NCI’s Roadmap to
Personalized Cancer Treatment

James H. Doroshow, M.D.
Director, Division of Cancer Treatment and Diagnosis
<table>
<thead>
<tr>
<th>Rank</th>
<th>Assignee</th>
<th>Number of Patents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Japan Sci and Tech Agency</td>
<td>1022</td>
</tr>
<tr>
<td>2</td>
<td>Univ. of California</td>
<td>543</td>
</tr>
<tr>
<td>3</td>
<td>Genentech*</td>
<td>421</td>
</tr>
<tr>
<td>4</td>
<td>United States Gov. (NIH)</td>
<td>334</td>
</tr>
<tr>
<td>5</td>
<td>Univ. of Texas</td>
<td>277</td>
</tr>
<tr>
<td>6</td>
<td>Millenium Pharmaceuticals*</td>
<td>272</td>
</tr>
<tr>
<td>7</td>
<td>Mass. General Hospital</td>
<td>201</td>
</tr>
<tr>
<td>8</td>
<td>Applera*</td>
<td>195</td>
</tr>
<tr>
<td>9</td>
<td>Novozymes*</td>
<td>162</td>
</tr>
<tr>
<td>10</td>
<td>Zymogenetics*</td>
<td>161</td>
</tr>
<tr>
<td>11</td>
<td>Johns Hopkins</td>
<td>154</td>
</tr>
<tr>
<td>12</td>
<td>Stanford</td>
<td>148</td>
</tr>
<tr>
<td>13</td>
<td>Human Genome Science*</td>
<td>141</td>
</tr>
<tr>
<td>14</td>
<td>Columbia</td>
<td>137</td>
</tr>
<tr>
<td>15</td>
<td>Univ. of Pennsylvania</td>
<td>133</td>
</tr>
</tbody>
</table>
Therapeutics Development Timeline

Hypothesis Generation

Clinical Candidate Development

Commercialization

Cumulative Investment

Time: 6-8 Years

Time: 12-15 Years
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
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
Biomarker, Imaging and QOL Studies Funding Program (BIQSFP)

• **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

**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
National Cancer Institute

TRWG Implementation
Next steps & Timeline

RFI for Translational Research Opportunities Pilot Immune Response Modifier Pathway

Late summer '09

Prioritize

Fall '09

Fund & Manage

2010
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 (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

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

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

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

25 mg/kg iv
NSC 724998

NSC 314622
NSC 706744 (MJ-III-65)
NSC 725776
NSC 724998

Vehicle

NSC 724998 (mg/kg)
Topo 1 (ng/ml/µg ptn)
• 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

**Oversight CMTE.**
- Oversee RAID applications
- Small molecule biologics
- Solicit applications in prioritized areas

**Project Initiation**
- Initial task

**Subsequent Task**
- Subsequent task

**Clinical “Go”/“No-Go” Decision**

**First-in-Human Trials**

**Active Project Management**

1/1/2007
1/1/2008
1/1/2009
12/31/2009

**Training Workshop**

**Develop Training Manuals**

**Access to Phase 0/1 Resources**

**Regulatory Support**
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

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

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

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

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

MCF-7 cells: In Vitro

Concentration

CYP2D6 Genotype and Endoxifen

**CYP2D6**

- **Wt/Wt**
- **Wt/*4**
- ***4/*4**

P<0.001, r²=0.24

**Plasma Endoxifen (nM)**

- **Wt/Wt**
- **Wt/*4**
- ***4/*4**

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)

HR 4.0
PM relative to EM

P<0.001

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

Chemistry / Biology Contracts

NCI/academic medicinal chemistry teams working closely with computational chemists

Structure-based drug design

CRO Contracts: support external/internal chemistry efforts

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**
- **HIS-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**

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

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

- **Target validation and Model Development**

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

• New Governance
  o 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
  o Launch of Chemical Biology Consortium to “jump start” NCI pipeline

• New Infrastructure
  o 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

- 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
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

- TCGA
- Biologic Discovery

Translational Science
From Genomics to Therapy

- Small molecules
- Biologics
- Biomarkers
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

- '09: Development of PD assays
- '10: Discovery, pre-clinical efficacy
- '11: Parallel track imaging agent development
- '12: Pharmacology, Toxicology, Formulation
- '13: First-in-Human Clinical Trials
- '14: Prospective biomarker validation clinical trial
- '15: Early combination & combined modality trials

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

- **CCR**
  - Lee Helman
  - Bob Wiltrout
  - Yves Pommier
  - Giuseppe Giaccone
  - Michelle Bennett
  - Pat Steeg

- **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 BSA

- 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?