



*NCI Experimental Therapeutics Program  
(NExT)*

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Division of Cancer Treatment and Diagnosis  
National Cancer Institute



*Clinical Trials & Translational  
Research Advisory Committee*

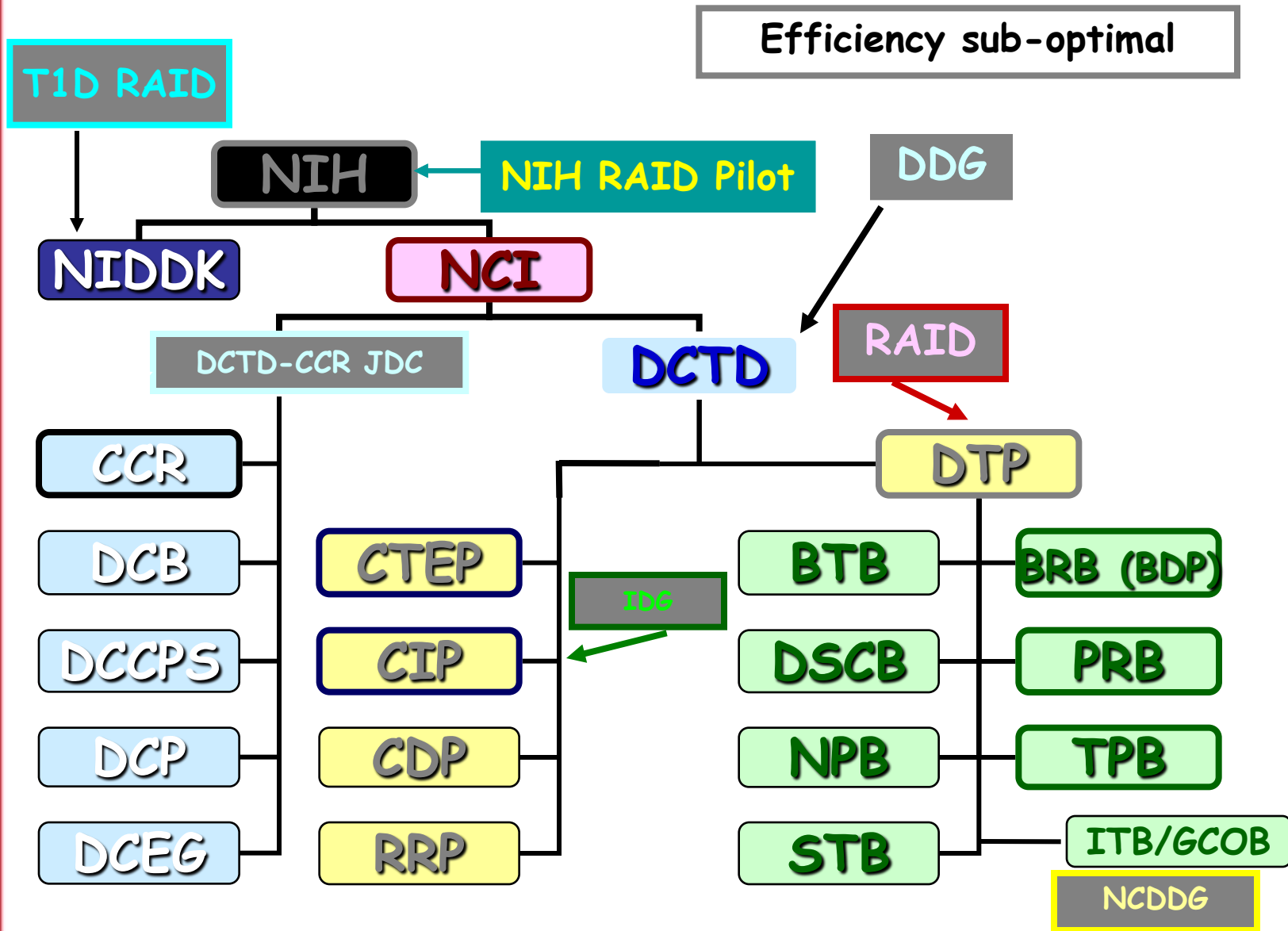
November 4, 2009

# Anticancer Drugs Discovered & Developed by NCI from Preclinical Stage

## 2009 Pralatrexate; ? Depsipeptide

<b>2004</b>	Cetuximab (NSC 632307)	<b>1977</b>	Carmustine (BCNU) (NSC 409962)
<b>2003</b>	Bortezomib (NSC 681239)	<b>1976</b>	CCNU (NSC 9037)
<b>1998</b>	Denileukin difitox (NSC 697979)	<b>1975</b>	Dacarbazine (NSC 45388)
<b>1996</b>	Polifeprosan 20 with carmustine implant (NSC 714372) Topotecan (NSC 609699)	<b>1974</b>	Doxorubicin (NSC 123127) Mitomycin C (NSC 26980)
<b>1995</b>	All-trans retinoic acid (NSC 122758)	<b>1973</b>	Bleomycin (NSC 125066)
<b>1992</b>	2-chlorodeoxyadenosine (NSC 105014) Paclitaxel (NSC 125973) Teniposide (NSC 122819)	<b>1970</b>	Floxuridine (FUDR) (NSC 27640) Mithramycin (NSC 24559) Mitotane (o-p'-DDD) (NSC 38721)
<b>1991</b>	Fludarabine Phosphate (NSC 312887) Pentostatin (NSC 218321)	<b>1969</b>	Cytarabine (ARA-C) (NSC 63878) Procarbazine (NSC 77213)
<b>1990</b>	Hexamethylmelamine (NSC 13875) Levamisole (NSC 177023)	<b>1967</b>	Hydroxyurea (NSC 32065)
<b>1989</b>	Carboplatin (NSC 241240)	<b>1966</b>	Pipobroman (NSC 25154) Thioguanine (NSC 752)
<b>1988</b>	Ifosfamide (NSC 109724)	<b>1964</b>	Melphalan (NSC 8806) Actinomycin D (NSC 3053)
<b>1987</b>	Mitoxantrone (NSC 301739)	<b>1963</b>	Vincristine (NSC 67574)
<b>1983</b>	Etoposide (NSC 141540)	<b>1962</b>	Fluorouracil (NSC 19893)
<b>1982</b>	Streptozotocin (NSC 85998)	<b>1961</b>	Vinblastine (NSC 49842)
<b>1979</b>	Daunorubicin (NSC 82151)	<b>1959</b>	Cyclophosphamide (NSC 26271) Thiotepa (NSC 6396)
<b>1978</b>	Cisplatin (cis-platinum) (NSC 119875)	<b>1957</b>	Chlorambucil (NSC 3088)

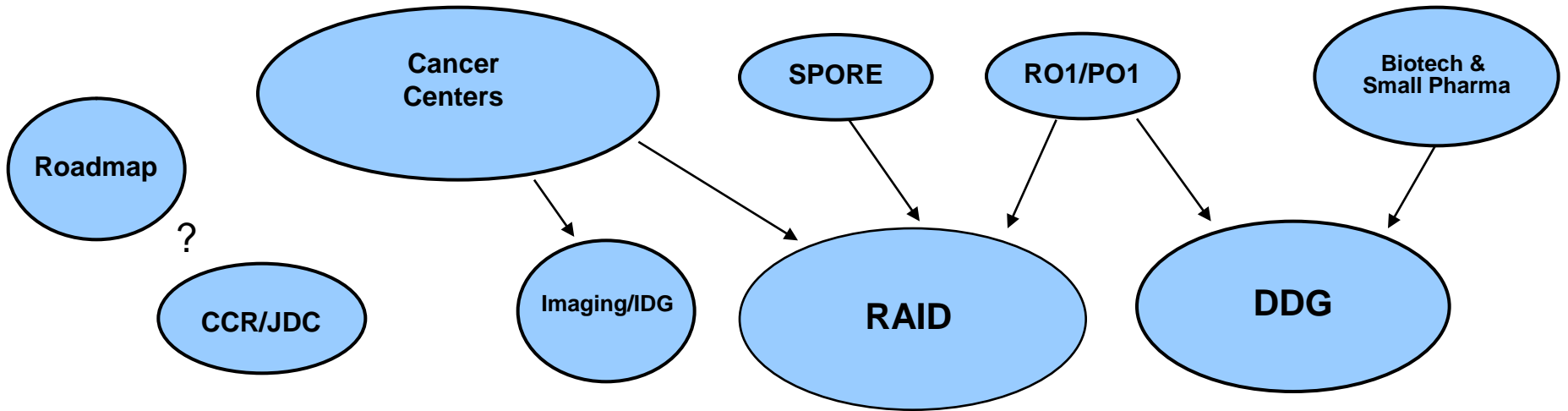
# Drug Development Programs: NCI & NIH



# 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



**The NCI Experimental Therapeutics (NExT) Pipeline:**  
Target discovery through early stage clinical trials

CBC Created

Exploratory  
Screen  
Development

Screening/  
Designed  
Synthesis

Lead  
Development

Candidate  
Seeking

Clinical  
Candidate

Phase 0 /  
I Trials

Phase  
II/III  
Trials

Registration

Post  
Launch

Drug Discovery

Early Development

Full Development

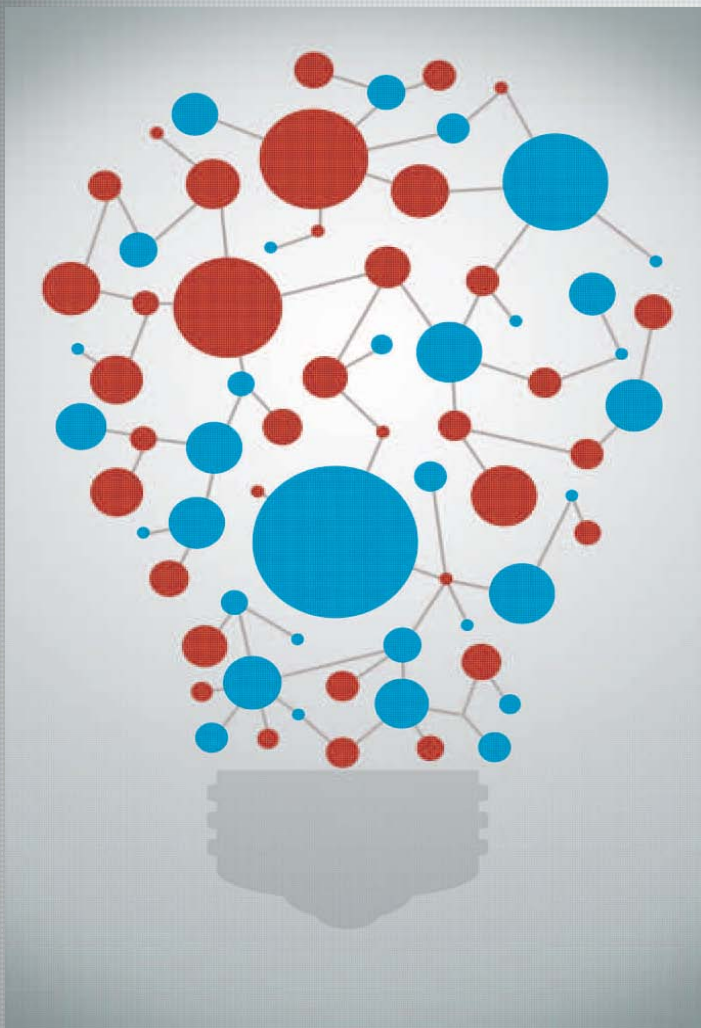
# NCI Chemical Biology Consortium (CBC)

- **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**



# The Chemical Biological Consortium: A New NCI Initiative



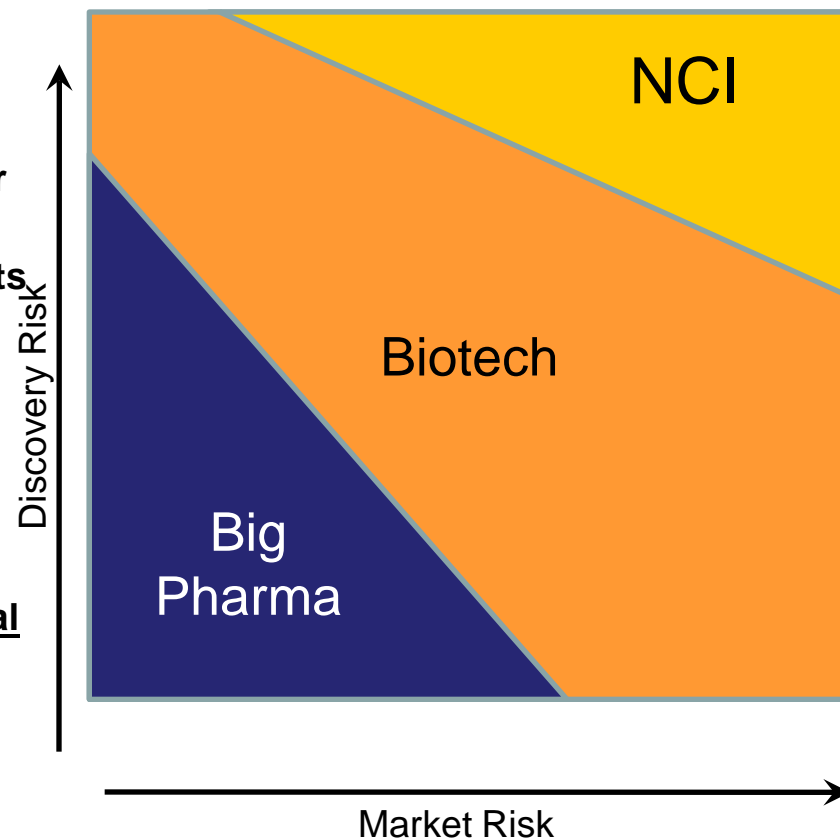
- **Burnham Institute**
- **Southern Research**
- **SRI International**
- **Vanderbilt**
- **Emory**
- **UCSF**
- **Univ. North Carolina**
- **Pittsburgh**
- **Univ. of Minnesota**
- **Georgetown**
- **NCI Intramural Chemical Biology**
- **NIH Chemical Genomics Center**
- **Affiliate Investigators**



# Chemical Biology Consortium Vision

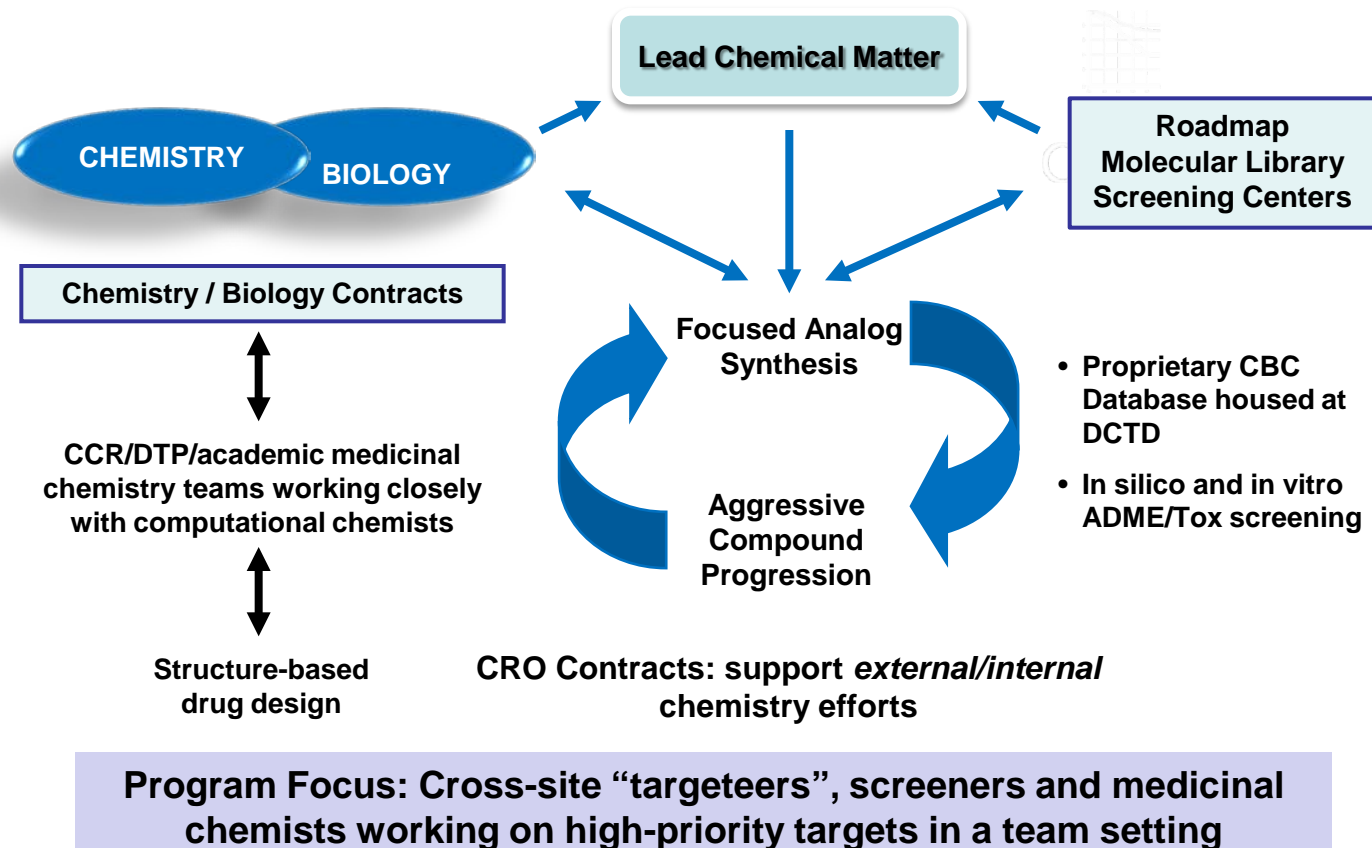
## Why is CBC different?

- 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



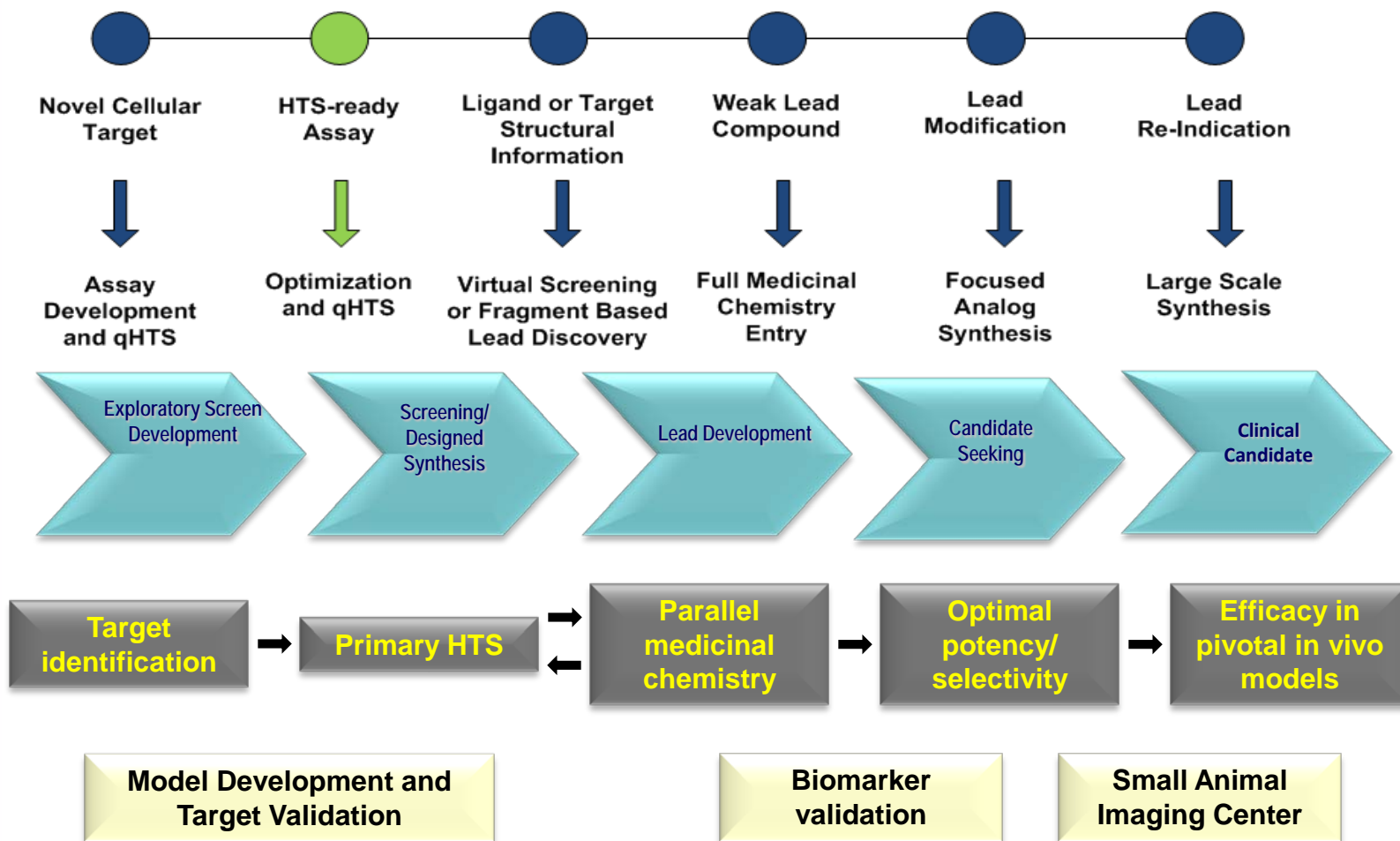


# Chemical Biology Consortium: Enabling Hit-to-Lead Discovery



## Integrated Program vs. Service-Driven Program

# Multiple Entry Points into the NExT



# 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:**

**Data Transfer**

**Data Sharing**

**Data Ownership**

## Therapeutics Discovery & Development Support Provided by NCI (NExT)

- Exploratory development of HTS
- Screening and iterative medicinal chemistry
- Chemical synthesis of small molecules, oligonucleotides, 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/PD/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
- Production of clinical dosage forms
- Stability testing of clinical dosage forms
- Regulatory support and early phase trials

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# Pre-Clinical Imaging Drugs and Technologies

## Agents for development

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

## Synthesis and GMP Scale up (including radiolabeling)


## Pre-clinical development (pharmacology and toxicology)

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



# 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>

 National Cancer Institute U.S. National Institutes of Health | [www.cancer.gov](http://www.cancer.gov)

## NCI Experimental Therapeutics (NExT)



### NExT Application Login

[NExT application Instructions](#)

User Name:

Password:




[Login](#)

[Register for an account](#)

If you have any problems or questions about this application please contact [Dave Segal](#)

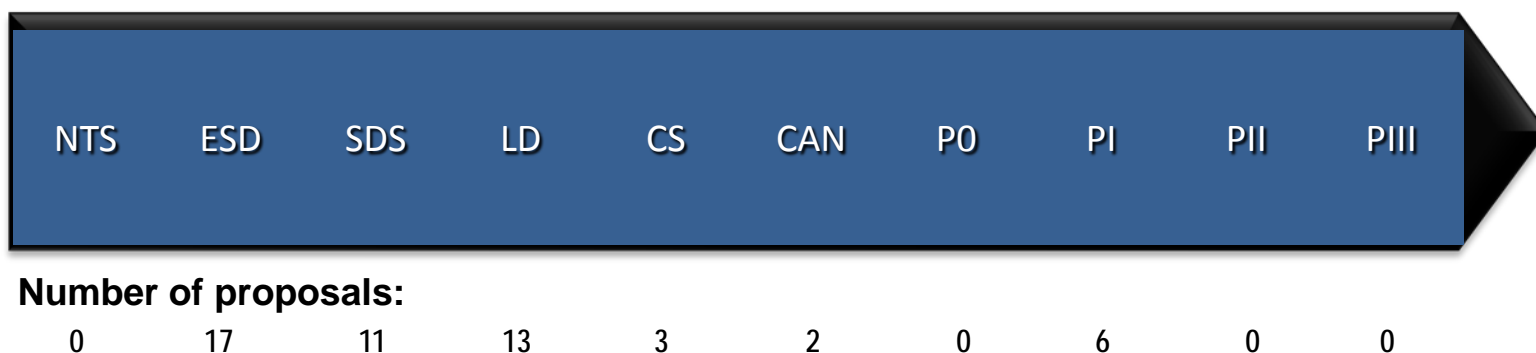
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# NExT Applications: Cycle 1 (9/15/09)

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



**Number of proposals:**

0      17      11      13      3      2      0      6      0      0

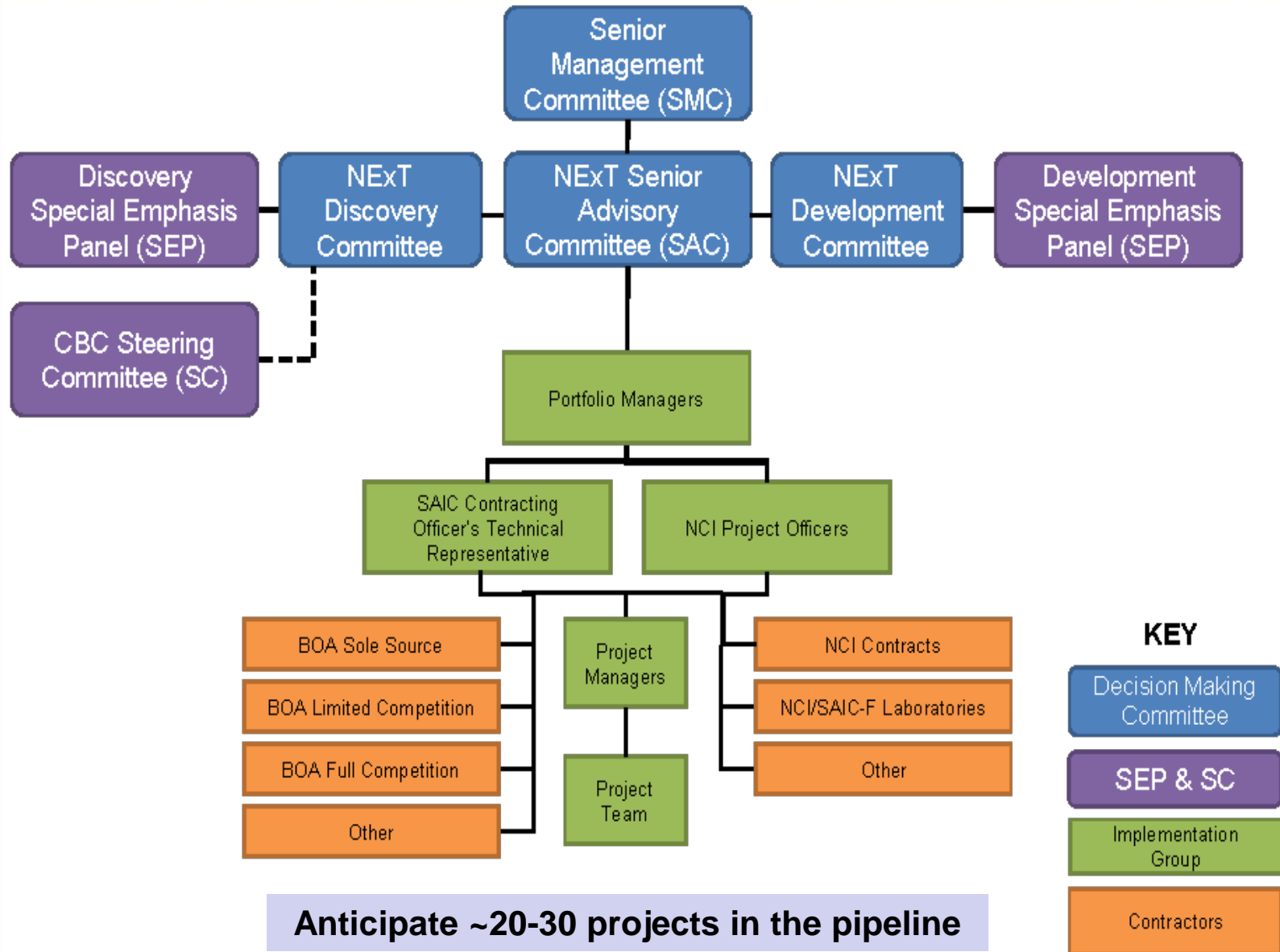
## **Discovery Definitions:**

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

# How Are Projects Selected?



**Anticipate ~20-30 projects in the pipeline**

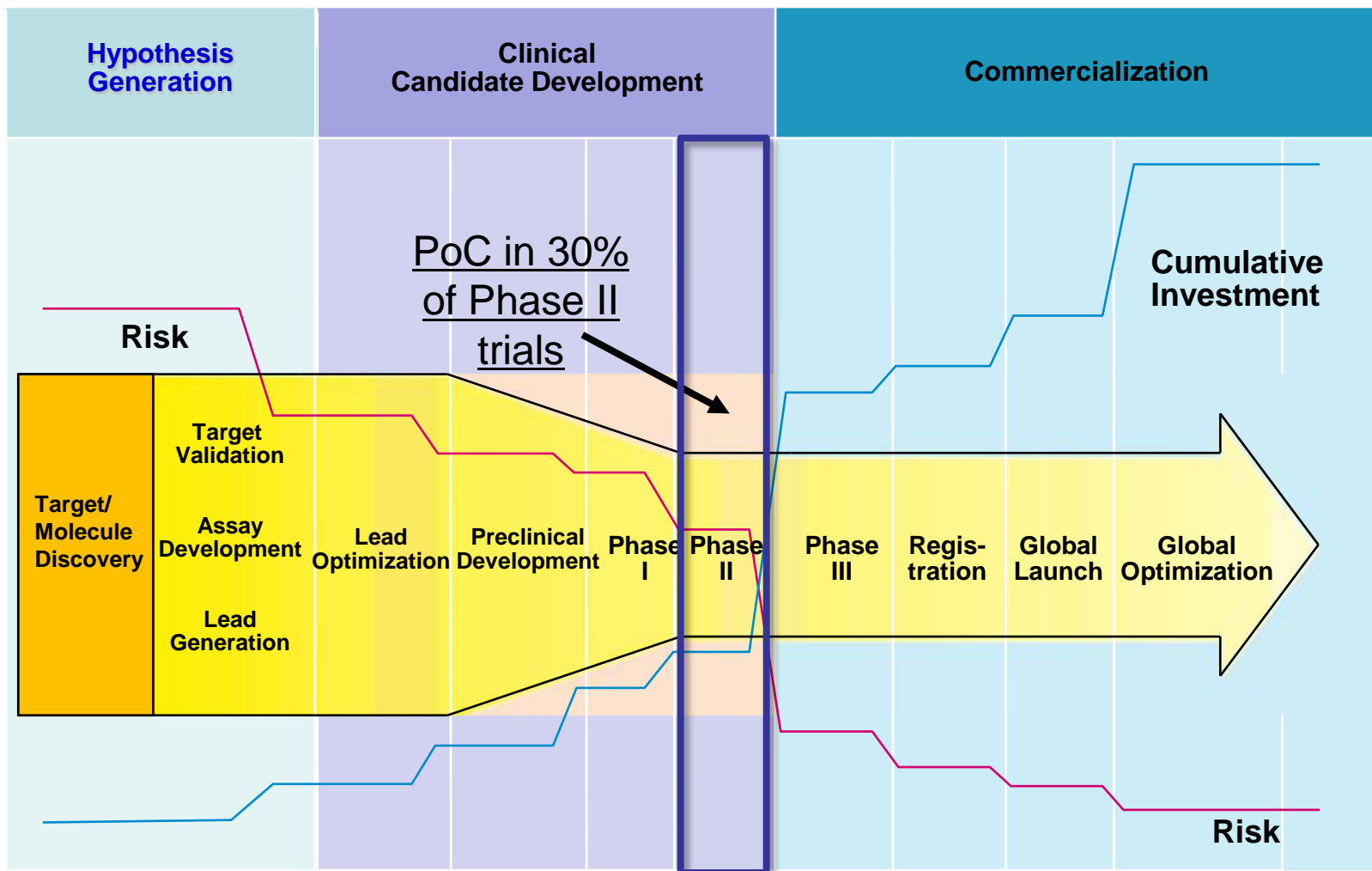


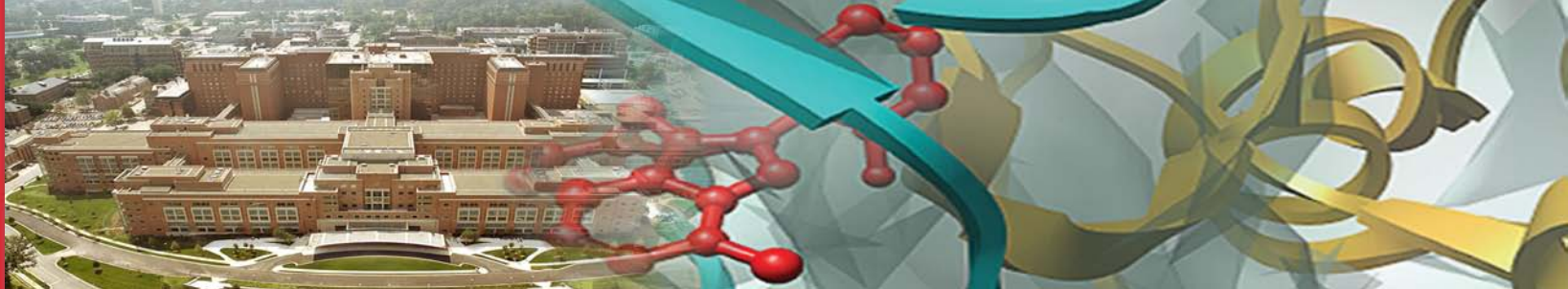
# Goals of the NCI's Therapeutics Platform

- 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
- 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

# Success: What Will it Look Like?

Transparent, Accountable, Inclusive, & Unified





<https://dctd.cancer.gov/nextregistration>

## **NExT/CBC Implementation Team**

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Jeff Abrams

Sanjay Malhotra

Heba Barazi

Barbara Mroczkowski

Michelle Bennett

Ralph Parchment

Jerry Collins

David Segal

James Crowell

Shizuko Sei

Jason Cristofaro

Tom Stackhouse

Mike Difilippantonio

Joe Tomaszewski

Gina Hayman

Robert Wiltrout

Lee Helman

Jamie Zweibel

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