National Cancer Institute

DCTD Division of Cancer Treatment and Diagnosis

Accelerating Cancer Diagnosis and Drug Development

NCAB *ad hoc* Experimental Therapeutics Subcommittee Meeting

Update on the Developmental Therapeutics Review Group (DTRG) Recommendations

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Deputy Director, DCTD, NCI
June 22, 2010

Developmental Therapeutics Review Group (September 1998)

- In 1997, the Director of the NCI formed the Developmental Therapeutics Review Group (DTRG) and charged it with the task of defining the future of the NCI with respect to the development and discovery of new chemical and biological therapies for the treatment of cancer. The DTRG closely examined the Developmental Therapeutics Program (DTP) at the NCI, a highly respected program that has made major contributions to the discovery and development of cancer chemotherapeutic agents.

DTRG Recommendations

- The DTRG recommendations focused on four areas:
  - allocation of funds and roles of the Extramural and Intramural programs;
  - monitoring and oversight of the DTP Research Portfolio;
  - the NCI Decision Network Committee; and
  - the special role of the DTP related to drug screening.

DTRG Major Recommendations

1. NCI should support a chemical diversity program with the explicit goal of finding small molecules that can manipulate the function of all proteins or processes relevant to cancer
2. NCI should undertake a major new interdisciplinary initiative to acquire structural information on cellular targets that are potentially relevant to cancer
3. NCI should reconfigure its program for screening compounds for anti-tumor activity
4. NCI should establish Centers of Excellence in a variety of scientific areas
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Implementation Activities and Status

- The NCI developed the following initiatives to address this recommendation including:
  - NCI RAID Program (DTP)
  - Drug Development Group (DTP, CTEP)
  - DCIDE Program (CIP, DTP)
  - Pharmacodynamic (PD)/Biomarkers Program (OD)
  - Phase 0 Program (OD)
  - DCTD/CCR Joint Development Committee (OD, CCR)
  - Chemical Biology Consortium (OD; DTP, CIP)
  - NCI Experimental Therapeutics (NExT) Program (OD; CCR, DTP, CTEP, CIP)

NCI RAID Program

"RAID" = Rapid Access To Intervention Development

Promote Agents For Academic Center Study

- Provide access to DTP pre-clinical contract research resources to academic (small business ... managed by DTP Staff)
- Allow ... to occur under investigator or academic center sponsorship instead of NCI
- Examples of RAID tasks:
  - Acquire / Produce / Formulate bulk drug
  - Produce biologicals
  - Test efficacy of agent in animals
  - Pharmacology / Toxicology studies
- Bridge the gap between a LEAD DISCOVERY and a DRUG

Not a Grant Program!

NCI RAID Program Status (June 2010)

- First Round – August 1998
- 22 Rounds through February 2009
- Round 23 (August 2009) combined with NExT Cycle 02
- 428 Applications / 137 Approved
- 115 Projects Complete / 22 On-going
- 50 INDs Filed
- 41 Agents Licensed
- (> 1650 Patients Treated)
- Has inspired the following clones: (AIDS IIP), RAPID, DCIDE, NIDDK T1D RAID, NIH RAID Pilot

Merged into Next Program – August 2010

Drug Development Group (DDG)

For Academics, Small Biotechs, Big Pharma, CCR

Drug Development Group (DDG)

http://dtp.nci.nih.gov/docs/ddg/ddg_descript.html

Whatever the source of the new agent (academia, industry, NCI, or other), if the clinical development of the agent is to take place under an NCI-held Investigational New Drug (IND) application, the NCI Drug Development Group (DDG) will be responsible for oversight and for pre-clinical and clinical decision-making at the key "go - no go" decision points. The DDG thus prioritizes use of NCI resources supporting pre-clinical development by DTP and clinical development by the Cancer Therapy Evaluation Program (CTEP), except that the Biological Resources Branch Oversight Committee (BRB-OC) governs acquisition and production of biologics approved by DDG, as described above.

Merged into Next Program – August 2010

The DDG is advisory to the Director, DCTD, who usually accepts its recommendations. In exceptional cases, the Director may approve the development of agents whose priority rating from the DDG is low, if the Director considers the scientific or societal impact to be substantial. In other cases, the Director may elect not to proceed with agents afforded high priority by the DDG, if competing priorities, scientific judgment, or other considerations do not support DCTD involvement.

DCIDE Program

Cancer Imaging Program: DCIDE

- This competitive program was designed to expedite and facilitate the development of promising investigational imaging enhancers (contrast agents) or molecular probes from the laboratory to IND status.
- CIP Funding and Review
- NCI DTP Drug Development Resources and Management (1° PRB, TPB)

- http://imaging.cancer.gov/programsandresources/specializedinitiatives/dcide

Merged into Next Program – August 2010

DCTD Pharmacodynamic Biomarkers Program

PD-Biomarkers Program

- **Goal:** Develop robust, SOP-driven pharmacodynamic assays for use in Phase 0/I to determine if the targeted agent is exerting its intended effect
- PADIS
  - Pharmacodynamic Assay Development and Implementation Section, LHTP
  - Preclinical assay development and validation
- NCTVL
  - National Clinical Target Validation Laboratory
  - Clinical assay validation and sample analysis
- SBIR Program
  - http://sbir.cancer.gov

Internal PD Assay Portfolio (Partial)

Concept		Feasibility & Development						Validation		Launch	
Target	Application	Platform	Exploratory/Feasibility	Development	Analytical Validation	Fit for Purpose	Specimen SOPs	Assay Transfer	Clinical Validation	Support NCI Clinical Trials	Transfer to Scientific Community
Surrogate Assays											
γ-H2AX Protein (tumor)	DNA Damaging Agents	qIFA	✓	✓	✓	✓	✓	✓	✓	●	Soon
γ-H2AX Protein (tumor)	DNA Damaging Agents	IA	✓	✓	H (calibrator)	✓	✓				
γ-H2AX (skin)	DNA Damaging Agents	IFA	✓	✓	✓	✓	✓	NA	✓	●	Soon
γ-H2AX (MNC)	DNA Damaging Agents	qIFA (cytospin)	✓	✓	✓	✓	✓	✓	✓	●	R
γ-H2AX (CTC)	DNA Damaging Agents	CellSearch IFA	✓	✓	✓	NA	✓	NA	NA	●	Soon
Top 1 Protein	TOPO Inhibitors	IA	✓	✓	✓	✓	✓	✓	✓	●	Soon
Top 1 Cleavable Complex	TOPO Inhibitors	IA	✓	✓	✓	●	✓	●			

KEY:

●	In Progress	✓	Completed	X	Dropped
●	Delayed	CA	Commercially Available	NA/UIN	Not Applicable or Uninformative
●	Technical Difficulty	H	On Hold/Planned	R	Ready

Merged into Next Program – August 2010

DCTD Phase 0 Clinical Trials Program

Exploratory IND Guidance

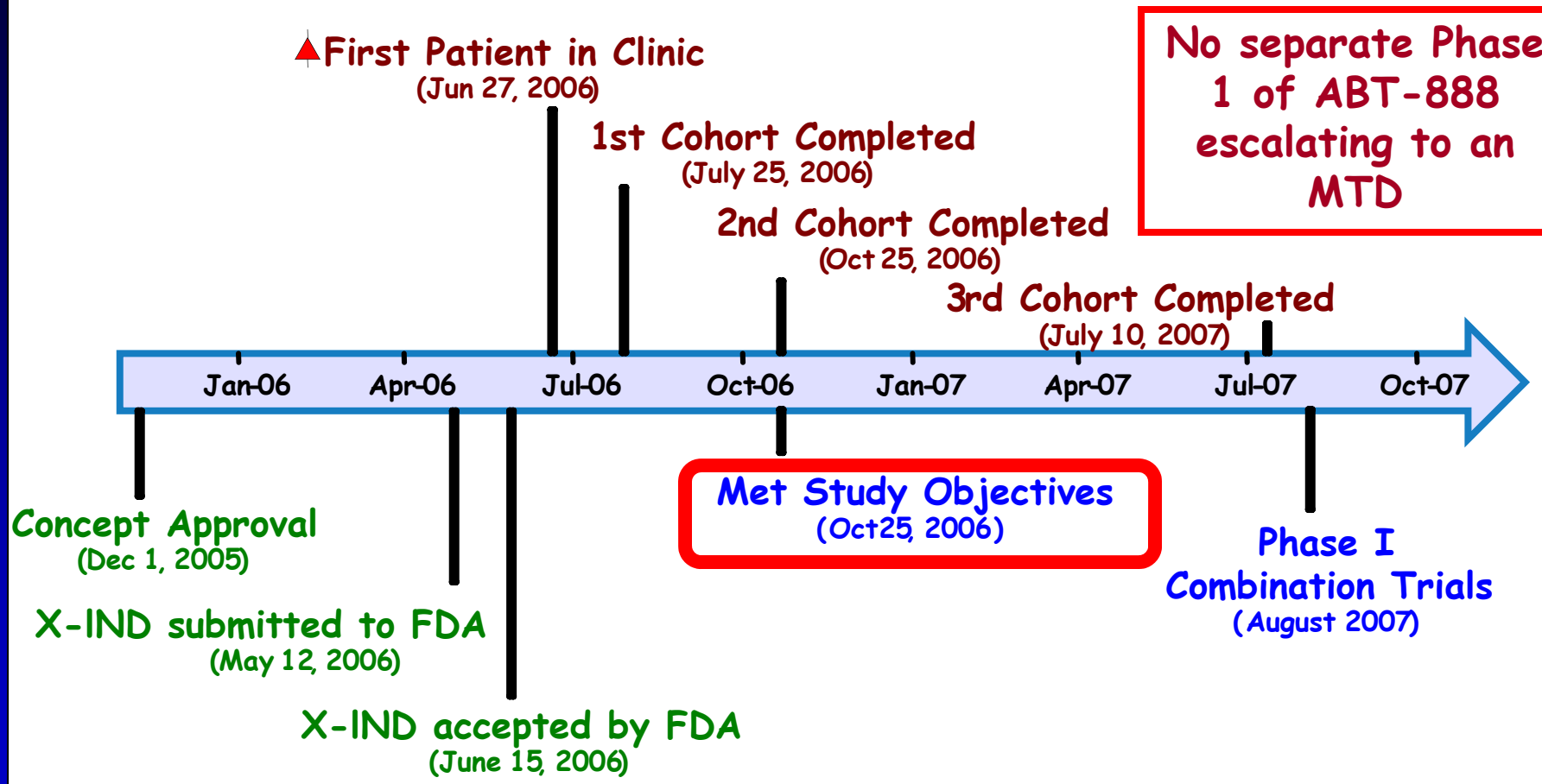
- *Exploratory IND study* is intended to describe a clinical trial that occurs very early in Phase 1, involves very limited human exposure, and has no therapeutic intent (e.g., screening studies, microdose studies). Such exploratory IND studies are conducted prior to the traditional dose escalation, safety, and tolerance studies that ordinarily initiate a clinical drug development program. The duration of dosing in an exploratory IND study is expected to be limited (e.g., 7 days).

Types of Exploratory Clinical Trials

- PK or Imaging – Microdose
- Multiple Products at Pharmacologically Active Doses
- Mechanism of Action

Merged into Next Program – August 2010

NCI's First Phase 0 - Timelines and Achievements



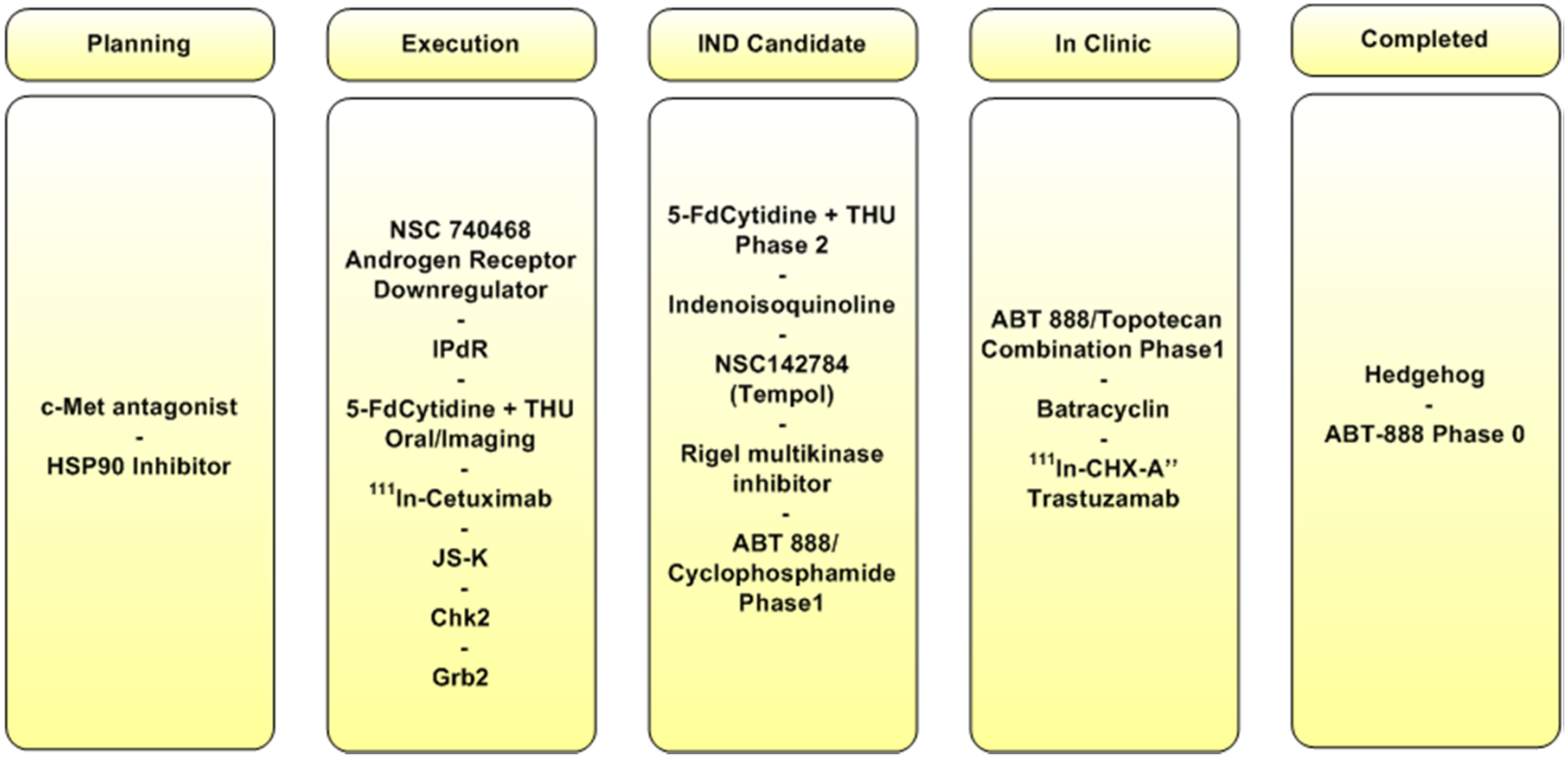
90 prior CTEP IND agents from '95 to '05: Median 900 days from 1st in human single agent to 1st in human combination trial

DCTD /CCR Joint Development Committee (JDC) Program

DCTD/CCR JDC Goals

- Co-ordination of discovery and early clinical trials resources across the NCI with major effort to involve all interested constituencies
  - Creation of integrated drug development teams across NCI for specific agents, and
  - Creation of a joint CCR/DCTD NCI drug development committee to oversee these teams, determine resource priorities, assess progress, identify gaps in the portfolio particularly suited to NCI drug development efforts, and evaluate new compounds for inclusion in the pipeline
- Overall focus on opportunities that favor strengths of NCI—Academic partnerships
- Initiated in September 2005

JDC Pipeline (Status: December 2008



Merged into Next Program – August 2010

Chemical Biology Consortium

NCI Chemical Biology Consortium (CBC)

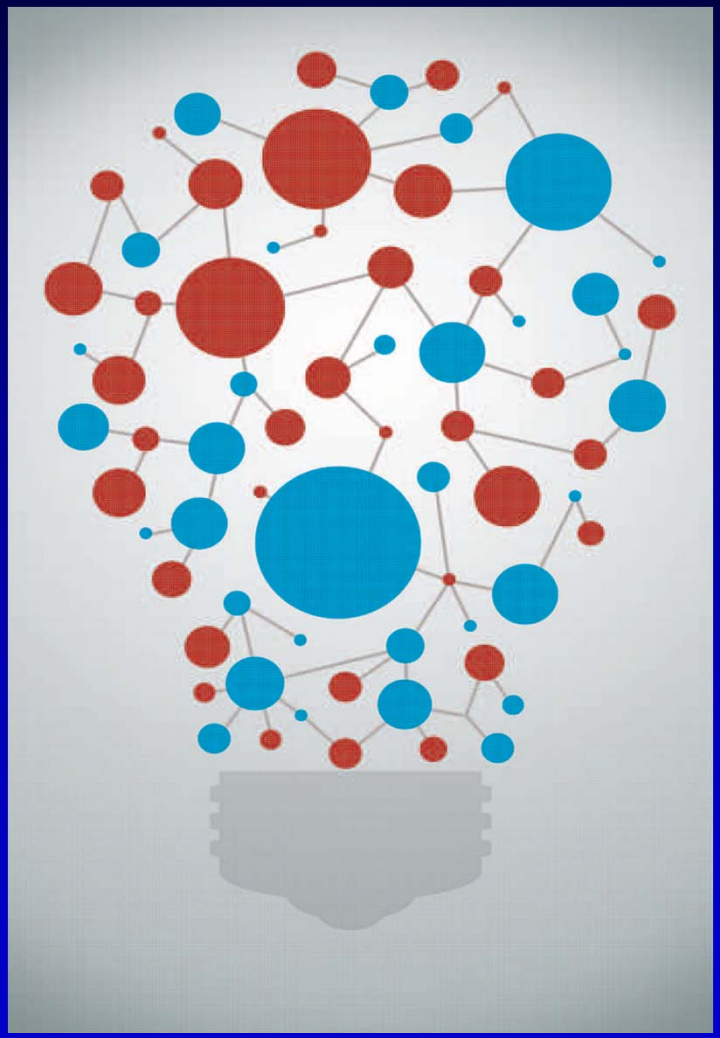
- ***Mission:*** Dramatically increase flow of early stage drug candidates into NCI therapeutics pipeline

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

Leverage NIH Roadmap Investment in MLSCN and NCI in Molecular Oncology!

NExT Discovery Engine!

The Chemical Biological Consortium: A New NCI Initiative



- Comprehensive Chemical Biology Screening Centers (4)
- Specialized Application Centers (3)
- Chemical Diversity Centers (4)
- Other (3)

Initiated in August 2010

Additional details will be provided by Dr. Doroshow on June 23, 2010.

NCI Experimental Therapeutics Program

Initiated in August 2010

NCI Experimental Therapeutics (NExT) Program

- Merger of existing NCI drug and imaging agent development programs
  - DDG
  - NCI RAID
  - DCTD/CCR JDC
  - DCIDE
- Creation of Chemical Biology Consortium
- Integration of PD-Biomarkers Program
- Development of Phase 0 Program
- Development of Functional Biology Consortium

Total NCI Pipeline: Current Programs

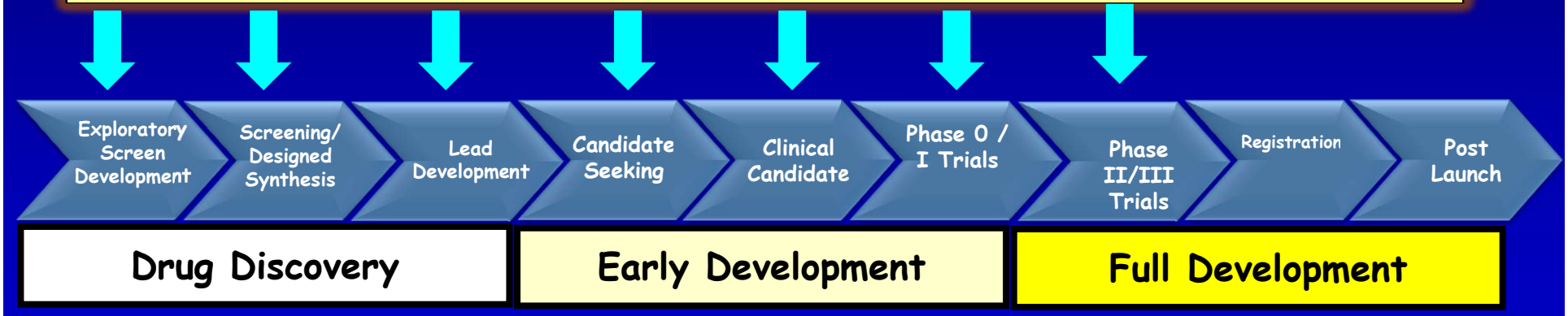
- NCI RAID
- JDC
- DDG
- DCIDE

Merged to……

The NExT Pipeline:

CBC Created

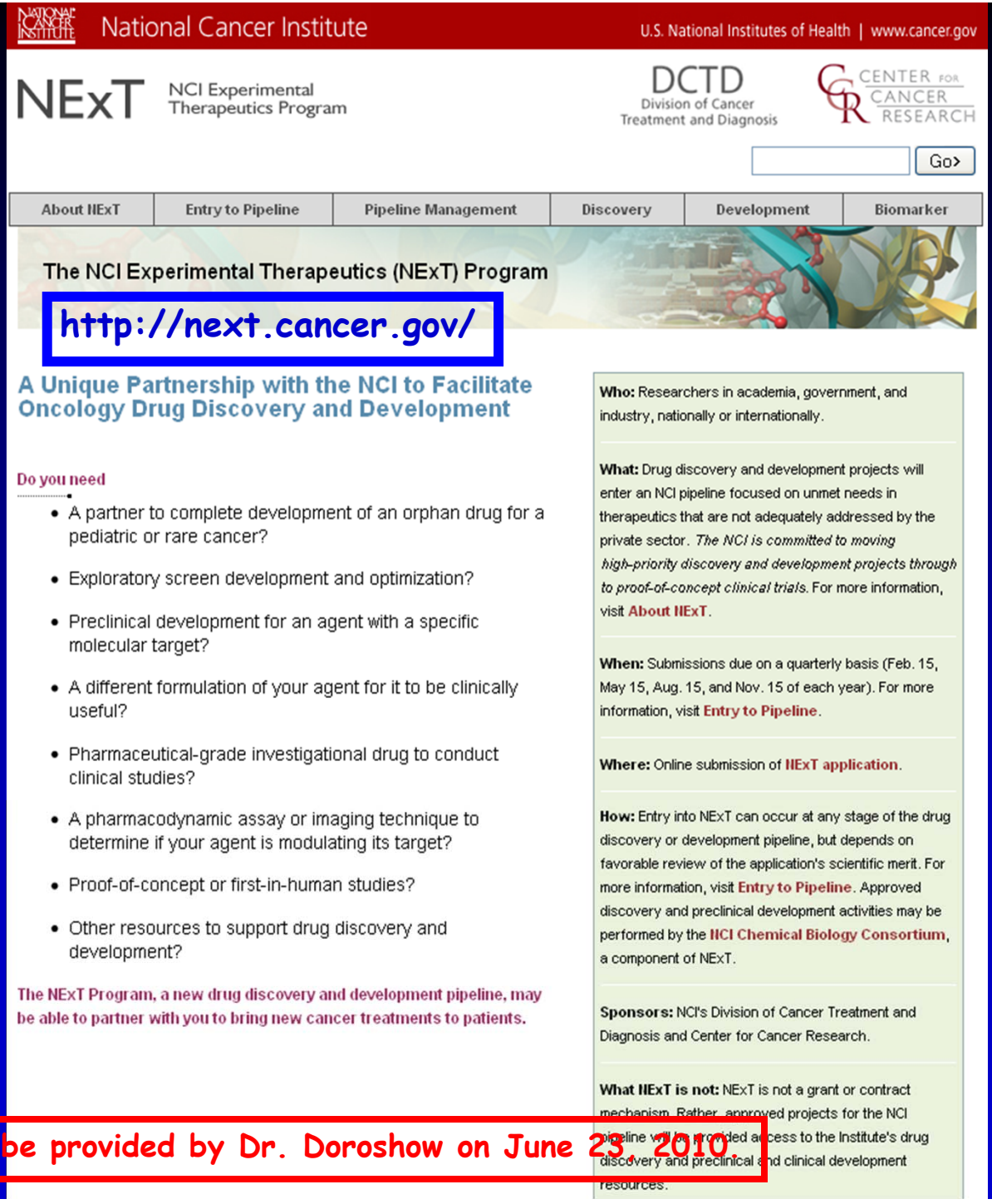
rget discovery through Clinical Trial(s)



Drug Development Resources

- Developmental Therapeutics Program
  - Drug Synthesis and Chemistry Branch (Lab, 6)
  - Natural Products Branch (Lab, 1)
  - Biological Testing Branch (Labs)
  - Pharmaceutical Resources Branch (Lab, 12)
  - Toxicology and Pharmacology Branch (Labs, 13)
  - Biological Resources Branch (Labs, SCs)
- Cancer Imaging Program (New)
  - Small Animal Imaging Facility in Frederick
  - NCI Imaging Clinic in NIH CC

NExT Web Site



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4. NCI should establish Centers of Excellence in a variety of scientific areas
5. NCI should expand the scope of the Biologic Resources Branch

Implementation Activities and Status

- NCI has addressed this recommendation by creating the following programs:
  - The Cancer Genome Atlas (TCGA)
  - TARGET
  - Genome-wide Association Studies (DCEG)
  - Cancer Target Discovery and Development Network (CTD2; OCG)
  - Functional Biology Consortium (DCTD)

Human Genomics Programs

- **TCGA Pilot** (The Cancer Genome Atlas)
  - Gliobastoma Multiforme
  - Ovarian (serous cystadenocarcinoma)
  - Lung (squamous carcinoma)
- **TARGET** (Therapeutically Applicable Research to Generate Effective Treatments in childhood cancers)
  - ALL, Neuroblastoma, AML, Osteosarcoma, Wilms tumor
- **GWAS** (Genome-wide Association Studies)
- **Other data/studies**

Functional Biology Consortium

FBC Goals

- Potential candidate targets identified by TCGA, GWAS, TARGET, etc, must be validated for biological activity and clinico-pathological association with tumor etiology and progression, and each validation should be confirmed by several assays.
- Is the putative target(s) linked to tumor formation and progression?

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Implementation Activities and Status

- NCI60 Screen is still the primary screen for molecules submitted to DTP
- Now highly annotated with molecular data
  - Protein levels
  - RNA measurements
  - Mutation status
  - Enzyme activity levels
  - Etc.
- CBC Created HTS uHTS and specialized screening centers,
  - Comprehensive Screening Centers
  - Specialized Application Centers

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Implementation Activities and Status

- The following centers have been established:
  - NCI Pharmacodynamic/Biomarker Centers [1]
    - PADIS and NCTVL for CBC/NExT and Phase 0/I
  - Comprehensive Screening Centers for CBC/NExT [1]
  - Specialized Application Centers for CBC/NExT [1]
  - Chemical Diversity Centers for CBC/NExT [1]
  - NCI Small Animal Imaging Facility for CBC/NExT

[1] Previously described

NCI-Frederick: Small Animal Imaging Program (SAIP)

- **Overview:** The NCI-Frederick Small Animal Imaging Program was established to provide NCI Investigators with a state-of-the-art *In Vivo* imaging facility. The SAIP became operational in October 2006 in Building 553 with the installation of a 3.0 Tesla MRI unit.
- Additional equipment including a Xenogen IVIS SPECTRUM for bioluminescence and fluorescence imaging, a CRi Maestro for fluorescence imaging, a VisualSonics Vevo 770 40Mhz Ultrasound unit for real time sonography, and a Siemens Inveon MicroPET scanner.
- Installed a Siemens Inveon microSPECT/CT imaging platform which will dock to the microPET device and a Fuji FLA-5100 autoradiography/fluorescence/chemiluminescence unit later in 2007.

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Implementation Activities and Status

- The Biological Resources Branch Oversight Committee was established in 1997-98
- New NCI RAID Biologics Special Emphasis Panel (SEP) Created – Fall 2006 - FACA
- Immunotherapy Agent Workshop, July 2007
  - Established priority list of 20 agents for NCI to obtain or produce for the immunotherapy community
- Cancer Immunotherapy Trials Network (CITN) approved March 2009
- Guidelines for the Notice (NOT-CA-10-025): IRM STRAP (Receipt date: July 15, 2010) issued
- Education Activity: "Working with the FDA: Biological Products and Clinical Development"

Additional details will be provided by Dr. Doroshow on June 23, 2010.

Questions for the NCAB

1. What new directions should DCTD and the NCI pursue in the area of drug discovery and development?

2. What is your opinion of the progress that has been made since the last DTRG?

3. What would be considered a measure of success for this program?

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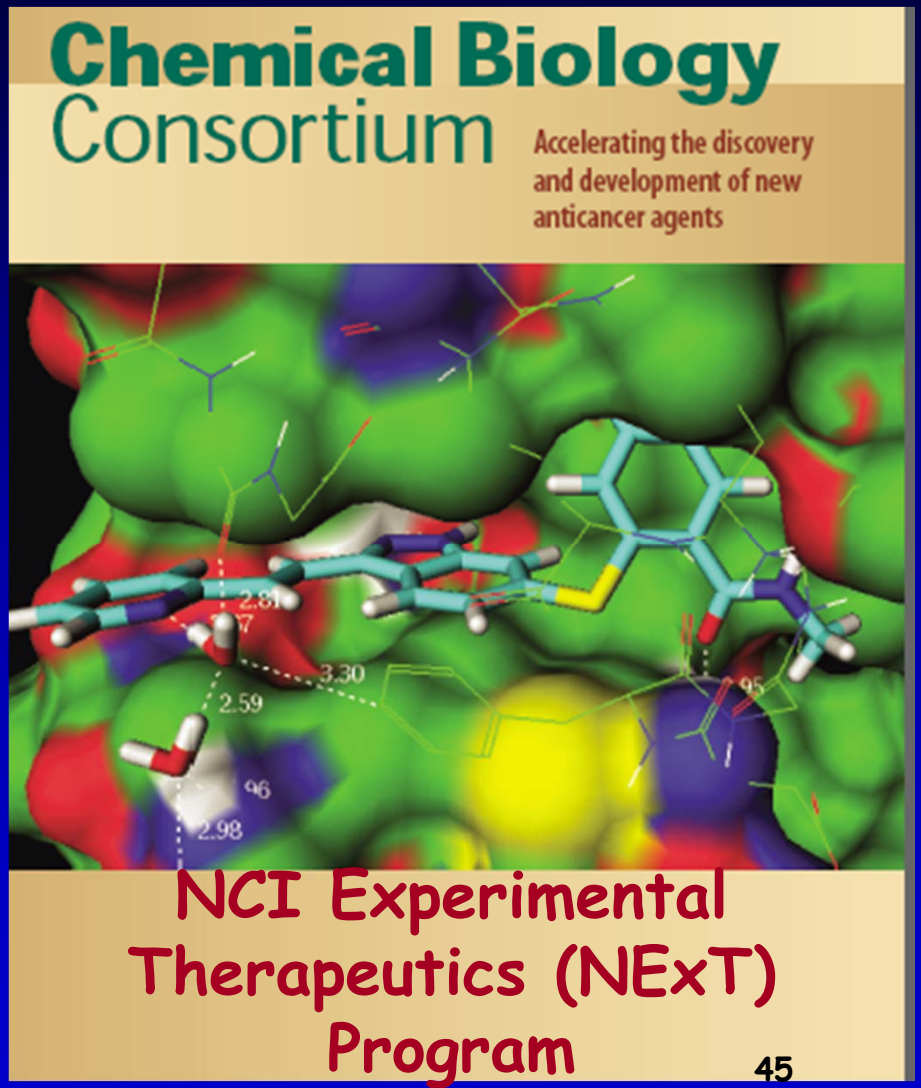
CAM

Accelerating Cancer Diagnosis and Drug Development

Questions and Discussion?

Thank you!



Contact Information

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- Web Address: http://dctd.cancer.gov/

The Chemical Biological Consortium: A New NCI Initiative

CCBSC	1. Sanford Burnham Inst for Med Res	John C. Reed, Kristiina Vuori
	2. Southern Research Institute	W. Blaine Knight
	3. SRI International	Lidia Sambucetti
	4. Univ. North Carolina – Chapel Hill	Stephen Frye
	❖ NIH Chemical Genomics Center	Chris Austin
SAC	1. University of California, SF	James A. Wells
	2. University of Pittsburgh DDI	John Lazo
	3. Emory University	Haian Fu, Fadlo Khuri, Dennis Liotta
CDC	1. Georgetown University	Milton L. Brown
	2. Vanderbilt Institute of Chem Biol	Gary Sulikowski, Alex Waterson
	3. University of Minnesota	Gunda I. Georg
	4. University of Pittsburgh	Donna Huryn
Others	❖ GVK Biosciences	Sreenivas Devidas
	❖ Starks Associates, Inc.	David Starks
	❖ NCI Intramural Chemical Biology	
	❖ Affiliate Investigators	

Next Application Statistics

Cycle	Received	Discovery	Development	Approved	Discovery	Development
01	52	44	8	10	8	2
02	53	20	33	9	3	6
03	23	11	12	6	3	3
04	46	18	28			
Total	174	93	81	25	14	11