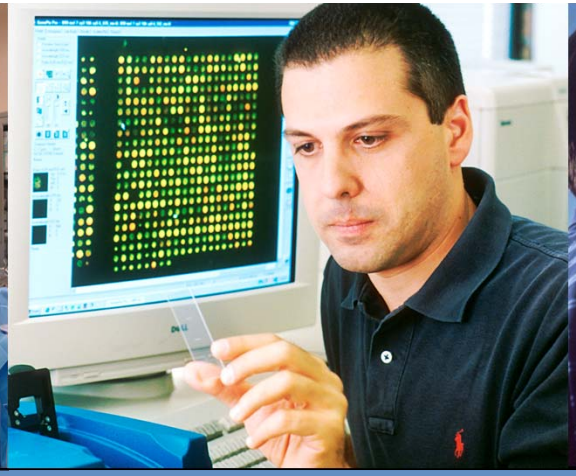
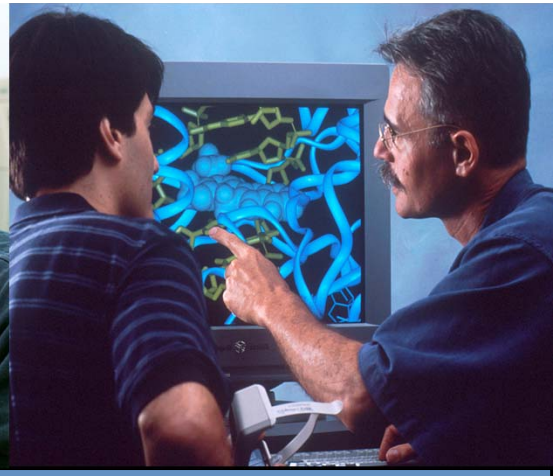

NCI's Experimental Therapeutics Program (NExT): A Status Report

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

National Cancer Advisory Board

Bethesda, MD

June 23, 2010

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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Anticancer Drugs Discovered & Developed by NCI *from Preclinical Stage*

2010	**Sipuleucel (Provenge®)** **? Eribulin**	**1979**	Daunorubicin
2009	**Pralatrexate** **Depsipeptide**	**1978**	Cisplatin
2004	**Cetuximab**	**1977**	BCNU
2003	**Bortezomib**	**1976**	CCNU
1998	Denileukin diftitox	**1975**	Dacarbazine
1996	Topotecan Gliadel® wafer	**1974**	Doxorubicin Mitomycin C
1995	All-trans retinoic acid	**1973**	Bleomycin
1992	2-chlorodeoxyadenosine Paclitaxel Teniposide	**1970**	FUDR Mithramycin Mitotane
1991	Fludarabine phosphate Pentostatin	**1969**	Cytarabine Procarbazine
1990	Hexamethylmelanime Levamisole	**1964**	Melphalan Actinomycin D
1989	Carboplatin	**1963**	Vincristine
1988	Ifosfamide	**1962**	5-FU
1987	Mixtoxantrone	**1961**	Vinblastine
1983	Etoposide	**1959**	Cyclophosphamide Thiotepa
1982	Streptozotocin	**1957**	Chlorambucil

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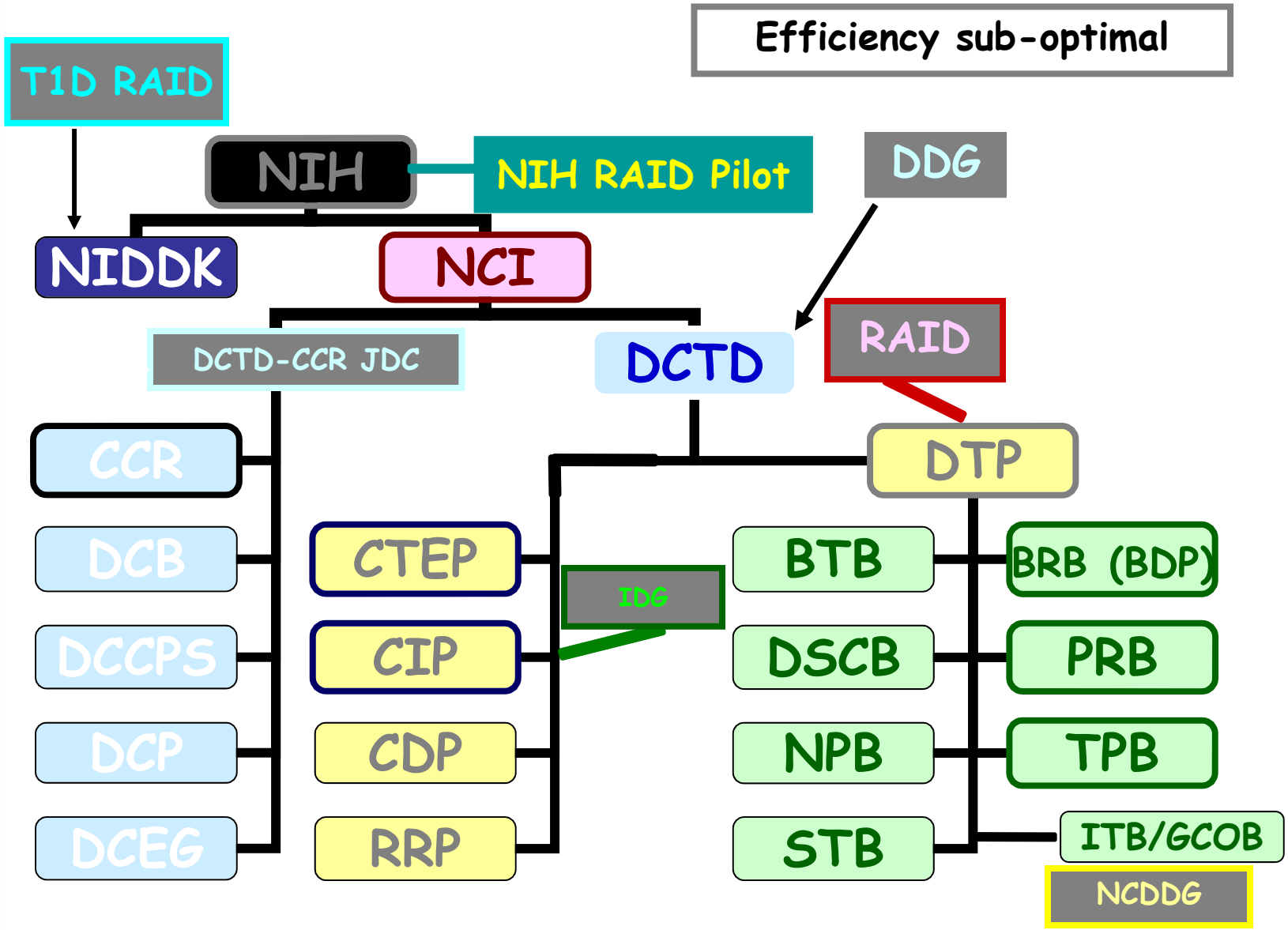
Drug Development Programs: NCI & NIH



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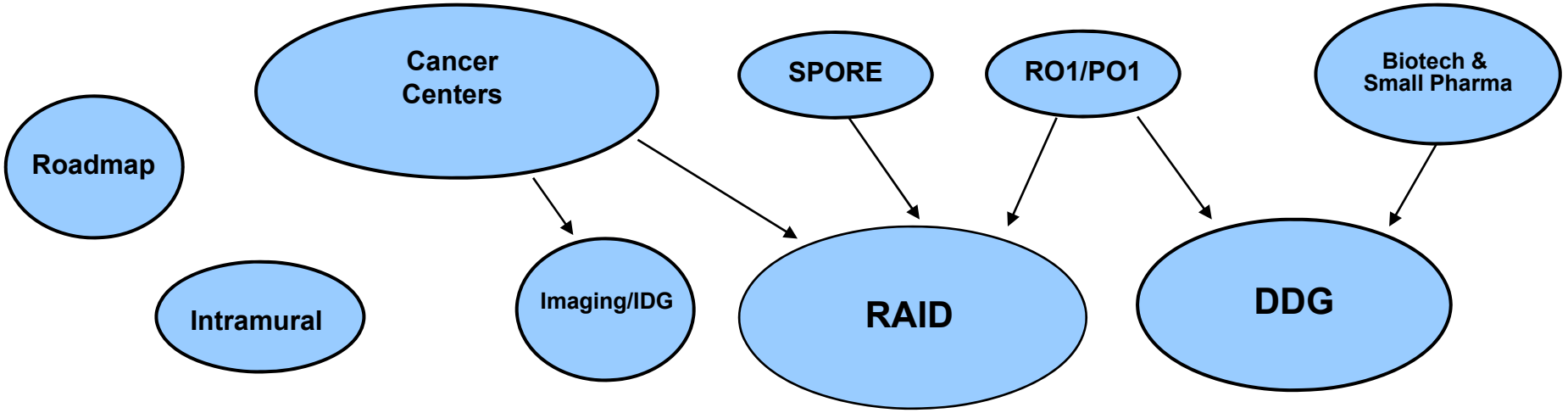
Decentralized NCI Drug Development

- **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?)

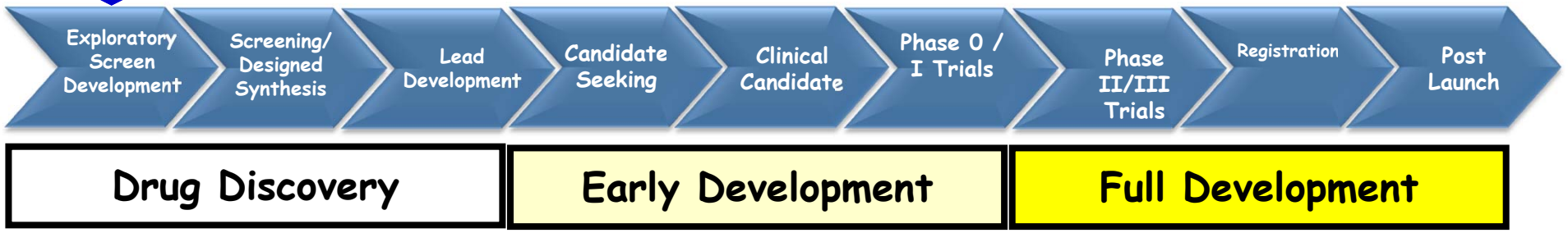
Transformation of the NCI Therapeutics Pipeline



CBC Created

The NCI Experimental Therapeutics (NExT) Pipeline:

Target discovery through early stage clinical trials



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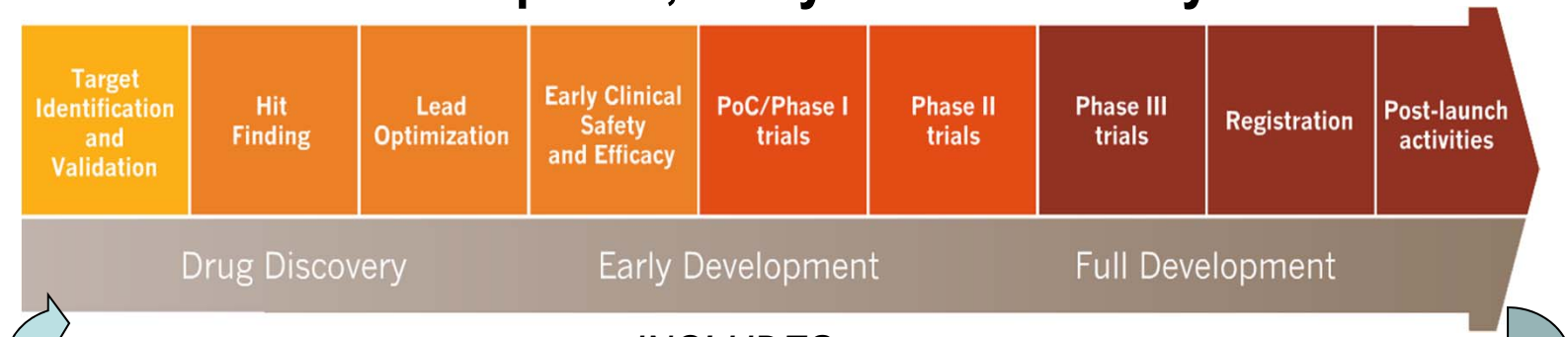
Where Did We Need to Go?

Rapid translation of discoveries into public health benefits

NCI Experimental Therapeutics Program: Unified Discovery & Development

A single pipeline for all therapeutic development resources: One Pipeline, Many Points of Entry



Targets ⟷ **Therapeutics**

INCLUDES

- Investigational drugs and biologics
- Investigational imaging agents
- Academic & Biotech & Pharma projects
- Includes Phase 0, I and II Programs

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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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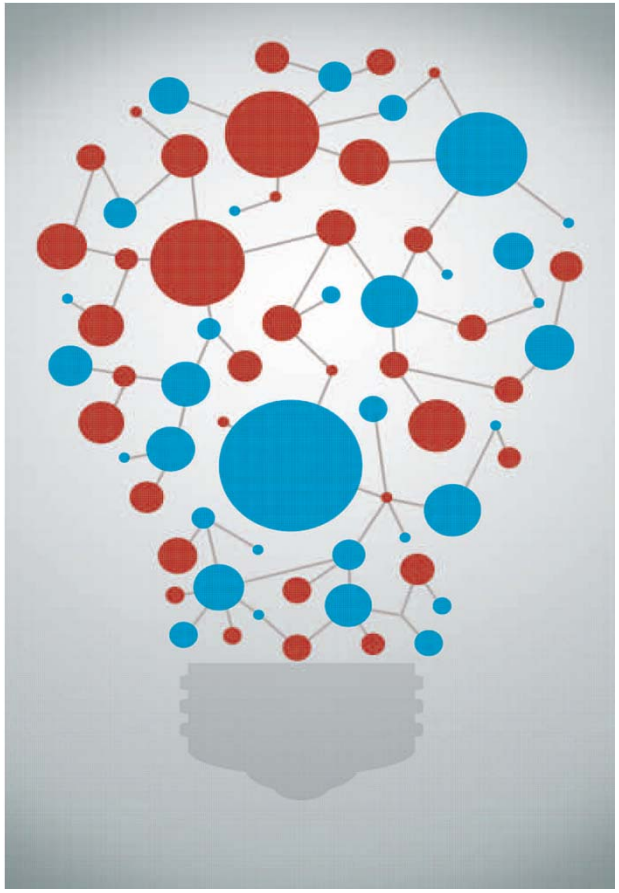
Chemical Biological Consortium



- **Comprehensive Chemical Biology Screening Centers (4)**
  - ✓ Identify targets, develop target assays and adapt these assays to HTS platforms, screen numerous compounds against a variety of different assays each year, and provide Structure- Activity Relationship (SAR) analysis and support chemistry
- **Specialized Application Centers (3)**
  - ✓ Provide expertise and experience in specific technologies needed to successfully develop and implement complex and technically difficult assays that may not be amenable to HTS
- **Chemical Diversity Centers (4)**
  - ✓ Capable of applying medicinal and synthetic chemistry to advance hits to lead status
- **Other (3)**

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Chemical Biological Consortium: Members

CCBSC	❖ Sanford Burnham Inst for Med Res	John C. Reed, Kristiina Vuori
	❖ Southern Research Institute	W. Blaine Knight
	❖ SRI International	Lidia Sambucetti
	❖ Univ. North Carolina – Chapel Hill	Stephen Frye
	❖ NIH Chemical Genomics Center	Chris Austin
SAC	❖ University of California, SF	James A. Wells
	❖ University of Pittsburgh DDI	John Lazo
	❖ Emory University	Haian Fu, Fadlo Khuri, Dennis Liotta
CDC	❖ Georgetown University	Milton L. Brown
	❖ Vanderbilt Institute of Chem Biol	Gary Sulikowski, Alex Waterson
	❖ University of Minnesota	Gunda I. Georg
	❖ University of Pittsburgh	Donna Huryn
Others	❖ GVK Biosciences	Sreenivas Devidas
	❖ Starks Associates, Inc.	David Starks
	❖ NCI Intramural Chemical Biology	
	❖ Affiliate Investigators	

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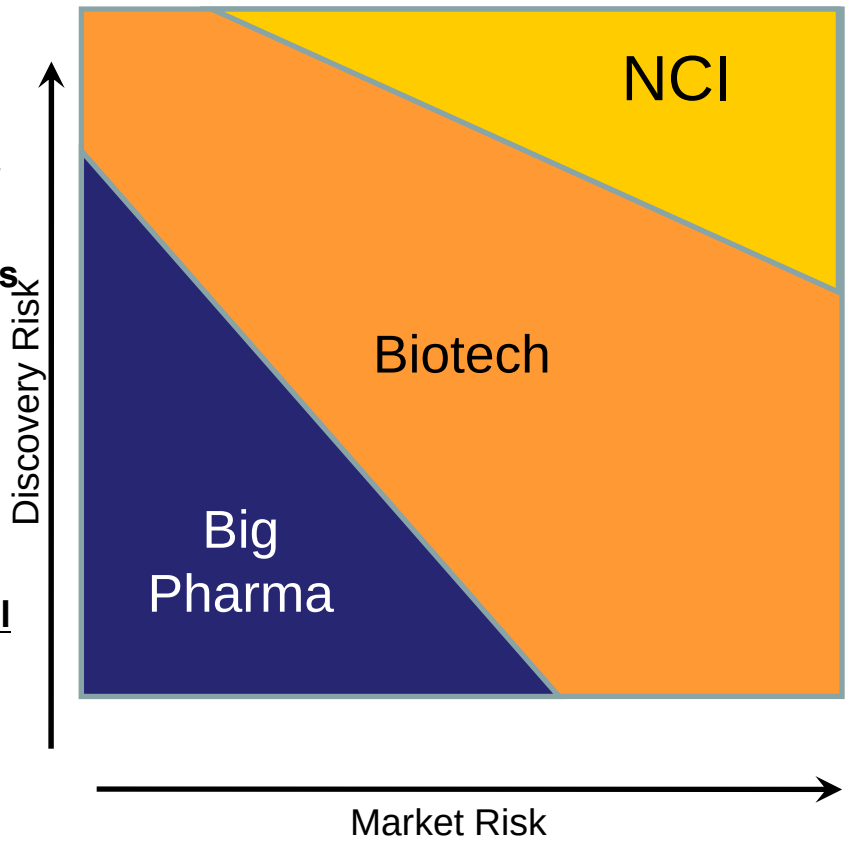
Chemical Biology Consortium Vision

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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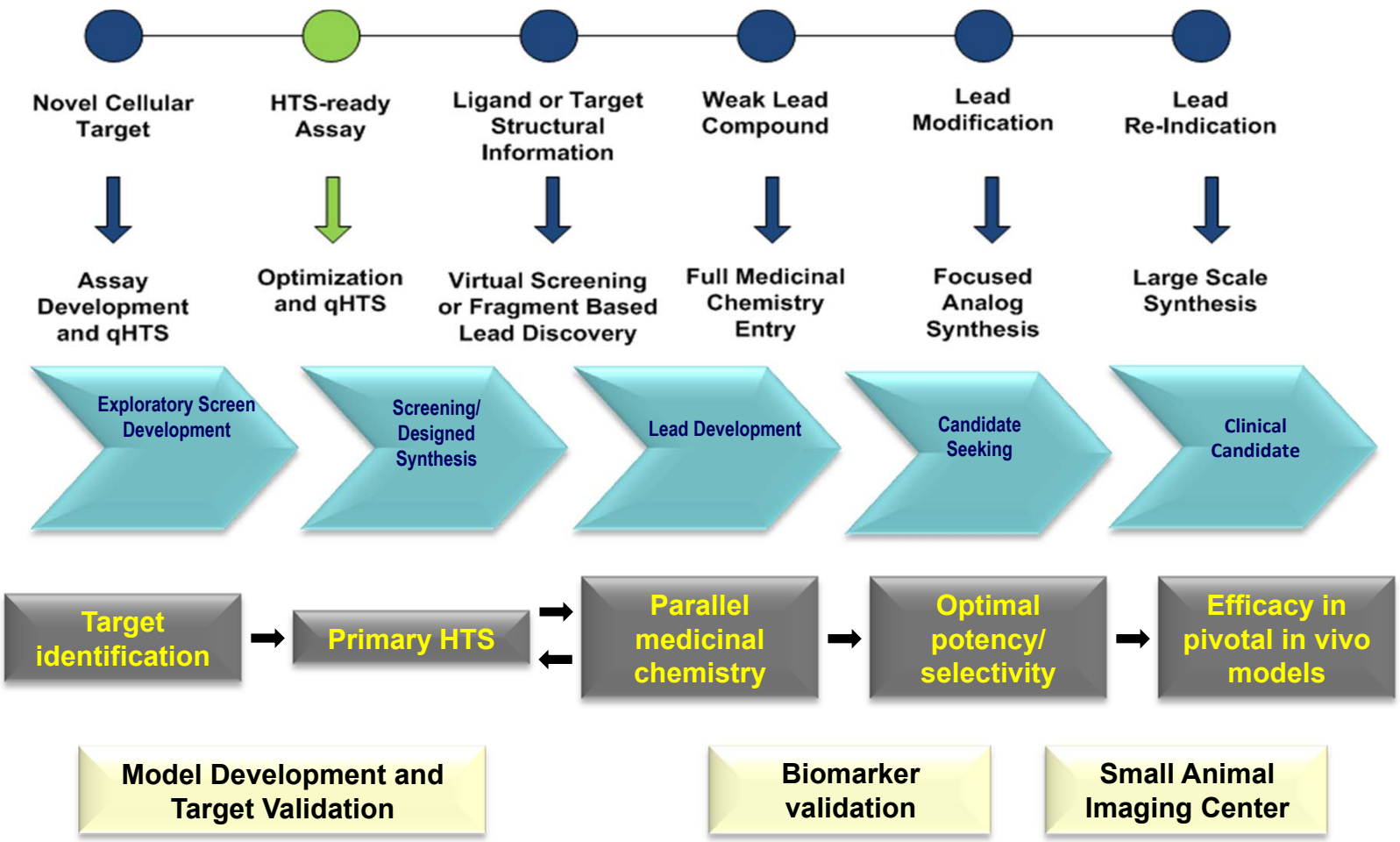
Multiple Entry Points into the NExT



Adapted with permission from the NIH Chemical Genomics Center

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Purpose and Scope of CBC Consortium Agreement

- **CBC participants sign a Consortium Agreement.**

  This agreement details:
  - **How CBC participants ensure timely entry of deliverable data into the database**
  - **How CBC participants manage IP ownership to ensure that other members of the consortium have adequate access to data for development**
  - **The preferred mechanism by which CBC participants manage joint inventions**
  - **CBC participant responsibilities to share research resources developed under the contract with the broader research community**

The Consortium Agreement addresses:

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NCI Experimental Therapeutics

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

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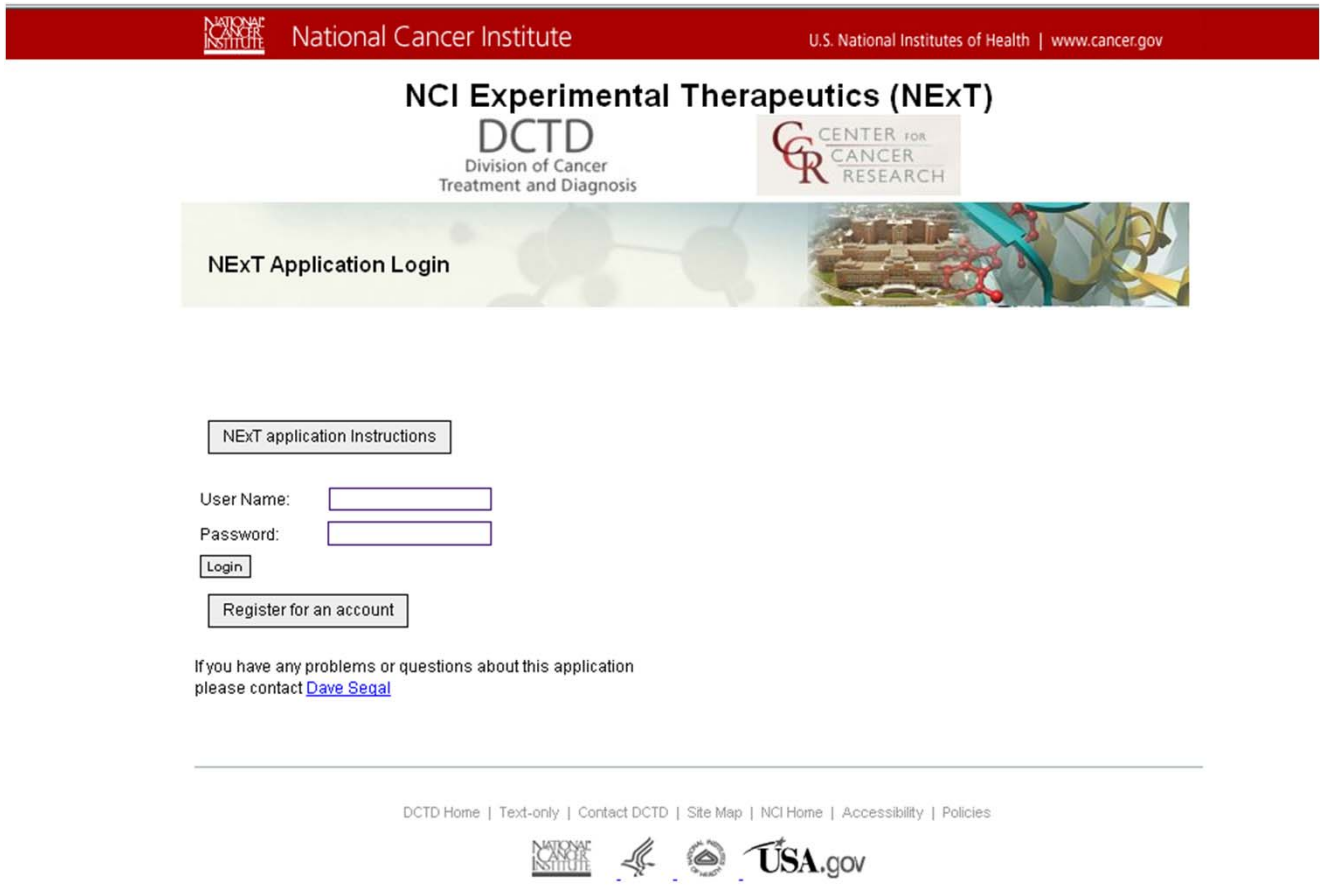
NExT Application Process

Extramural scientists may propose targets, screens, or molecules for entry into the NExT pipeline; quarterly receipt dates

https://dctd.cancer.gov/nextapp or
https://dctd.cancer.gov/nextregistration



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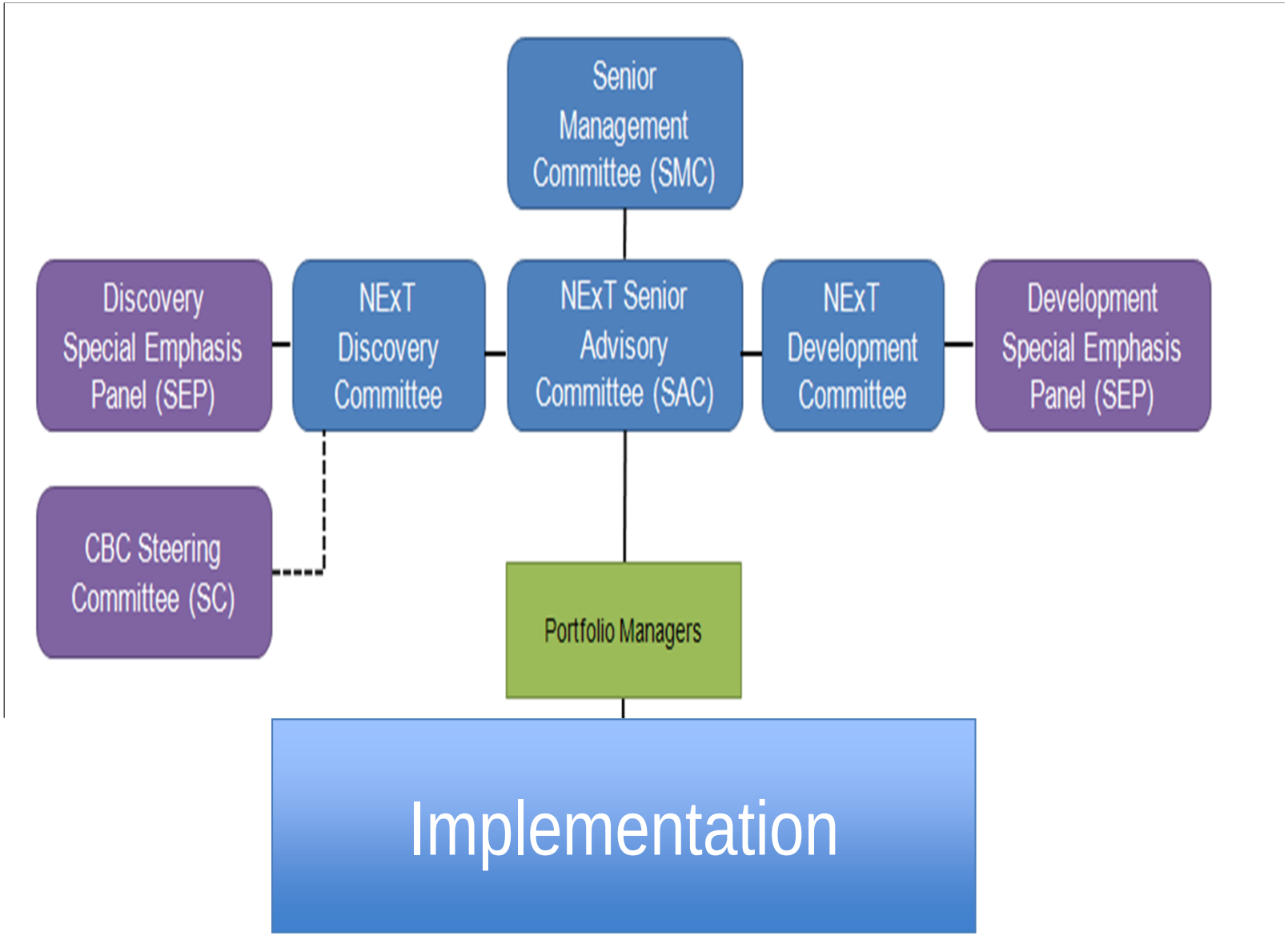
How Are Projects/Compounds Selected?



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Prioritization Process Used To Ascertain Which Compounds To Move Forward?

- This selection 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
- This evaluation process is also to provide guidance about the priority utilization of the capacity – based resources provided by NCI

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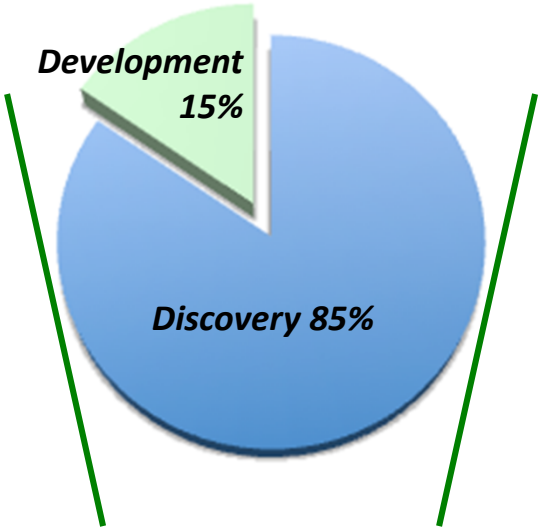
NExT Cycle 1: September 2009

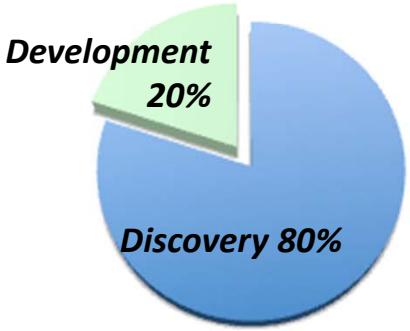
Total Number of Applications:

52



Top Tier Applications:

10



Applicant PI	Center	Project
John Frangioni	Beth Israel Deaconess Medical Center	A NIR Fluorophore for Clinical Translation of Image-Guided Oncologic Surgery
Lance Leopold	Ascenta Therapeutics	AT-406, a pan, oral IAP Inhibitor, for the Treatment of Cancer
John Reed	Sanford-Burnham	Chemical Modulators of Autophagy for Cancer Therapy
Jennifer Grandis	University of Pittsburg	Discovery and Optimization of Inhibitors of STAT3 Activation
Bert Vogelstein	Johns Hopkins University	MTAP Isogenic Drug Screen in DLD-1 Colorectal Cancer Cell Lines
Raymond Deshaies	California Institute of Technology	Development of Small Molecule Inhibitors of the AAA ATPase p97
Anne Bresnick	Albert Einstein School of Medicine	Development of S100A4 Inhibitors for the Prevention of Metastatic Disease
Shelton H. Earp	Univ North Carolina-Chapel Hill	Developing Small Molecule Mer Inhibitor Candidates for ALL
James Hsieh	Washington University-St. Louis	Optimization of Lead Small Molecule Inhibitors of Taspase 1 for Cancer Therapeutics
John Reed	Sanford-Burnham	Chemical Activators of the PML Tumor Suppressor Pathway

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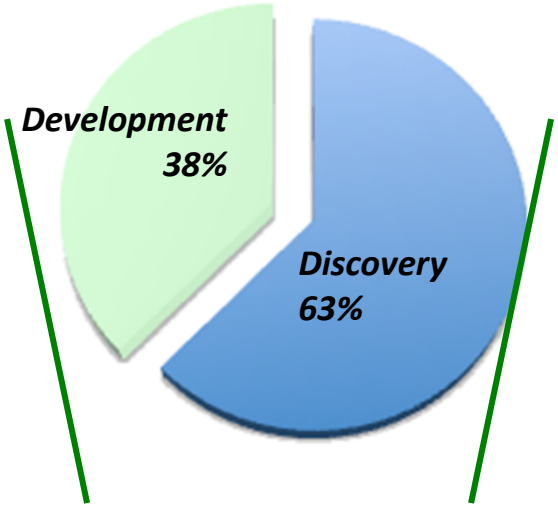
NExT Cycle 2: November 2009

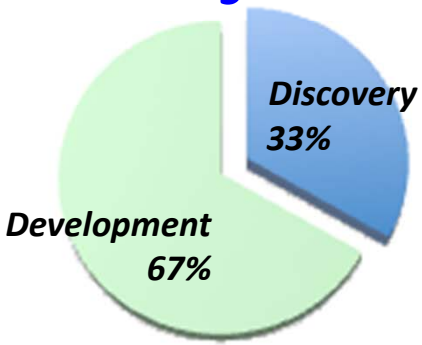
Total Number of Applications:

53



Top Tier Applications:

9



Applicant PI	Center	Project
Richard B. Roden	Johns Hopkins University	Production of an HPV16 L2E6E7 Vaccine with GPI-0100 Adjuvant for the Treatment of HPV-Associated Disease
Ari Melnick	Joan & Sanford I Weill Medical College	Clinical Translation of a BCL-6 Inhibitor
Dario C. Altieri	University of Massachusetts Medical School	Clinical Development Of Mitochondria-Targeted Hsp90 Antagonists, Gamitrinibs
Donald W. Kufe	Dana-Farber Cancer Institute	The Development of a Novel Anti-Cancer Agent Against the MUC1 Oncoprotein
Bryan Leigh	Tracon Pharmaceuticals	Development of TRC105 as a Novel Anti-angiogenic Monoclonal Antibody
John Kovach	Lixte Biotechnology Holdings, Inc.	Novel Inhibitor of PP2A Potentiates Chemotherapy
Chi Dang	Johns Hopkins University School of Medicine	Development of FX11, a Lactate Dehydrogenase A (LDHA) Inhibitor, as an Anti-neoplastic Agent
Cyrus Vaziri	University of North Carolina at Chapel Hill	Inhibition of the DNA Repair Enzyme Rad18 as a Novel Strategy for Sensitizing Tumor Cells to Platinum Drugs
Edward V. Prochownik	Children's Hospital of Pittsburgh	Evaluation of Rationally-Designed Small Molecules Directed Against the c-Myc Oncoprotein

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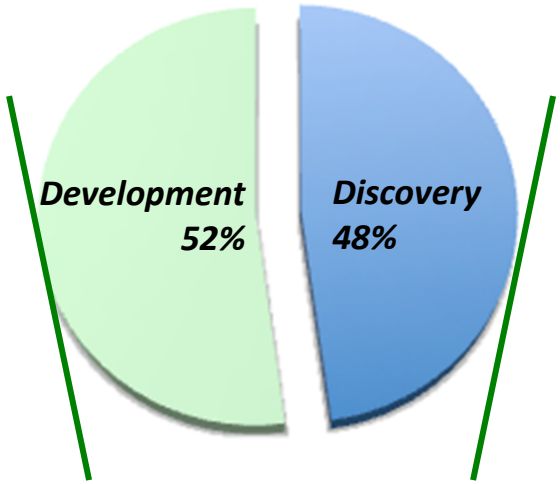
NExT Cycle 3: February 2010

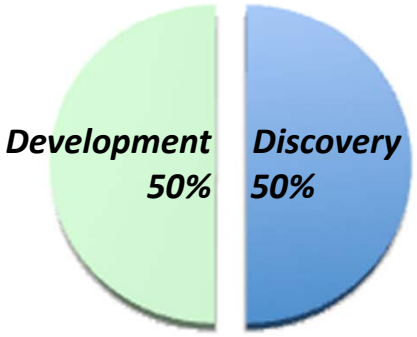
Total Number of Applications:

23



Top Tier Applications:

6



Applicant PI	Center	Project
Thomas Waldmann	National Cancer Institute	Anti-IL-15 Receptor Antibody Therapy of Celiac Disease Associated Lymphoma
Raveen Marapaka	MedImmune	HA 22 Randomized PIII-HCL
Thomas Davis	Celldex Therapeutics, Inc.	Clinical Development of CDX-1308 Vaccine Regimen
Marianne Sadar	BC Cancer Agency/British Columbia Cancer Agency	IND-Directed Preclinical Studies of EPI-001 for Prostate Cancer Treatment
Shyam Biswal	Johns Hopkins University	Development of NRF2 Inhibitors for Cancer Chemotherapy
Stephen Fry	University of North Carolina at Chapel Hill	Assay Development and Hit Discovery for IDH1-based Approaches Targeting Glioblastoma

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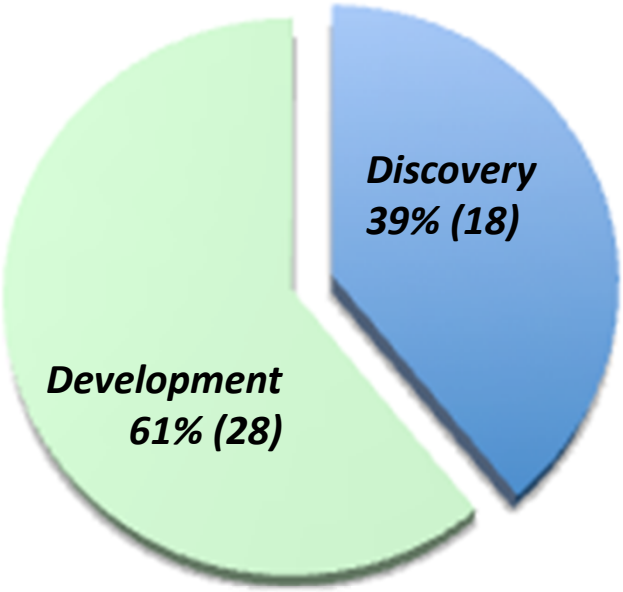
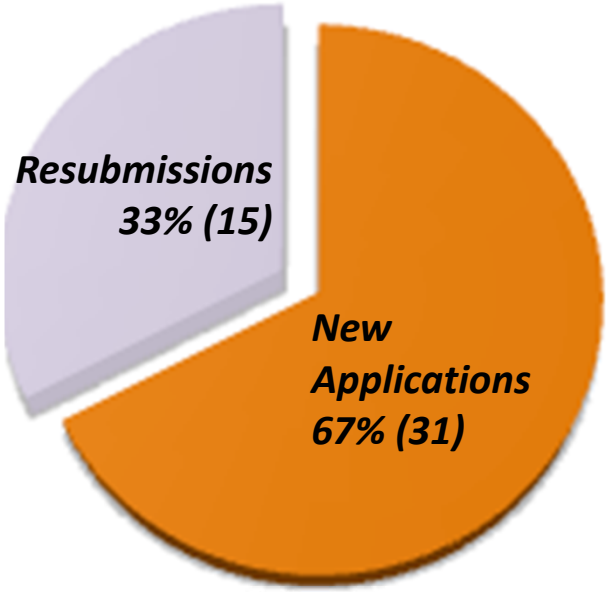
NExT Cycle 4: May 2010

Total Number of Cycle 4 Applications:

46





Total Number of Cycles 1 to 4 Applications: 174

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NCI RAID and NExT Programs: Statistics

	NCI RAID	NExT
Time Period	9.5 yrs	10 months
No. Applications	428	128 (174 [2])
No. Approved	137	25
% Approved	32.0	19.5
Discovery Apps [1]	(0)	14
Development Apps [1]	137	11

[1]Approved Applications

[2] Total number Cycles 1-4

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Goals of the NCI's Therapeutics Platform

- Develop 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
- Move discoveries from TCGA into drug discovery
- Support development of biological agents
- Success measured by:
  - IND filings (first in human studies)
  - Licensing of novel therapeutics
  - Improved cancer therapeutics success rate
  - Approved NDA's developed from academic and small biotech research

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Top 20: Immunotherapy Workshop Reagent List

Input from AAI and its members helped compile this list; NCI now acquiring reagents

- IL-15
- Anti-PD-1, Anti-B7-H1
- IL-12
- Anti-CD40, CD40L
- IL-7
- CpG
- 1-Methyl Tryptophan
- Anti-CD137 (anti-4-1BB)
- Anti-TGF-beta
- Anti-IL10 receptor, Anti-IL10
- Flt-3 Ligand
- TNF Receptor (GITR)
- CCL-21 Adenovirus
- Mono-P Lipid A (MPL)
- Poly IC, Poly ICLC
- Anti-OX40L
- Anti-B8H4
- Resiquimod,852A
- LIGHT, LIGHT vector
- Anti-lymphocyte activation Gene -3 (LAG-3)

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Prioritized Needs of the Immunotherapy Community

Agents with High Potential for Use in Cancer Therapy and Infrastructure

AGENT	FUNCTION	AVAILABILITY
IL-15	T-cell growth factor	**NCI-in production; NCI IND approved**
Anti-PD-1	T-cell checkpoint inhibitor	Commercial
IL-12	Vaccine adjuvant	**NCI—in hand**
Anti-CD-40	APC stimulator	Commercial
IL-7	T-cell growth factor	**NCI-in production**

GMP 80L fermentation of rhIL-15: Production and pooling of several of products from several fermentations needed for one 1gram lot of rhIL-15

Cancer Immunotherapy Network:

- **established to stimulate multisite phase I and II clinical immunotherapy trials across a range of malignancies**
- **bring novel immunotherapy agents, combinations, and approaches to the clinic**
- **up to 25 institutions**
- **standardized immunomonitoring and biomarker studies**
- **funded end of 2010**
- **NCI will produce reagents that lack a commercial sponsor**

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ch14.18 (anti-GD2 monoclonal antibody)

- Over 99% of neuroblastomas express GD2
- ch14.18 demonstrated preclinical activity in neuroblastoma cell lines and xenografts
- ch14.18 manufactured by NCI-DCTD-DTP for Phase I, II, and III clinical trials
- NCI's Children's Oncology Group conducted ANBL0032 phase 3 trial to determine efficacy of ch14.18 for high-risk neuroblastoma

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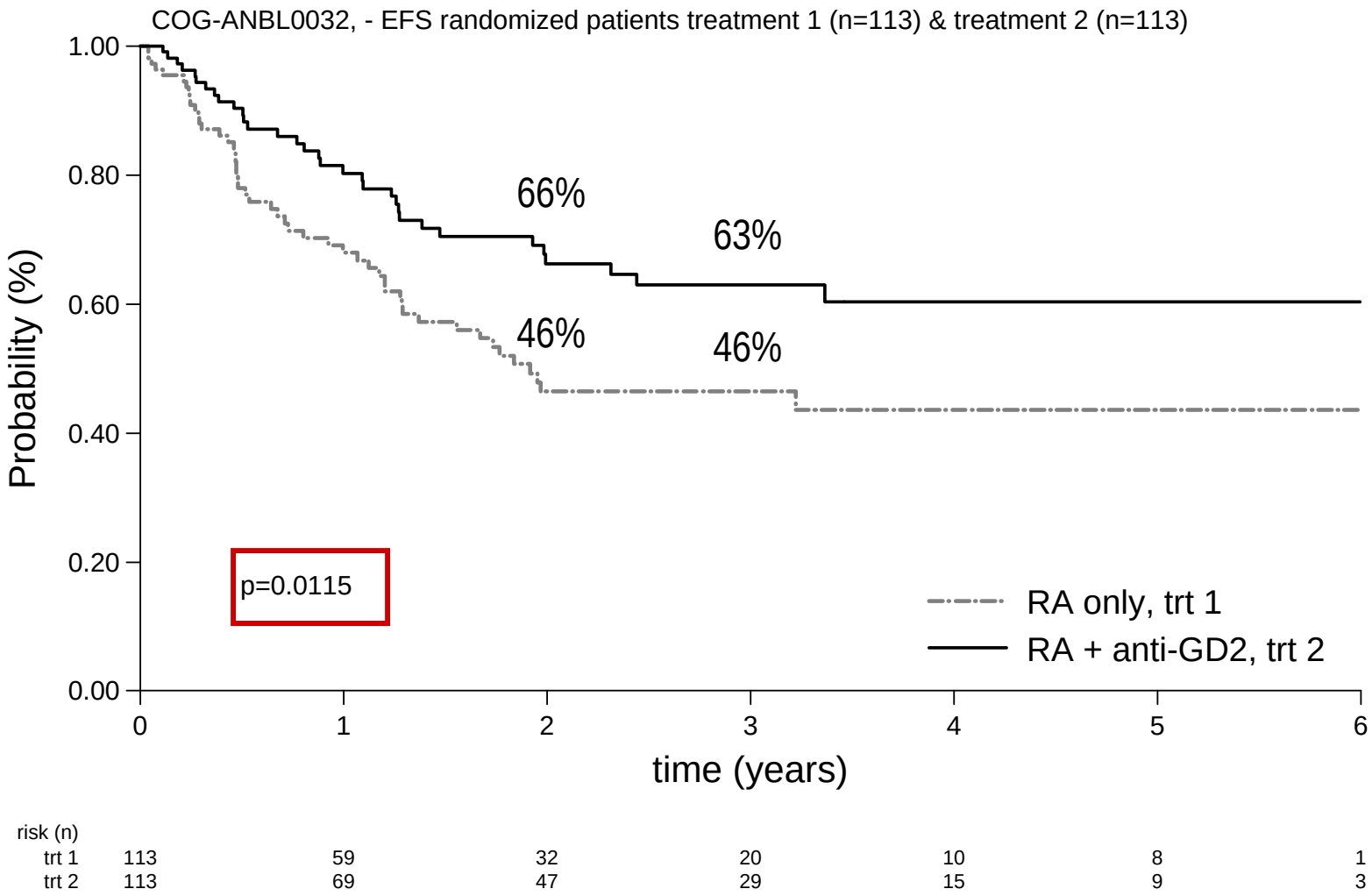
ch14.18 Immunotherapy Improves Survival for Children with High Risk Neuroblastoma



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ch14.18 for Neuroblastoma

- **Results define a new standard therapy for children with high-risk neuroblastoma who have completed autologous stem cell transplantation**
- **NCI is manufacturing additional ch14.18 to make it available through COG clinical trials for all children who meet eligibility criteria, and, in consultation with FDA, to complete registration trial**
- **NCI is taking the necessary steps to license ch14.18 for high-risk neuroblastoma**

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Recently-Approved NExT Small Molecule Projects

- **Targeting mutant IDH1 in glioblastoma multiforme**
- **STAT3 in head and neck cancer**
- **Mer kinase as a target in pediatric leukemia**

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UNC LINEBERGER COMPREHENSIVE CANCER CENTER
NC CANCER HOSPITAL

UNC ESHELMAN SCHOOL OF PHARMACY

Targeting mutant *IDH1* in glioblastoma

- Heterozygous mutations in isocitrate dehydrogenase-1 occur in glioblastoma multiforme (and in AML)

  ✓Missence mutations at a single residue
  ✓Zhao and colleagues (UNC): *Glioma-derived mutations in IDH1 dominantly inhibit IDH1 catalytic activity and induce HIF-1α* Science 324: 261-265, 2009
  ✓Dang and colleagues: *Cancer-associated IDH1 mutations produce 2-Hydroxyglutarate* Nature 462: 739-744, 2009

- UNC investigators proposed the development of mutant enzyme inhibitors

Stephen Frye
Shelley Earp
Yue Xiong
University of North Carolina

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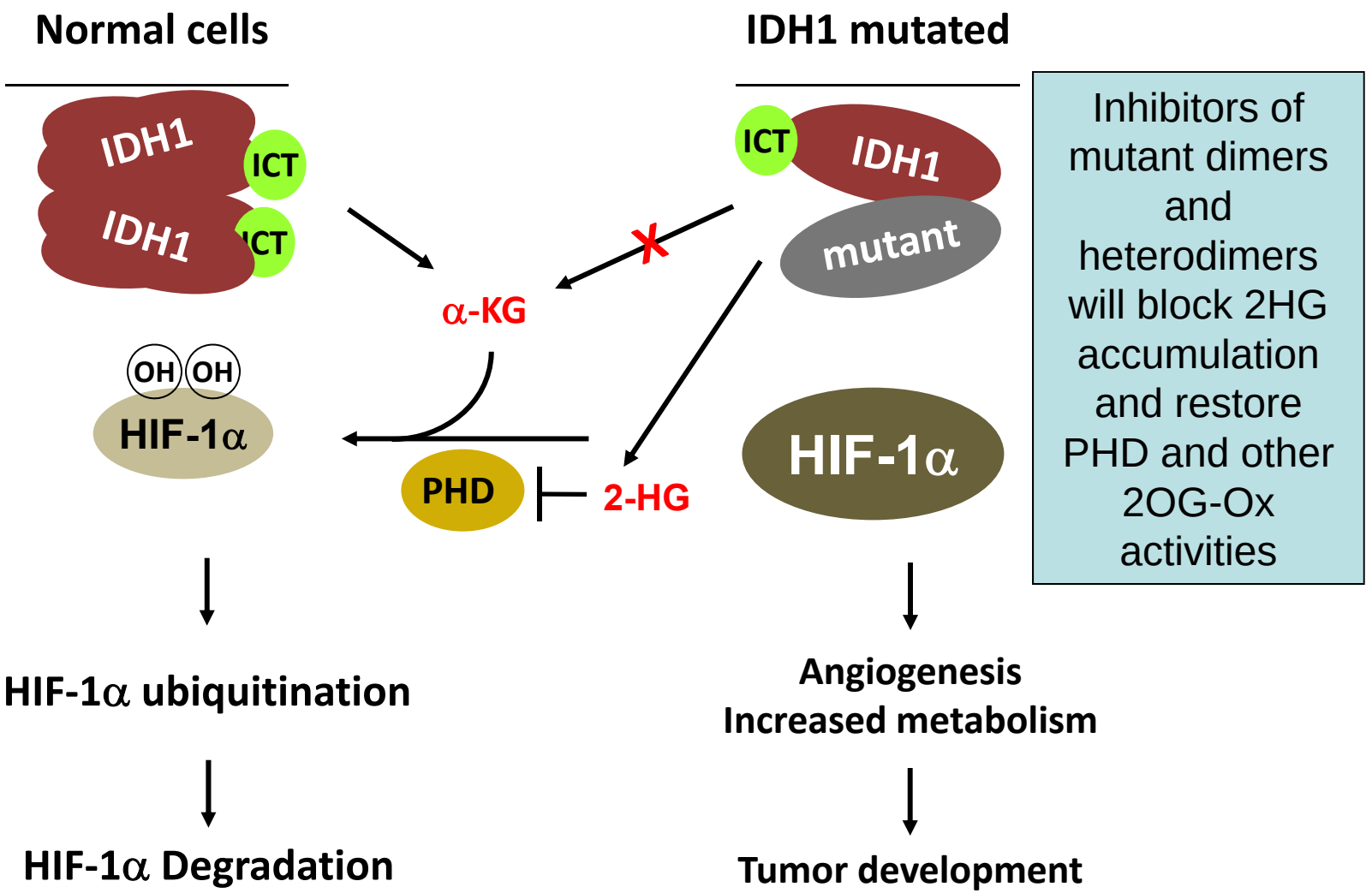
Targeting *IDH1*–Mutated Glioblastoma Multiforme



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Targeting *IDH1*: Rationale and Current Status

RATIONALE

- IDH1 is a high-risk target
  - by-product of TCGA program
  - focuses on an unmet need: GBM
- Excellent partnership with laboratories at forefront of field
- Answer the question: "Is mutant IDH1 a druggable target"

STATUS

- α-KG and 2-HG prodrugs prepared for further biochemical studies
  - mechanism of oncogenesis
  - downstream 2-oxoglutarate oxidases
- Mutant (R132H) and wildtype clones available for assay development
- Diversity screening library (100K) will be supplemented via structure-based virtual screening
- Anticipate 18 months to develop assays, run HTS, and work-up hits

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STAT3 in Head and Neck Cancer

NExT Project: **"Discovery and optimization of inhibitors of STAT3 activation for the treatment of squamous cell carcinoma of the head and neck"**

PI: Jennifer R. Grandis, MD

University of Pittsburgh

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STAT3: A Therapeutic Target in Cancer

- **Constitutively activated STAT3 mediates cellular transformation**
- **Increased activated STAT3 is found in many different human cancers where activation levels are associated with reduced survival**
- **STAT3 activation induces survival, angiogenesis, proliferation, and invasion/metastasis**
- **Caveat: STAT3 is highly homologous to STAT1, which in contrast to STAT3, functions as a tumor suppressor gene**

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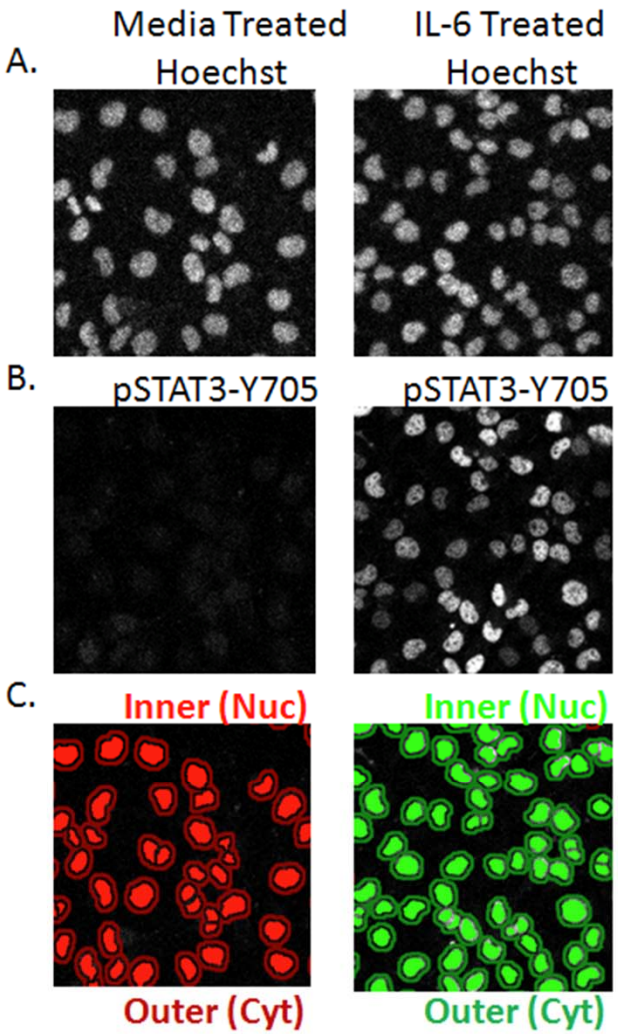
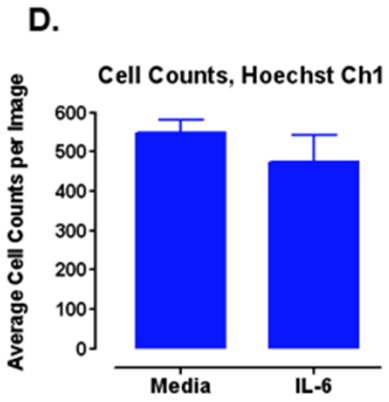
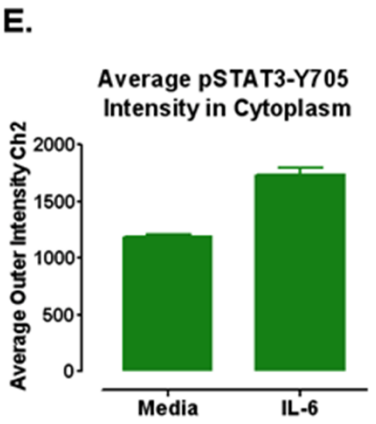
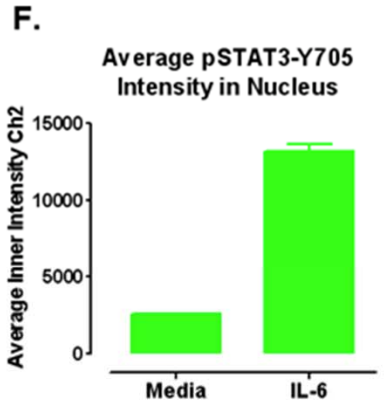
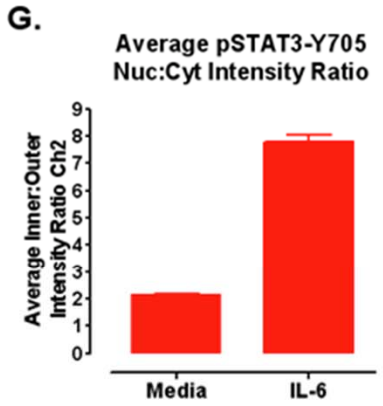
Assay Development: IL-6 induces STAT3 Tyrosine Phosphorylation and Nuclear Translocation in H&N Cancer Cells











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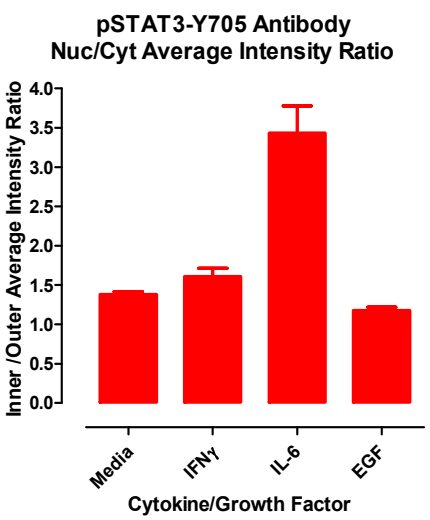
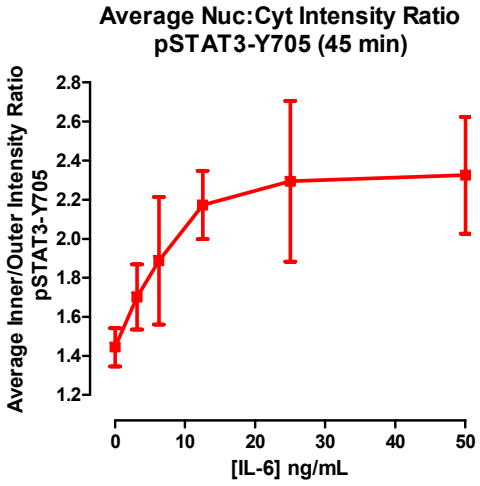
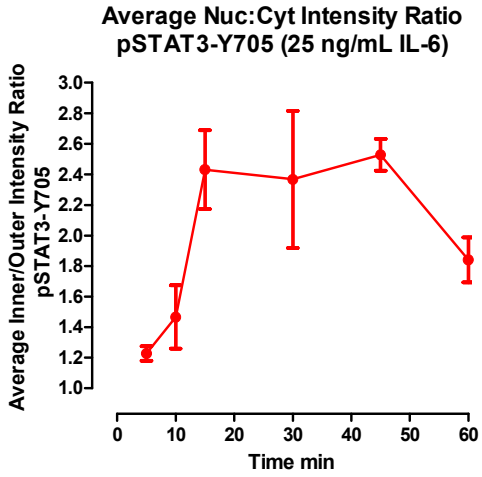
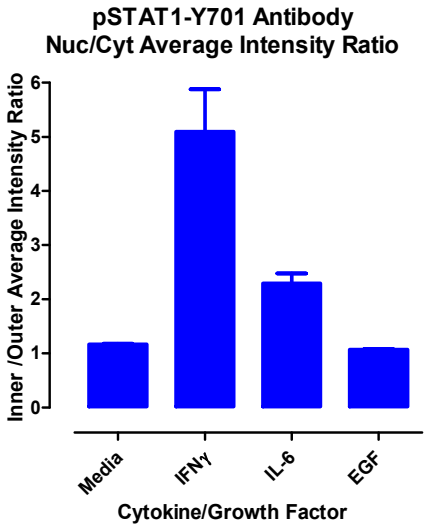
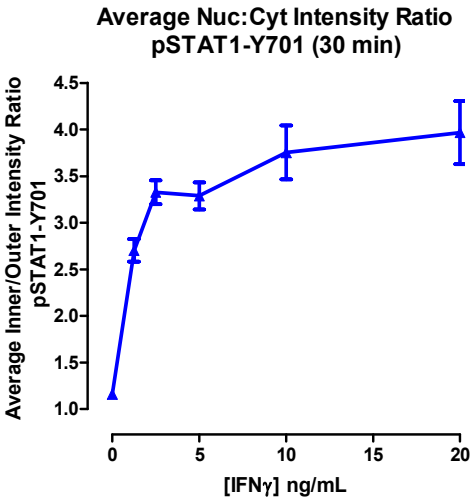
HCS Assay Distinguishes pSTAT3 from pSTAT1 Activation and Nuclear Translocation

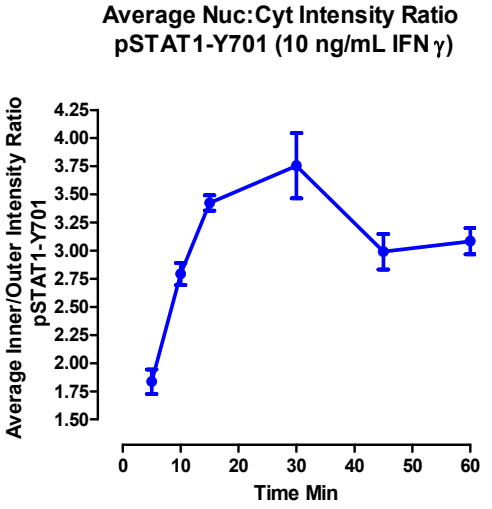












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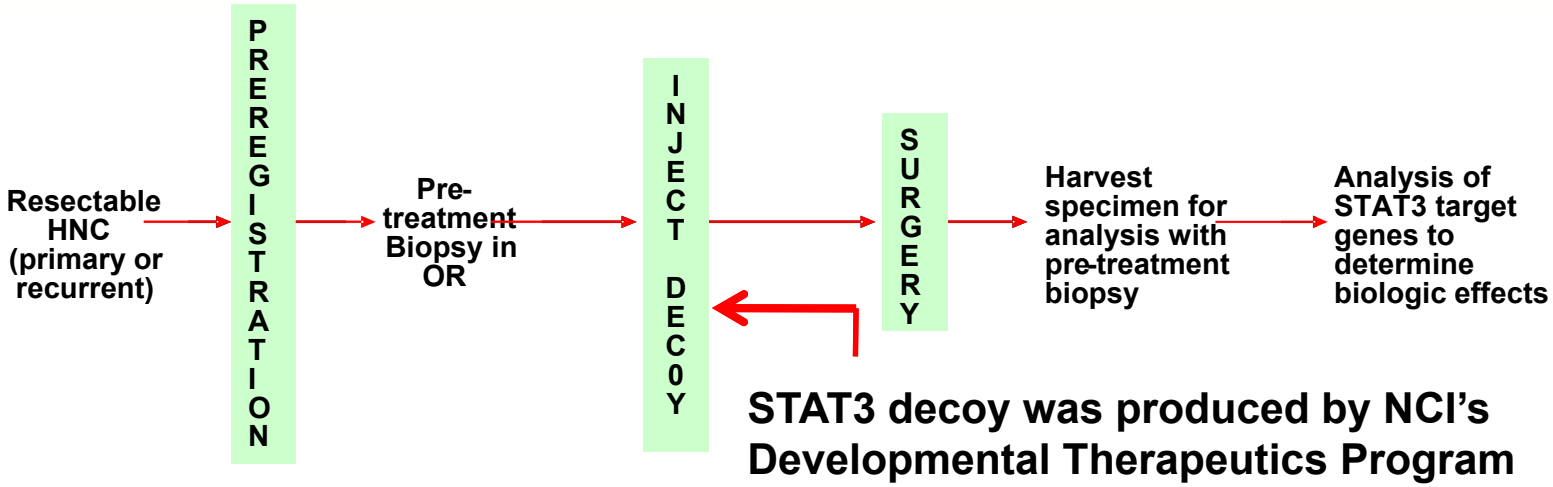
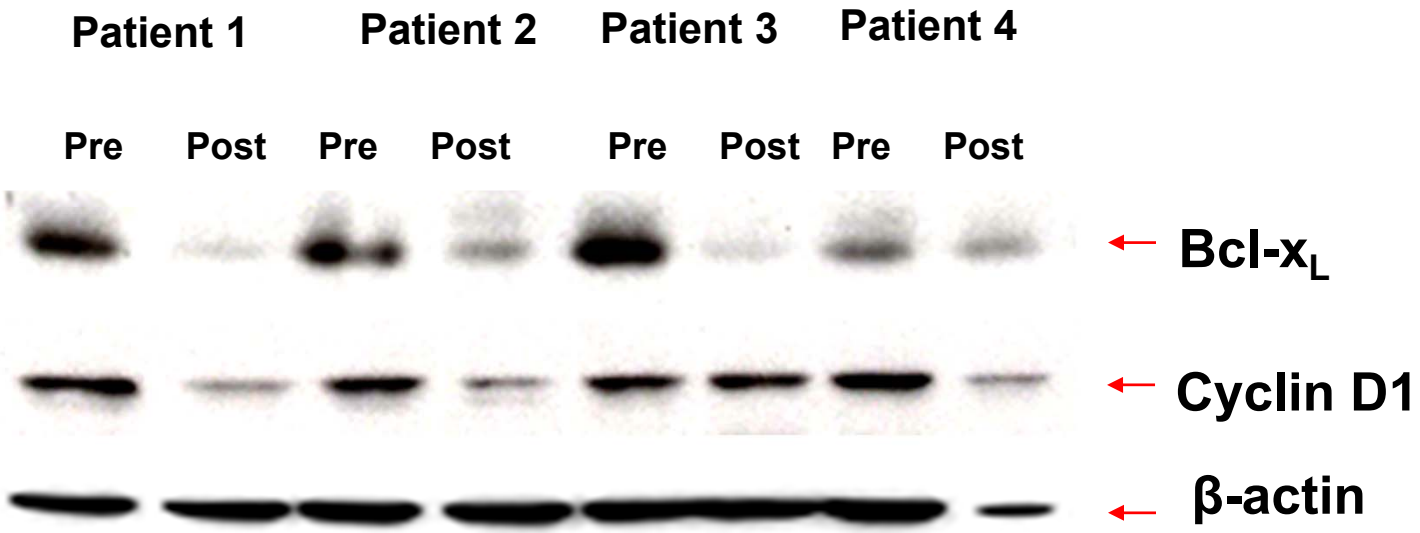
Schema of Phase 0 Trial of STAT3 Decoy



STAT3 decoy was produced by NCI's Developmental Therapeutics Program

STAT3 Decoy Decreases Target Gene Expression in Human HNSCC



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STAT3: Rationale and Current Status

RATIONALE

- STAT3 decoy molecule (GMP oligomer produced by NCI) inhibited target gene expression following direct injection in human head and neck cancers demonstrated by PI, Dr. Jennifer Grandis
  - focuses on an unmet need: head and neck cancer
- Excellent partnership with laboratory at forefront of field
- Focuses on use of both high content (cellular imaging) screens as well as HTS

STATUS and GOALS

- High content screening assays in hand but require optimization
- Confirm and validate hits with appropriate secondary and counter-screening assays
- SAR and MOA studies

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UNC LINEBERGER COMPREHENSIVE CANCER CENTER
NC CANCER HOSPITAL

UNC ESHELMAN SCHOOL OF PHARMACY

Mer kinase as a target in childhood leukemia

- Mer kinase – a member of the Tyro3/Axl/Mer RTK family
  - Expressed in monocytes, functions to clear apoptotic material
  - Never expressed in normal T or B lymphocytes
- Mer kinase expressed in most T and B cell ALL lines
- Mer expression in childhood leukemias
  - Mer mRNA expressed in 30-40% T cell ALL (Clin Cancer Res 2006, 12:2662)
  - New data :Mer protein expressed in 41% B ALL (16 of 16 E2A-PBX1 ALLs)
  - Mer protein expressed 54% T cell ALLs and 68% pediatric AML

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University of North Carolina
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University of Colorado

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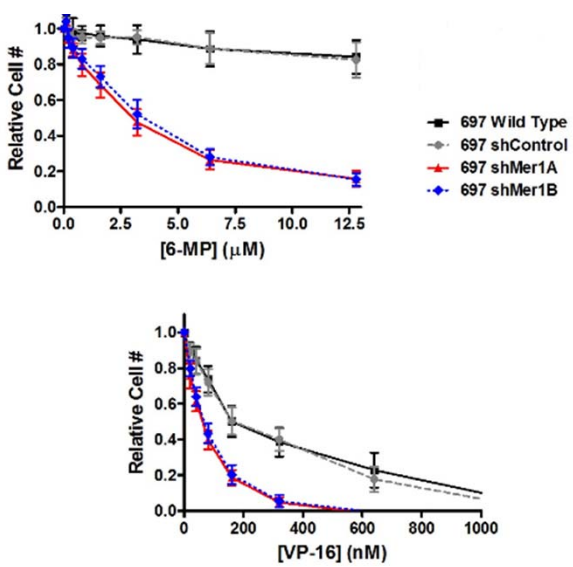
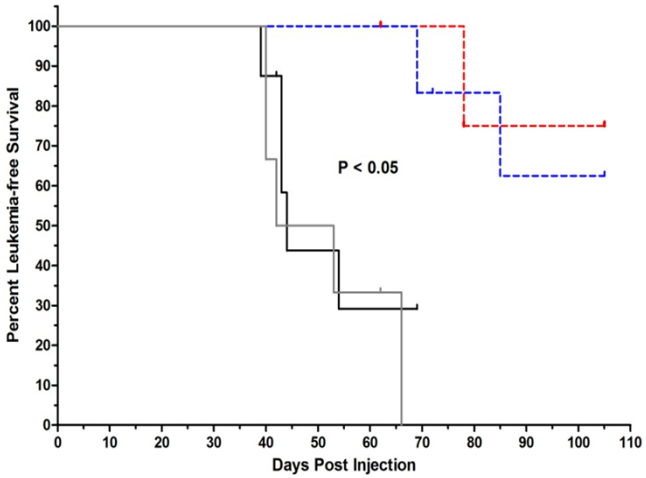
Inhibition of Mer Expression Alters Chemosensitivity and In Vivo Outcome



697 B cell (E2A-PBX) chemosensitivity altered by Mer knockdown



In vivo leukemia model: injection of $5x10^5$ 697 cells in Nod/SCID mice. Enhanced survival with Mer shRNA knockdown.

Target validation with shRNA, Linger *et al.*, Blood, 2009 114:2678

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Therapeutic Strategy – Mer kinase inhibitor

- Protein kinases are tractable targets for small molecule drug discovery – rich target-class knowledge base exists
- UNC has significant expertise in kinase drug discovery
  - Dr. Frye's kinase/cancer department at GSK discovered two of the nine FDA approved kinase inhibitors (Lapatinib and Pazopanib)
  - Drs. Earp and Graham's labs are the leaders in understanding the biology, survival signaling, and clinical relevance of Mer
- Initial goal is to discover multiple, tractable mer kinase inhibitor hit series in order to successfully optimize one series to a drug candidate suitable for *i.v.* administration (3 year time line); followed by an orally available candidate (4 year time line)
- Clinical utility will be chemosensitization of ALL in patients ectopically expressing Mer – other indications will likely emerge
- Unmet need; Pharma not interested in chemotype

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Targeting Mer Kinase: Current Status

STATUS

- Project has been underway for 1.5 years
- Structure-based hit generation has yielded one lead series:
  - low nanomolar K_i's, robust structure-activity relationships
  - Promising initial dmpk (UNC569, mouse, 4.4h $t_{1/2}$, 57% F)
  - Broad kinase profiling underway
  - Cellular assays being optimized – compounds appear to have <1 μM IC50's
  - Lead optimization on UNC569 series is top priority
  - Compounds suitable for *in vivo* testing are in hand
- Additional hit generation is ongoing via focused screening and further structure-based design
  - Typically need 2-3 lead series to deliver one candidate due to attrition of series during lead optimization
  - Expect 1-2 additional leads during the next 12 months
- Initial crystals of the Mer kinase domain have been obtained – optimizing conditions to develop a system for routine co-crystal structures
- Cellular assay optimization for IC_{50} determination and cellular mechanism of action (UNC, Earp, Johnson)
  - *In vitro* metabolism and p-450 interactions (underway)

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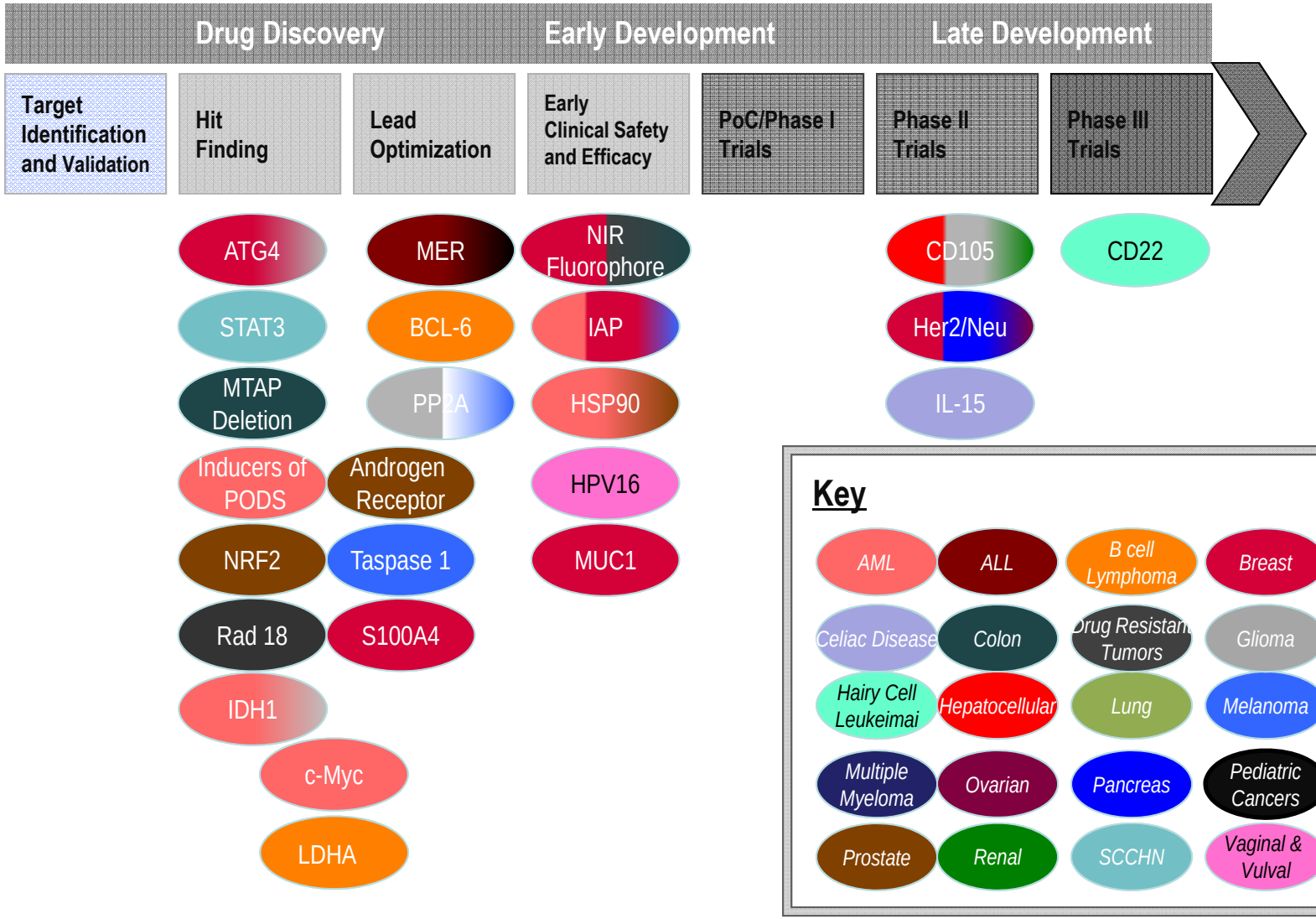
NCI Experimental Therapeutics Pipeline



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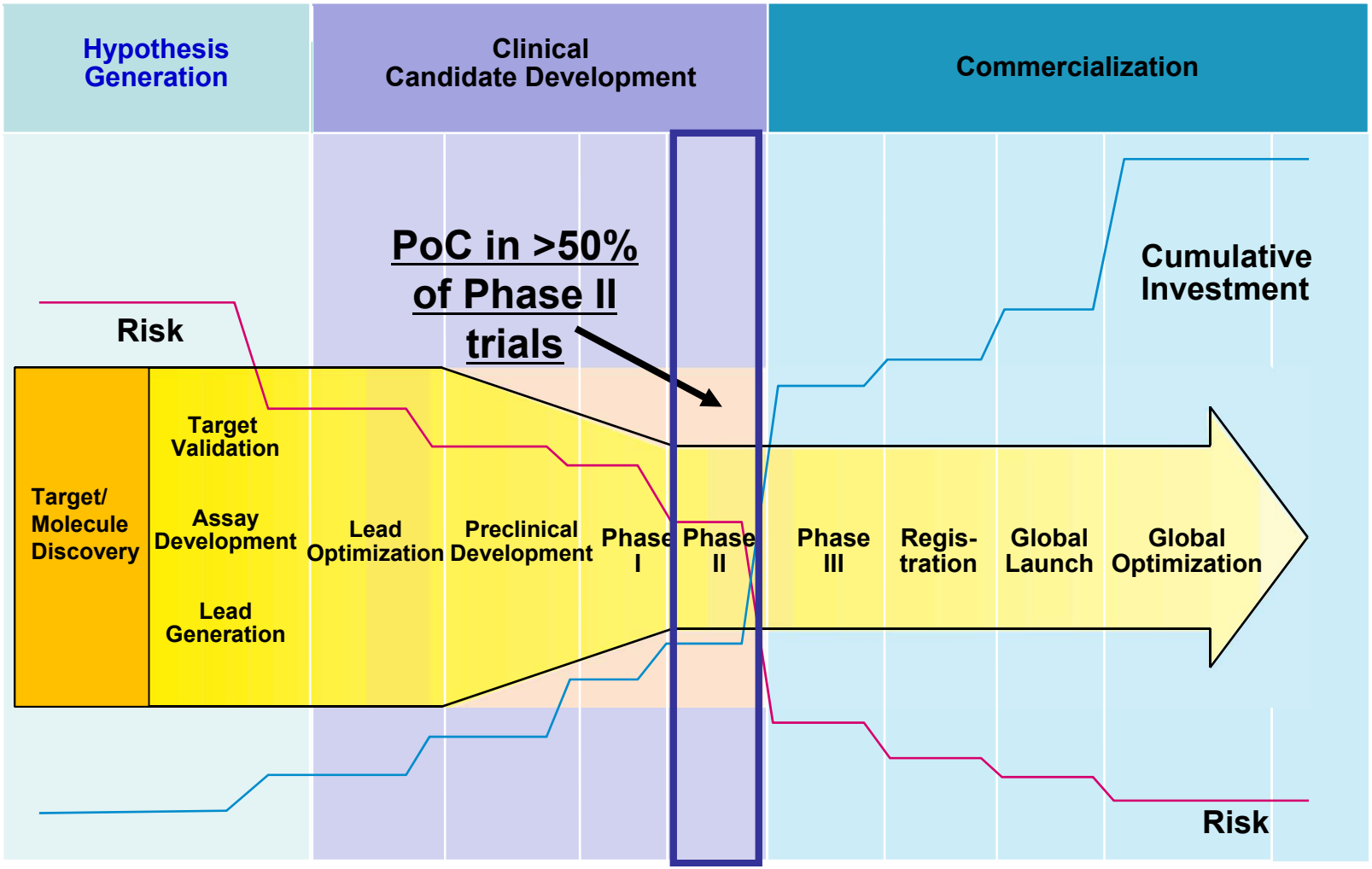
Success: What Will it Look Like?

Transparent, Accountable, Inclusive, & Unified



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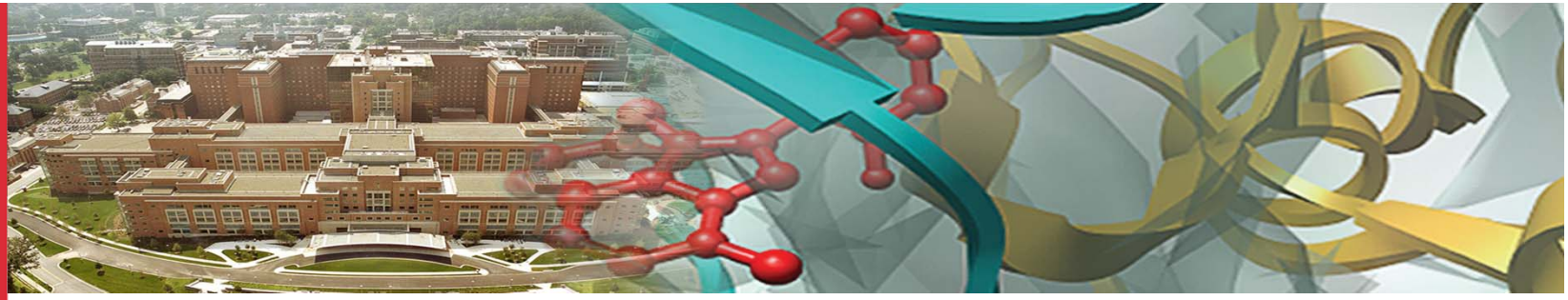

https://dctd.cancer.gov/nextregistration

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