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

Preclinical Toxicology of Drugs Developed for Cancer & Other Diseases

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NCI Board of Scientific Advisors
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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
Why does NCI need preclinical pharmacology and toxicology contracts and what do they provide?
"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.”
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
FDA Preclinical Pharmacology & Toxicology Requirements

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

**Biologica**
- Most Relevant Species
- Clinical Route & Schedule
- Biodistribution

*Study designs are agent-directed & IND-Enabling.*
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
Preclinical Toxicology and Pharmacology are required for decision-making throughout drug discovery and development and for IND filing for clinical trials.
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?)
The NCI Experimental Therapeutics (NExT) Pipeline:
Target discovery through early stage clinical trials
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.
How Does An Extramural Investigator Access NCI’s Drug Discovery and Development Resources?
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
Cycle 1: Total of 52 NExT proposals for cycle 1 received

Number of proposals:

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<th>SDS</th>
<th>LD</th>
<th>CS</th>
<th>CAN</th>
<th>P0</th>
<th>PI</th>
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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
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
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*
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
Late-stage drug development requires model development and target validation to ensure efficacy and safety. This process is crucial for identifying potential treatments and validating their mechanisms of action. The diagram outlines the steps involved in model development and target validation, highlighting the importance of biomarker validation and small animal imaging in advancing drug candidates. This information is adapted with permission from the NIH Chemical Genomics Center.
How Are Projects/Compounds Selected?

National Cancer Institute

Implementation

- Discovery Special Emphasis Panel (SEP)
- CBC Steering Committee (SC)
- NExT Discovery Committee
- NExT Senior Advisory Committee (SAC)
- NExT Development Committee
- Development Special Emphasis Panel (SEP)
- Senior Management Committee (SMC)
- Portfolio Managers
How Are Projects/Compounds Selected?

NCI Pharm & Tox staff will manage resource capacity of entire pipeline; an integrated effort to achieve the milestones for projects (molecules) according to their prioritization by SEPs.
Which Compounds Will Actually Move Forward?

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

- 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

Scoring:
- 1 = Exceptional
- 3 = Excellent
- 6 = Satisfactory
- 9 = Poor
NCI Drug Discovery and Development Accomplishments via Preclinical Pharmacology and Toxicology Contracts During Current Funding Cycle
What Did We Get For Our Toxicology and Pharmacology Investment?

Status of Projects/Molecules Supported by DTP Pharmacology & Toxicology

- Exploratory Independent Pursuit: 1
- Pending committee decision: 5
- Project terminated: 19
- Development – Ongoing: 6
- IND not yet filed by PI: 11
- IND filed: 17
- Phase 1 Clinical: 12
- Phase 2 Clinical: 3
- Approved: 1
- Total Projects: 74
What Did We Get For Our Toxicology and Pharmacology Investment?

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- Approved
- Total Projects

INDs Recently Filed
1-Methyltryptophan
IPdR
DB-67
MR1-1 Pseudomonas exotoxin
Fenretinide plus Safingol
Delta-24-RGD OncoVirus
Azurin p28 peptide
GGTI-2418
SQ109
PX-866
SRX245
Akt Inhibitor
B201
TYRP2
Status of Compounds with Filed INDs Supported by These Contracts That Have Entered the Clinic

Current Status of Compounds with Filed INDs

- Unknown Status of Trial, 9%
- Phase I Clinical trials Underway, 32%
- Phase II Clinical trials Underway, 4%
- Licensed, 23%
- Trial Approved, 18%
- Clinical Hold, 5%
- In negotiations to License, 4%
- Approved for use, 5%
## 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 Adenoviral Vector
  - Chimeric 11-1F4 monoclonal
  - Replication-Competent
  - Herpes Simplex Viral Mutants

### Phase II
- 17-DMAG
- Fluorodeoxcytidine/THU

### Approved by ODAC
- Depsipeptide
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.
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)
Total Utilization of Contracts is Driven by Portfolio Needs/Capacity and Available Funds

- **Total Capacity (Tox & Pharm)**: 50 million
- **Total funding (Tox & Pharm)**: 40 million

Utilization lower than total capacity for the period 2004-2009.
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 $C_{\text{Max}}$ of 210 nM was achieved in at least 1 participant
Pharmacokinetics of Single Oral Dose of ABT-888

- 10 mg (N = 3)
- 25 mg (N = 3)
- 50 mg (N = 7)
- 0.21 µM target

Plasma Concentration (µM) ± SD

Time (hr) After ABT-888 Administration
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.
Total Utilization of Contracts is Driven by Portfolio Needs/Capacity and Available Funds

Utilization lower than total capacity

2004-2009

Total Capacity (Pharm) 9.7
Total funding (Pharm) 9

Millions

National Cancer Institute
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
• Overview of Pharmacology and Toxicology Program
• Pharmacology Contract
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
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, 1 Dose Level); None in iv Q4D x 3 and ip Q4D x 3

- **Myelotoxicity:**
  - iv Dx5 > iv Q4D x 3 ~ ip Q3H x 8 Q4D x 3 > iv Q4D x 3; ip Q4D x 3 - 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*
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
Indenoisoquinoline Proof of Mechanism Randomized Phase I Trial

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

Dose Response: Indenoisoquinoline Treated A375 Xenografts

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

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

Vehicle Controls

Solid red line = Avg vehicle control  Dashed red line = Avg ± 1 and 2 SD
Black line = Dose Response
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mouse IC90 (nM) ± SD (range)</th>
<th>Human IC90 (nM) ± SD (range)</th>
<th>Ratio Mouse/Human</th>
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<td>Topotecan HCl</td>
<td>120 ± 50 (64 - 160)</td>
<td>5.9 ± 5.1 (1.7 - 15)</td>
<td>20.3</td>
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<tr>
<td>(Hycamptin)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NSC 724998</td>
<td>29 ± 12 (18 - 41)</td>
<td>27 ± 14 (7.1 - 45)</td>
<td>1.1</td>
</tr>
<tr>
<td>NSC 706744</td>
<td>47 ± 6 (47 - 48)</td>
<td>8.1 ± 2.9 (4.4 - 11)</td>
<td>5.8</td>
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*FDA IND approved 10/20/09*
Total Utilization of Contracts Driven by Portfolio Needs/Capacity and Available Funds

- Total Capacity (Toxicology) 2004-2009: 40
- Total Funding (Toxicology) 2004-2009: 31

Utilization lower than total capacity

Millions

2004-2009
• 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
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.
Success: What Will it Look Like?

Transparent, Accountable, Inclusive, & Unified

- Hypothesis Generation
- Clinical Candidate Development
- Commercialization

Target/Molecule Discovery
- Target Validation
- Assay Development
- Lead Generation

Lead Optimization
- Preclinical Development

Phase I
Phase II
Phase III

Registration
Global Launch
Global Optimization

PoC in 30% of Phase II trials

Cumulative Investment

Risk
Accelerating Cancer Diagnosis and Drug Development

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

DCTD
Jason Cristofaro
Barbara Mrochowski

CTEP
Jamie Zweibel
Jeff Abrams

Center for Cancer Research
Yves Pommier
Lee Helman
Bob Wiltrout
Shivaani Kummar

Cancer Imaging
Jim Tatum
Paula Jacobs

Cancer Diagnosis
Jim Jacobson
Sheila Taube
Questions?

- Toxicology Program
- Integrated Drug Development Effort
Comparing Development Costs: NCI vs. Pharma

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

- Preclinical*: 198 Bio, 136 Pharma, 150 Pharma (time-adjusted)**
- Clinical: 361 Bio, 316 Pharma, 522 Pharma (time-adjusted)**
- Total: 559 Bio, 452 Pharma, 672 Pharma (time-adjusted)**

* 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