NCI’s Roadmap to
Personalized Cancer Treatment

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Director, Division of Cancer Treatment and Diagnosis

National Cancer Advisory Board
Bethesda, MD
June 11, 2009
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<tr>
<th>Rank</th>
<th>Assignee</th>
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Therapeutics Development Timeline

Hypothesis Generation

Chem-Biol Cons

TCGA & Ca Biol Discovery

Target/ Molecule Discovery & Biological Characteriz.

Target Validation

Assay Development

Lead Generation

Lead Optimization

Pre-Clin. Development

Phase I

Phase II

Phase III

Registration

Global Launch

Global Optimization

Cumulative Investment

Risk

Cumulative Investment

Time: 6-8 Years

Time: 12-15 Years

$20-60 MM

$200-300 MM

$500-600 MM

$1200 MM
Critical Requirements for the Development of Personalized Cancer Treatment: Phase I-III Transition

- Timely prioritization & dedicated resources for essential biomarker validation studies, utilizing standardized laboratory practices.
- Accelerate prioritized translational research initiatives in the area of personalized therapy.
- Support for the coordination of hypothesis-driven biomarker studies across the entire clinical/translational science continuum.

**Focus:** Improve the specificity of treatment while reducing the high rate of failure (and cost) during the Phase I to III transition.
• Biomarker, Imaging, and QOL Studies Funding Program

• Development of Special Translational Research Acceleration Program (STRAPs)

• Grand Opportunity: Coordination of Clinical/Translational Research Across the NCI
Purpose

- Ensure that the most important correlative science and quality of life studies can be initiated in a timely manner in association with clinical trials
- Intent is to fund studies conducted in association with Phase 2/3 trials when cost is too high to be covered by Cooperative Group or other mechanisms

Prioritization Criteria

- Correlative science (essential marker and imaging)
  Developed by the Task Force of the Program for the Assessment of Clinical Cancer Tests (PACCT) and approved by CTAC in July 2007

- Quality of Life and Symptom Management
  Developed by the Symptom Management and Health-Related QOL (SxQOL) Steering Committee and approved by CTAC in November 2007
Prioritization: Integral and Integrated Studies

1st **Integral** studies: a test that must be performed in order for the trial to proceed
- Test to establish patient eligibility
- Test for patient stratification
- Test to assign patient to treatment arm, including early response endpoints for assignment of treatment during a trial

2nd **Integrated** studies: studies that are intended to identify or validate markers and imaging tests or QOL instruments that might be used in future trials
- Study plans clearly described in trial protocol
- Tests performed on all cases although results not used to guide decisions in current trial
N0723: Predictive Marker Study Design

NCCTG (Study Chair: Alex Adjei) + CALGB, ECOG, SWOG, NCIC
Others: C-Path & industry partners, Pharma, FDA

Initial Registration

2nd line NSCLC with specimen

FISH Testing

4 years accrual, 1196 patients

Strata

EGFR FISH + (~ 30%)

EGFR FISH − (~ 70%)

Randomize

Erlotinib

Pemetrexed

Erlotinib

Pemetrexed

957 patients

Outcome

1° PFS
2° OS, ORR

1-2 years minimum additional follow-up

- PFS endpoint
  - Less influenced by treatment crossover
  - Will require synchronized treatment schedules, independent blinded imaging review
- Power
  - 90% to detect 50% PFS improvement favoring erlotinib in FISH+, 2.5---3.75m
  - 90% to detect 30% PFS improvement favoring pemetrexed in FISH−, 1.92--2.5m
  - > 90% to detect interaction
- IHC, mutational analysis, PGN evaluation in addition to FISH
Contributions of CTWG/TRWG Implementation to Personalized Therapeutics

- Biomarker, Imaging, and QOL Studies Funding Program

- Development of Special Translational Research Acceleration Program (STRAPs)

- Grand Opportunity: Coordination of Clinical/Translational Research Across the NCI
How can we best assure that:

- The most promising concepts enter the developmental pathways?
- Concepts that do enter advance to the clinic or to productive failure?
- Progress is as rapid, efficient and effective as possible?
Select several projects/year that are “ripe” for translation

• Translational Research Acceleration Process Will:
  • Gather information on translational opportunities
  • Prioritize translational research opportunities
  • Develop a funding & project management plan to accelerate prioritized opportunities

• Translational Research Acceleration Process Will NOT:
  • Impact Discovery research
  • Replace existing infrastructure or mechanisms for clinical or translational research
Critical Elements for a Process to Prioritize Translational Research Opportunities

Intra-pathway Prioritization
Pathway-specific criteria determined and weighted; prioritization performed by extramural content experts

Inter-pathway Prioritization
Performed by the Clinical and Translational Research Advisory Committee (CTAC) of the NCI

Executive Decisions
NCI leadership
Special Translational Research Acceleration Project (STRAP)

- Requirements:
  - Goal of completing early stage human studies
  - Project management plan
  - Specific development milestones and timelines
  - Development/commercialization strategy
- Funds for new and/or expanded projects
- Project management would link new or existing teams and projects and facilitate hand-offs between groups
- Opportunities to include industry/foundation funding or participation

Proposed Funding Strategy
TRWG Implementation

Next steps & Timeline

- **Late summer '09**
  - RFI for Translational Research Opportunities Pilot
    - Immune Response Modifier Pathway

- **Fall '09**
  - Prioritize

- **2010**
  - Fund & Manage
• Biomarker, Imaging, and QOL Studies Funding Program

• Development of Special Translational Research Acceleration Program (STRAPs)

• Grand Opportunity: Coordination of Clinical/Translational Research Across the NCI (RFA-OD-09-004)
Facilitate high impact translational research by rewarding collaborative team science

Studies associated with multi-institutional clinical trials, conducted by consortia of SPORES, Cancer Centers, Cooperative Groups, PO1s, or other partners that, for example:

- Validate therapeutic biomarkers
- Correlate immunological signaling pathways with outcome from immunotherapy
- Perform pharmacogenomic profiles to understand therapeutic efficacy or toxicity

Due May 27, 2009; supported by ARRA initiative; funding start date: September 30, 2009
Critical Requirements to “Personalize” Early Phase Trials

- Increase focus on proof-of-mechanism early phase clinical trials
  - Consider the first-in-human study as the culmination of pre-clinical development
  - Demand evidence that personalized therapies affect relevant pathways in tumor tissue (associated with efficacy)
  - Employ surrogate tissues only when there is a clear relationship between effect on the target in surrogate and in tumor

- “Clinical readiness” of pharmacodynamic assays
  - Pharmacodynamic assay development with validated analytical performance
  - Tissue acquisition and handling in the clinical setting
  - Storage transferability
  - Stability of analyte
  - Inter-, intratumoral variability
Novel Approaches to Early Phase Personalized Trials

"Clinical" Approach to Mouse Models

Phase 0 Trial of ABT-888
Indenoisoquinoline Proof of Mechanism
Randomized Phase I Trial

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

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

Dose Response: Indenoisoquinoline Treated A375 Xenografts

Vehicle Controls
Solid red line = Avg vehicle control   Dashed red line = Avg ± 1 and 2 SD
Black line = Dose Response
• How best to support academic investigators who wish to move from target or molecule discovery to clinical trials (preclinical testing, toxicology, GMP production, and regulatory support)

• Addressing the “pharmacogenomics divide” (courtesy of Drs. Ames and Goetz, Mayo Clinic)

• Establishing a scientific rationale for combinations of targeted therapies
Reorganization of RAID Drug Development

**Decision Support**
- new project acceptance
- milestones
- no-go
- portfolio prioritization
- outcome metrics

**Management Support**
- modular tasks
- project managers

**Infrastructure Support**
- RAID workshops
- training manuals
- regulatory support
- clinical trials support
- phase 0/1 clinical trials

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**OVERSIGHT CMTE.**

**EVALUATE RAID APPLICATIONS**
- Small Molecule Biologics

**SOLICIT APPLICATIONS IN PRIORITIZED AREAS**

**PROJECT INITIATION**

**INITIAL TASK**

**OVERSIGHT CMTE. & Subcmte.'s**

**SUBSEQUENT TASK**

**OVERSIGHT CMTE. & Subcmte.'s**

**SUBSEQUENT TASK**

**Clinical "Go"/"No-Go" Decision**

**Active Project Management**

**First-in-Human Trials**

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**1/1/2007**

**Training Workshop**

**Develop Training Manuals**

**Access to Phase 0/1 Resources**

**Regulatory Support**
NCI Experimental Therapeutics Center

Extramural

NExT Center

DTP/CCR/Chemical Biology Medicinal Chemistry Teams

DTP Pharmacology and Toxicology

NCI Molecular Imaging

CTEP/RRP/CCR

Lead Optimization

Lead Profiling

Clinical Candidate

Phase 0/1

Discovery Development Clinical Investigation
Oxford Overview: 5 Years of Tamoxifen vs Not
ER Positive vs ER Negative

≈5 Years Tamoxifen vs Not
Recurrence
ER+/ER Unknown
Entry age ≥50

Control 40.3%
≈5-yr TAM 23.5%
10-yr gain 15.0% (SE 1.1)
Logrank 2P<0.00001

Loss 1.9% (SE 1.5)
Logrank 2P>0.1; NS

≈5 Years Tamoxifen vs Not
Recurrence
ER – Poor PR – Poor

≈5-yr TAM 29.0%
Control 27.1%
Classical Understanding of Tamoxifen Pharmacology (1975-2005)

- Selective Estrogen Receptor Modulator
- Disrupts ER activity by stabilizing ER protein, blocking estrogen binding to the receptor
- Partial anti-estrogenic effects in the breast
- Estrogenic effects in uterus and bone
- Wide variability in the concentrations of tam and its metabolites without any association with drug response or toxicity
Tamoxifen Pharmacology (2009)

- Not all tamoxifen metabolites are created equal
- Tamoxifen metabolites exhibit marked differences in
  1) ER binding
  2) Inhibition of cell proliferation

Stearns et al. JNCI 2003
Tamoxifen Metabolic Pathway (Humans)

Tamoxifen (TAM)

200-300 nM

CYP2D6
(CYP2B6, CYP2C9, CYP2C19, CYP3A)

5-10 nM

CYP3A4/5
(CYP2C9 + other CYP isoforms)

200-300 nM

N-desmethylTAM

400-600 nM

Endoxifen

20-180 nM

Endoxifen and 4-OH-Tamoxifen are Equipotent as Inhibitors of Estrogen Stimulated Cell Proliferation

MCF-7 cells: In Vitro

Concentrations in humans

- Tam (300-500 nM)
- 4HT (5-10 nM)
- Endoxifen (20-180 nM)

CYP2D6 Genotype and Endoxifen

CYP2D6*4 (most common genetic variant associated with the CYP2D6 poor metabolizer state)

Time to Recurrence According to CYP2D6 Metabolizer Status* in Women Receiving Adjuvant Tamoxifen

- EM/EM, EM/IM: (n=108)
- EM/PM, IM/IM, PM/IM: (n=65)
- PM/PM: (n=16)

P<0.001

HR 4.0
PM relative to EM

Goetz et al., Updated NCCTG 89-30-52, SABCS 2008
• CYP2D6 critical for endoxifen exposure and, thus, tamoxifen drug effect; endoxifen potently inhibits ERα as well as other traditional mechanisms
  – Metabolic activation of tamoxifen limits drug activity
  – Administration of endoxifen would bypass pharmacogenetic limitations of tamoxifen

• However, no IP possible for 30-year old metabolite, even though it is a new “drug”
  – Preclinical pharmacology, toxicology
  – Drug formulation and GMP production
  – IND submission
  – Phase I clinical trial

NCI has undertaken to produce clinical grade drug to begin the development process leading to a phase I study of endoxifen
Chemical Biology Consortium (CBC)

Vision

• Develop an integrated network of chemists, biologists, and molecular oncologists, with synthetic chemistry support.
  o Unify discovery with NCI preclinical and clinical development.
  o Link to other NCI initiatives with CCR as an integral partner.
  o Active mining of grant pool.

• Focus on unmet needs in therapeutics such as “undruggable” targets and under-represented “orphan” malignancies.
• Enable a clear, robust pipeline from target discovery through clinical trials for academic, small biotech, and pharma investigators.
CBC: Enabling Hit-to-Lead and Lead Discovery

Program Focus: Cross-site medicinal chemists (*academia, NIH, contractors*) working on high-risk, high-impact targets in a team setting.
Entry Points into NCI Drug Discovery and Development Platform

- Novel Cellular Target
  - Assay Development and qHTS

- HIS-ready Assay
  - Optimization and qHTS

- Ligand or Target Structural Information
  - Virtual Screening or Fragment Based Lead Discovery

- Weak Lead Compound
  - Full Medicinal Chemistry Entry

- Lead Modification
  - Focused Analog Synthesis

- Lead Re-Indication
  - Large Scale Synthesis

Screen development and high-throughput screening → Hit to Lead → Lead Optimization → Candidate Seeking

- Target Identification
  - Target validation and Model Development

- Primary HTS
  - Parallel medicinal chemistry

- Optimal potency/selectivity
  - Efficacy in pivotal in vivo models

- Prospective toxicity screens:
  - Cytotoxicity, genetic toxicity, hERG binding, drug-drug interactions, metabolism-mediated toxicity
2009 and Beyond: Working towards Success

- **New Drug Discovery and Development Platform**
  - New Stage Gate process: agreed milestones
  - Projects are driven by a Project Team led by a Project Leader and Project Manager
  - Specific criteria (i.e., milestones) must be met to progress through each stage gate

- **New Governance**
  - External Special Evaluation Panels and Internal Review Committees will work together to approve and prioritize new projects and review stage-gate progression
  - A standard, defined drug development process will provide metrics for informed portfolio analysis
  - **Launch of Chemical Biology Consortium to “jump start” NCI pipeline**

- **New Infrastructure**
  - Adding Contract Research organizations (CROs) and increasing in house capacity to invigorate early phase drug discovery at the NCI
Tdp1 is a Rational Anticancer Target

- Tdp1 repairs DNA lesions created by Top1 trapping
- No Tdp1 specific inhibitors
- Tdp1-deficient cells are hypersensitive to Top1 inhibitors
- In Tdp1-knockout yeast, this hypersensitivity appears only when cells are also defective for checkpoints and repair pathways
CBC Early Discovery Activities-Tdp1 Pilot with Pommier Laboratory

Joint collaboration between CCR/DCTD/NCGC

Screen development and high-throughput screening → Hit to Lead → Lead Optimization → Candidate Seeking

Target Identification
Pommier Laboratory

Primary uHTS → Parallel medicinal chemistry → Optimal potency/selectivity → Efficacy in pivotal in vivo models

NIH Chemical Genomics Center

Secondary biochemical and cell-based screens
-Pommier Laboratory

Co-crystallization with HTS “Hits”

Biacore: compound-enzyme affinity constants

Computational Docking
Initial CBC Participants

- Burnham
- Southern Research
- SRI International
- Vanderbilt
- Emory
- UCSF
- Univ. No. Carolina
- Pittsburgh
- Univ. of Minnesota
- Georgetown
- NCI Intramural Chemical Biology
- Affiliate Investigators
**Therapeutics Development Timeline**

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<th>Hypothesis Generation</th>
<th>Clinical Candidate Development</th>
<th>Commercialization</th>
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<td><strong>Chem-Biol Cons</strong></td>
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<td><strong>Risk</strong></td>
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<td><strong>Target/ Molecule</strong></td>
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<td><strong>Target Validation</strong></td>
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**Cumulative Investment**

- **$20-60 MM**
- **$200-300 MM**
- **$500-600 MM**
- **$1200 MM**

**Time:**
- 6-8 Years
- 12-15 Years
The Cancer Genome Atlas

- Pilot includes glioblastoma, ovarian and lung cancers
- **Glioblastoma** (80 percent tumor purity, with matched normal controls)
  - Genomic analysis of 214 patient cases; 168 patient cases sequenced
  - Identified NF1, Erbb2, and PIK3R1 as highly associated with GBM (EGFR, p53)
  - At least 4 subtypes emerging
- New data integration and analysis underway
Personalized Cancer Medicine

Translational Science
From Genomics to Therapy

- Small molecules
- Biologics
- Biomarkers

TCGA
• Biologic
• Discovery
NCI’s Roadmap to Personalized Cancer Treatment

Patient selection
- NCI Ca Ctrs.
- SPOREs
- CCOPs & NCCCP
- Coop. Grps.
- Multisite Networks

NIH Clinical Ctr.

- Academic res. labs
- Private sector
NCI’s Timeline to Personalized Medicine in Cancer Treatment

- Development of PD assays
- Pharmacology, Toxicology, Formulation
- First-in-Human Clinical Trials
- Prospective biomarker validation clinical trial
- Parallel track imaging agent development
- Early combination & combined modality trials

Timeline:
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015

FDA
NCI’s Roadmap to Personalized Medicine in Cancer Treatment

- **DCTD**
  Jerry Collins
  Joe Tomaszewski
  Melinda Hollingshead
  Ralph Parchment
  Jim Tatum
  Jeff Abrams
  Jamie Zweibel
  Toby Hecht
  Norm Coleman
  Barbara Mroczkowski
  Meg Mooney

- **NCIOD**
  Sheila Prindiville
  Deborah Jaffe
  Ray Petryshyn
  Anna Barker
  Daniela Gerhard

- **DCB, DCP, & DCCPS**

- **NCI-Frederick**
  Craig Reynolds

- **CTAC**
Personalized Cancer Treatment: Questions for the NCAB

• How should NCI support a coordinated approach to characterizing the functional biology of the output of its TCGA program in the context of personalized therapeutics?
  – How can we add value beyond that of the genomic discovery effort itself and ongoing investigator-initiated studies that will follow from TCGA?
  – What approaches would be most appropriate?
• What are the major continuing or new roadblocks to the development of personalized cancer medicines in the academic and biotech arena in 2009?
• What new/enhanced resources should the NCI consider developing to accelerate progress in the field of “personalized” cancer therapeutics?