NCI’s Experimental Therapeutics Program (NExT): Promoting Collaboration Between Public, Industry, and Investigator

Naoko Takebe
Investigational Drug Branch
Cancer Therapy Evaluation Program
DCTD/NCI/NIH
Overview

• To introduce NCI Cancer Therapy Evaluation Program (CTEP) as an example for collaboration between Public, Industry, and Investigator in anti-cancer therapeutics development.
  – NCI CTEP Model: Promoting Investigator Initiated Clinical Trials
  – Introduction to the NCI Experimental Therapeutics (NExT) Program: Source of Anti-cancer Agent
  – Conclusion: What Can Industry-Academia-Government Cooperative Model Do?
Selected NCI/CTEP-sponsored Group Trials Contributing to FDA-approved Indications for New Oncology Agents

• 1991
  – Fludarabine phosphate (SWOG)
  – Pentostatin (CALGB, SWOG)

• 1992
  – Paclitaxel (GOG, CALGB, ECOG, NCCTG, SWOG)

• 1993
  – Melphalan IV (CALGB)

• 1994
  – Pegasparagase (POG)

• 2001
  – Imatinib mesylate (COG, SWOG)

• 2004
  – Letrozole (NCIC, Intergroup)
  – Oxaliplatin (NCCTG, Intergroup);
  – Taxotere (SWOG)

• 2005
  – Nelarabine (COG, CALGB)

• 2006
  – Bevacizumab (ECOG, Intergroup);
  – Rituximab (ECOG, Intergroup)
  – Herceptin (NSABP, NCCTG, Intergroup)

• 2008-2011 (May)
  – Nelarabine (COG, CALGB)
  – Imatinib mesylate/GIST-adjuvant (ACOSOG)
  – Bortezomib (MSKCC)
  – Bevacizumab/RCC (CALGB)
  – Romidepsin (NCI CCR)
  – Dasatinib (SWOG)

Updated by Sherry Ansher
Total CTEP R&D Agreements Executed and Active Between 1997-2008

Number of Agreements

Year


Total Active R&D Agreements
Total Executed R&D Agreements
NExT (CTEP) by Numbers

• CTEP sponsored only Investigator-Initiated Clinical Trials
• Currently sponsors over 100 INDs
• Approx. 11,000 registered investigators at over 3,300 institutions
• Over 750 active protocols
• 150-250 new protocols/year
• Approx. 30,000 patients accrued/year
• Over 80 collaborative agreements (CRADAs, CTAs, and CSAs) with pharmaceutical companies (Collaborators)
新規化合物がNCに入り臨床試験実施までの流れ:
NCI Experimental Therapeutics Program (NExT)
### CTEP各部門の機能

<table>
<thead>
<tr>
<th>部門</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAD</td>
<td>CTEPのディレクター・オフィス、各部門を統括</td>
</tr>
<tr>
<td>ARC</td>
<td>CTEP研究者へのAdministrative support</td>
</tr>
<tr>
<td>RAB</td>
<td>研究者、企業、FDAなどとの契約 CRADA, MTA, IND.</td>
</tr>
<tr>
<td>OIB</td>
<td>臨床試験がスムーズに行われるよう各部門を統括</td>
</tr>
<tr>
<td>CGCB</td>
<td>臨床試験の予算とプロポーザル・マネジメント</td>
</tr>
<tr>
<td>PMB</td>
<td>薬剤の管理・搬送と症例のRandomizing</td>
</tr>
<tr>
<td>CTMB</td>
<td>臨床試験のモニタリング</td>
</tr>
<tr>
<td>IDB</td>
<td>新規化合物の開発(早期臨床試験)</td>
</tr>
<tr>
<td>CIB</td>
<td>臓器別に臨床試験第Ⅱ相以降を担当</td>
</tr>
</tbody>
</table>

竜傷内科 Vol.8 No.3  Sep 2011
CTEP Therapeutics Development Program

Agents Selected Through NExT Program

Pre-Clinical
- Developmental Therapeutics Group/IDB
  - NCI/DCDT

Phase 0
- Biomarker Group/IDB
  - Phase 1 Program

Phase 1
- IDB
  - Pediatric Phase 1 Consortium
  - ABTC
  - PBTC

Phase 2
- IDB
  - Phase 2 Program
  - *Other (Centers, SPORES, R21, R01, P01, etc.)

Phase 3
- CIB
  - Cooperative Groups
  - *CCOPs

CCOPs: community clinical oncology program
IDB: Investigational Drug Branch
CIB: Clinical Investigational Branch
*Non-CTEP Funded Resources
Access to NExT

Who: Researchers in academia, government and industry, nationally and internationally.

http://next.cancer.gov/
<table>
<thead>
<tr>
<th>Year</th>
<th>Agents</th>
<th>Role of NCI</th>
<th>Mechanism of Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Sipuleucel (Provenge®)</td>
<td>RAID project</td>
<td>National Cooperative Drug Discovery Grant</td>
</tr>
<tr>
<td>2010</td>
<td>Eribulin (Halaven)</td>
<td>Natural product discovery; screening; formulation of clinical product; efficacy testing; clinical candidate selection; first-in-human trial</td>
<td>DCTD/DTP Frederick labs;</td>
</tr>
<tr>
<td>2009</td>
<td>Pralatrexate</td>
<td>RAID project; NCI produced GMP bulk drug</td>
<td>DCTD/DTP contract resources for production of GMP quality bulk drug</td>
</tr>
<tr>
<td>2009</td>
<td>Romidepsin (Depsiptide)</td>
<td>Developed safe human dosing schedule in large animals; PK and Tox; produced drug for clinical trials; conducted first-in-human trials in NIH CC</td>
<td>DCTD/DTP pharmacology and toxicology and drug production</td>
</tr>
<tr>
<td>2004</td>
<td>Cetuximab</td>
<td>Produced first lots for imaging and chimeric clones</td>
<td>DTP Contracts; Cooperative Drug Discovery Grant</td>
</tr>
<tr>
<td>2004</td>
<td>5-Azacytidine</td>
<td>Pre-clinical molecular pharmacology; produced pre-clinical and clinical drug supply; conducted pivotal trial</td>
<td>DTP Contracts; Frederick</td>
</tr>
<tr>
<td>2003</td>
<td>Bortezomib</td>
<td>Extensive analog screening; MOA and PD studies; PK &amp; Tox; clinical formulation</td>
<td>DCTD/DTP Frederick labs; formulation, PK, Tox</td>
</tr>
<tr>
<td>2000</td>
<td>Temozolomide</td>
<td>Scale up synthesis and clinical formulation</td>
<td>DCTD/DTP bulk drug and formulation contracts</td>
</tr>
</tbody>
</table>
Transformation of the NCI Therapeutics Pipeline

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

Harmonize Activities into Single Pipeline

MLPCN: molecular libraries probe production centers network,
Chemical Biological Consortium

Mission

Dramatically increase the flow of early-stage drug candidates into the DCTD therapeutics pipeline. Provide the extramural community the opportunity to participate in a highly collaborative drug discovery partnership with the NCI.

• Comprehensive Chemical Biology Screening Centers (4)
  ✓ Identify targets, develop 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

• 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

SAIC issued RFP in Oct 2008 seeking technical proposals from screening and chemistry centers to support early drug discovery activities.

August 2009 11 centers awarded contracts.
NCI Chemical Biology Consortium (CBC)

- The University of Pittsburgh
- University of Minnesota
- The University of Pittsburgh Specialized Application Center
- The NIH Chemical Genomics Center (NCGC)
- Georgetown University Medical Center
- North Carolina Comprehensive Chemical Biology Center
- The Fragment Discovery Center (FDC at UCSF)
- SRI International
- Sanford Burnham Institute
- Vanderbilt Institute of Chemical Biology
- Emory Chemical Biology Discovery Center
- Southern Research
Multiple Entry Points Into CBC

- Target identification
- Primary HTS
- Parallel medicinal chemistry
- Optimal potency/selectivity
- Efficacy in pivotal in vivo models

- Model Development and Target Validation
- PD Endpoint Validation
- Small Animal Imaging Center

- New Cellular Target
- HTS-Ready Assay
- Ligand or Target Structural Information
- Weak Lead Compound
- Lead Modification
- Lead Re-indication

- Assay Development and qHTS
- Optimization and qHTS
- Virtual Screening or Fragment-Based Lead Discovery
- Full Medicinal Chemistry Entry
- Focused Analog Synthesis
- Large-Scale Synthesis
Early Development Platform

Contracts and in-house FFRDC Laboratory Facilities

- Pharmacokinetics/Pharmacodynamics
- Toxicology
- GMP Scale-Up
- Development of PD assays during preclinical stages is supported by the Pharmacodynamics Assay Development & Implementation Section (PADIS), and during clinical stages by the National Clinical Target Validation Laboratory (NCTVL).
- Clinical Assay Development Program (CADP) to facilitate development and validation of clinical assays (including diagnostics).
From Bench to Bedside: NCI Experimental Therapeutics Program (NExT)- Collaboration Between DCTD and Center for Cancer Research

- **NCI**
- **Industry**
- **Academia**

**AGENTS**
- Application

**Agents Review**
- Discovery SEP
- Development SEP

**Development Plan**
- Preclinical Development
- Clinical Development

- Molecular imaging
- PD marker (NCTVL)
- Exploratory IND

**Disc. or Dev. Committee**

**SAC**

**Solicitation**

**Investigators**

**NCI CTEP**

**Approval**

**Letter of Intent**

**STUDIES**

- Clinical, Pre-Clinical Development: Guided by a new DCTD Developmental Therapeutics Project Management Office

NCTVL: National Clinical Target Validation Lab

http://nexttest.cancer.gov/
NExT Pipeline – Phases of Development and Associated Oversight

INPUT

OUTPUT

DTP/CTEP

Discovery / Development

腫瘍内科  Vol.8 No.3  Sep 2011
NExT Pipeline – Phase and Agreement Types

Chemical Biology Consortium target discovery through lead compound

Formerly RAID and DDG – “Mid-phase projects”

CTEP – Sponsored Clinical Trials

CBC Consortium Agreement

“NExT MTA”, CDA’s, MTA’s

CTA’s, CRADA’s and CSA’s subject to CTEP IP Option

Associated Agreement

Slide Graphic courtesy of Barbara Mrockowski
Collaborative Research and Development Agreement (CRADA) For An Agent X

**Pharma**
- Provide the agent
- Support for proprietary assays (e.g. PK)
- CRADA fund
- Supplemental fund (optional) to sites for additional data or correlative studies

**CTEP**
- Develop scientific strategy; solicit clinical trial concepts and develop biomarker assay available to public in collaboration with DTP
- Sponsor the trials (IND holder, funding and monitoring the trial)
- Support infrastructure of clinical trial network
- Device master IP, contract language

**Investigators:**
- Propose and conduct clinical trials

**CTEP clinical trial network**
- Phase I/II trial consortia, academic institutions; NCI intramural program
- Cooperative groups (ECOG, SWOG, CALGB, NCCTG, NSABP, RTOG, GOG, COG ..)
- Community based oncology programs
- Ex-US sites (Canada, Europe, Southeast Asia-Pacific, Japan, Korea, Latin America, Israel, Saudi Arabia, others)
Industry-NCI/CTEP-Investigator Agreements

- **Master agreement designed** to encourage companies to contribute investigational agents for combination studies
  - **IP option**: Each collaborator receives fully paid, non-exclusive, royalty-free licenses to any inventions from the combination studies

**Common Data Sharing and IP Option Agreement Language**

- Collaborative Agreement
- Investigational Agent A
- Collaborator A
- Investigational Agent B
- Collaborator B
- NCI/CTEP
- Funding Agreement (N01 U01 Group)
- MTA (for non-clinical studies)

**Accepted by collaborators. ➔ > 120 trials combining investigational agents**
Summary

- Public-industry-investigator collaboration is an important strategy to expedite and expand the cancer drug development
- CTEP experience indicated that such collaboration can be productive, and beneficial to investigators, the company, and most importantly, to patients
- NCI’s non-overlapping drug development of agents with pharmaceutical and biotech companies will result in economical growth by generating new intellectual properties
- Each partner in drug development can provide unique and valuable contribution to the process. Concerted effort is critical and should continue to address the most challenging tasks in modern day oncology drug development
  - Optimize the efficacy of new drug development, amongst many targets and many agents (NCI example, clinical development is performed in collaboration with government support for PD, PK, imaging, and Clinical Diagnostic groups etc.)
  - Better understanding and characterization of the tumor biology and heterogeneity
  - Prioritize and develop rational combination studies especially molecular targeting agents. CRADA makes it possible to combine novel-novel drugs in clinics
  - Biomarker studies to enable personalized medicine for minimizing toxic treatment exposure to only patients with predicted efficacy and high efficacy study due to patient enrichment
Acknowledgement

• CTEP
  – James Zwiebel, M.D. Percy Ivy M.D., Helen Chen M.D. Investigational Drug Branch
  – Sherry Ansher, Ph.D., Regulatory Affairs Branch

• NExT Program
  – Dr. Barbara Mroczkowski PhD, Special Asst to the DCTD Director at NCI
  – Jason Cristofaro J.D. PhD., Intellectual Property Advisor DCTD

Naoko Takebe Takeben@mail.nih.gov
NExT Program: http://next.cancer.gov/
CTEP website: http://ctep.cancer.gov
Clinical trials: www.ClinicalTrials.gov