NCI’s Precision Medicine Initiative for Oncology

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### Precision Medicine Initiative

#### Proposed FY16 Support

<table>
<thead>
<tr>
<th>Agency</th>
<th>$ Million</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>200</td>
</tr>
<tr>
<td>• <em>Cancer</em></td>
<td>70</td>
</tr>
<tr>
<td>• <em>Cohort</em></td>
<td>130</td>
</tr>
<tr>
<td>FDA</td>
<td>10</td>
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<tr>
<td>Office of the National Coordinator for Health Information Technology</td>
<td>5</td>
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<tr>
<td>TOTAL</td>
<td>$215</td>
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</table>
Precision Medicine Initiative: Oncology

What Problems Are We Trying to Solve?

• For most of its 70-year history, systemic cancer treatment has relied on drugs marginally more toxic to malignant cells than to normal tissues.

• Molecular markers to predict benefit or understand therapeutic resistance in the clinic have usually been lacking.

Proposed Solution to These Problems

• Use genomics to identify and target molecular vulnerabilities of individual cancers.
A Modified Definition of Precision Medicine

Interventions to prevent, diagnose, or treat a disease (e.g., cancer), based on a molecular and/or mechanistic understanding of the causes, pathogenesis, and/or pathology of the disease. Where the individual characteristics of the patient are sufficiently distinct, interventions can be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Modified by D. Lowy, M.D. from: IOM’s Toward Precision Medicine, 2011
Precision Medicine/Oncology in Practice

<table>
<thead>
<tr>
<th>Non-clinical models for targets</th>
<th>Translational research with clinical models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sequencing</td>
</tr>
<tr>
<td></td>
<td>Methylation</td>
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<tr>
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<td>FISH</td>
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<tr>
<td></td>
<td>IHC</td>
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<td>Expression array</td>
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</tbody>
</table>

Patients eligible for early or late phase clinical trials
Analysis of tumor and other tissues for pathway activation or resistance
Patient assigned to trial based on molecular characterization of tumor
Patient monitoring
Patient monitoring: post-treatment molecular re-analysis

Clinical observations:
- Clinical response
- PK
- Functional imaging
- CTCs, CECs

Precision Medicine Initiative: Oncology

Increase Genomics-Based Clinical and Preclinical Studies of Cancer Treatment

- Expand genomics-based clinical trials
- Understand & overcome resistance to targeted drugs; drug combinations; and mechanistic understanding of immunotherapy
- Repository of patient-derived pre-clinical models for evaluating targeted therapeutics
- National cancer database to integrate genomic information with clinical response and outcome
Precision Oncology
Trials Launched
2014:
MPACT
Lung MAP
ALCHEMIST
Exceptional Responders

2015:
NCI-MATCH
ALK Inhibitor
MET Inhibitor

NCI-MATCH: Features (1)
[Molecular Analysis for Therapy Choice]

• Foundational treatment/discovery trial; assigns therapy based on molecular abnormalities, not site of tumor origin for patients without available standard therapy

• Regulatory umbrella for phase II drugs/studies from > 20 companies; single agents or combinations

• Available nationwide (2400 sites); CIRB
NCI-MATCH: Features (2)
[Molecular Analysis for Therapy Choice]

- Validated and standardized gene sequencing at 4 sites; >96% concordance for “locked down” analysis of mutations in 143 genes using Ion Torrent PGM™ custom panel; fresh biopsies at study entry

- Co-developed by NCI and ECOG-ACRIN, part of NCTN; PI’s drawn from all network groups; trial planning by >150 clinical and pre-clinical scientists

- First patients to be entered July 2015
• Conduct across 2400 NCI-supported sites
• Pay for on-study and at progression biopsies
• Initial estimate: screen 3000 patients to complete 20 phase II trials; target 25% ‘rare’ tumors; primary endpoint RR 5% vs. 25%

1 CR, PR, SD, and PD as defined by RECIST
2 Stable disease is assessed relative to tumor status at re-initiation of study agent
3 Rebiopsy; if additional mutations, offer new targeted therapy
Biopsy Received at Quality Control Center

Tissue Fixation Path Review

3-5 DAYS

1 DAY

Nucleic Acid Extraction

1 DAY

Library/Template Prep

1 DAY

Sequencing, QC Checks

1 DAY

Centralized Data Analysis

1 DAY

DNA/RNA yields >20 ng

Library yield >20 pM

Tumor content >70%

Test fragments Total read Reads per BC Coverage NTC, Positive, Negative Controls

aMOIs Identified

Clinical Laboratory aMOI Verification

3 DAYS

10-12 days

Rules Engine Treatment Selection
## NCI-MATCH: Initial Ten Studies

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Molecular Target(s)</th>
<th>Estimated Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>ALK Rearrangement (non-lung adenocarcinoma)</td>
<td>4%</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ROS1 Translocations (non-lung adenocarcinoma)</td>
<td>5%</td>
</tr>
<tr>
<td>Dabrafenib and Trametinib</td>
<td>BRAF V600E or V600K Mutations (non-melanoma)</td>
<td>7%</td>
</tr>
<tr>
<td>Trametinib</td>
<td>BRAF Fusions, or Non-V600E, Non-V600K BRAF Mutations (non-melanoma)</td>
<td>2.8%</td>
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<tr>
<td>Afatinib</td>
<td>EGFR Activating Mutations (non-lung adenocarcinoma)</td>
<td>1 – 4%</td>
</tr>
<tr>
<td>Afatinib</td>
<td>HER2 Activating Mutations (non-lung adenocarcinoma)</td>
<td>2 – 5%</td>
</tr>
<tr>
<td>AZD9291</td>
<td>EGFR T790M Mutations and Rare EGFR Activating Mutations (non-lung adenocarcinoma)</td>
<td>1 – 2%</td>
</tr>
<tr>
<td>TDM1</td>
<td>HER2 Amplification (non breast cancer)</td>
<td>5%</td>
</tr>
<tr>
<td>VS6063</td>
<td>NF2 Loss</td>
<td>2%</td>
</tr>
<tr>
<td>Sunitnib</td>
<td>cKIT Mutations (non GIST)</td>
<td>4%</td>
</tr>
</tbody>
</table>

Agents and targets below grey line are pending final regulatory review; economies of scale—larger number of agents/genes, fewer overall patients to screen ≈ 35%
PMI Oncology: Improving Cancer Treatment through Genomics

2006 -2014
TCGA
Targeted Trials: MPACT, ALCHEMIST, Exceptional Responders, LungMAP
Oncogenic drivers of the same tumor type may be heterogeneous, but same driver may be found in several different tumor types

2015
NCI-MATCH
Announced June 1, Opens in July throughout the US (2400 sites)
*Unprecedented & incorporates all tenets of precision medicine
*Treatment is based on genes and their mutations rather than on organ site

2015 & Beyond
THE PRECISION MEDICINE INITIATIVE FOR ONCOLOGY
ACCELERATING PROGRESS FOR PATIENTS

• Dramatically expand NCI-MATCH umbrella: to include new trials, new agents, new genes, and new drug combinations
• Increase mechanistic understanding of immunotherapy: to broaden its appropriate use
• Create a repository of patient-derived pre-clinical models and evaluate liquid biopsies: to improve understanding of cancer and drug resistance and to identify drug combinations that overcome resistance
• Establish a national cancer database integrating genomic information with clinical response and outcome: to accelerate understanding of cancer and improve its treatment
PMI for Oncology

Opportunities Enabled by PMI for Oncology: Expanding Genomically-Based Cancer Trials

• Accelerate Launch of NCI-Pediatric MATCH

• Broaden the NCI-MATCH Umbrella:
  ✓ Expand/add new Phase II trials to explore novel clinical signals—mutation/disease context
  ✓ Add new agents for new trials, and add new genes to panel based on evolving evidence
  ✓ Add combination targeted agent studies
  ✓ Perform Whole Exome Sequencing, RNAseq, and proteomic studies on quality-controlled biopsy specimens—extent of research based on resource availability
  ✓ Add broader range of hematologic malignancies

• Perform randomized Phase II studies or hand-off to NCTN where appropriate signals observed

• Apply genomics resources to define new predictive markers in novel immunotherapy trials

• Expand approach to ‘exceptional responders’: focus on mechanisms of response/resistance in pilot studies
Mechanisms of Resistance To Targeted Cancer Therapeutics

- Broad range of mechanisms
- Until recently, tools to interrogate possibilities in vivo quite limited
- Resistance to single agents inevitable: 1º or acquired; requires combinations but data to provide molecular rationale for the combination (both therapy & toxicity) not often available
Principles of Combination Therapy to Overcome Resistance: Then (1975) and Now (2015)

**Cytotoxic**
- Drugs are each active against the tumor in question (ORR)
- Drugs have different mechanisms of action to minimize resistance
- Drugs have different clinical toxicities to allow full dose therapy
- Intermittent intensive > continuous treatment for cytoreduction & to reduce immunosuppression

*Cancer* 35: 98, 1975

**Targeted**
- Agent has therapeutic effect on molecular pathway in vivo
- Agents have complementary effects on the same target or other targets in the same pathway or pathways that cross-talk to control tumor growth
- Toxicities not overlapping with cytotoxics & moderate to allow prolonged administration; consider physiological consequences of target engagement—strong relationship to toxicity profile
- Schedule to maximize target inhibition: Either continuous Rx or high dose to suppress target a reasonable goal

*Needs Full Experimental Verification*

New Patient-Derived Models for Precision Oncology to Study and Overcome Drug Resistance

- Patient-derived xenografts (PDX) & conditionally reprogrammed cell lines
- Tumorigenesis
- Create reprogrammed cell lines
- Transplantation into NSG mice
- Tumor/patient heterogeneity
- Molecularly characterize, treat/screen mice bearing transplants & cells with relevant drugs.

“Pre-clinical clinical trials”

NCI Patient-Derived Models Repository

• A national repository of Patient-Derived Models (PDMs) comprised of clinically-annotated patient-derived xenografts (PDXs), patient-derived tumor cell cultures (PDCs, including conditionally-reprogrammed tumor cell cultures) developed from 1º or metastatic tumors and/or PDXs, tumor cell lysates, DNA, & RNA, and cancer-associated fibroblast cell lines (CAFs, autologous when possible) to serve as a resource for academic discovery efforts and public-private partnerships for drug discovery.

• NCI to provide long-term home for >1000 PDX and PDC models each produced from tissues and blood supplied by NCI-designated Cancer Centers and NCI-supported clinical trials networks.

• Targeting collections of tumors less prevalent in current resources, such as: Small Cell Lung, Pancreatic, Head and Neck, Ovarian, and Bladder cancers, as well as Sarcomas, Melanomas, and Pediatric Cancers

• Goals:
  ✓ ~50 unique patient models (both solid tumor and derived tumor line) per disease (minimum) such that the size of each molecularly-characterized subgroup is sufficient to power subsequent validation and/or efficacy studies
  ✓ Comprehensive pre-competitive molecular characterization of samples and earliest passage PDXs: MPACT mutation panel, WES, RNAseq, copy number, histology, growth curves, and proteomics/phospho-proteomics (pilot study)
  ✓ All models and associated data made available through a publicly available website
Salivary Gland Adenocarcinoma

In vitro

Fibroblast Culture

Tumor Cell Culture

In vivo

Passage 0 in Mice

P0 Growth Curve
Preclinical MPACT Trial

Colon adenocarcinoma. aMOI: PIK3C-E545K and KRAS-G12D. Assign: Trametinib

PDX originated from Biopsy

Urothelial Cancer. aMOI: TP53-R248Q. Assign: MK1775+Carboplatin

<table>
<thead>
<tr>
<th>(Group) NSC</th>
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<tr>
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<tr>
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<td>(G6) 752840</td>
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Precision Medicine Approaches to Overcoming Resistance: Opportunities

TUMOR CELL AUTONOMOUS

- Develop panel (>1000) of clinically annotated low passage organoids and conditionally reprogrammed lines for mutational evaluation, large scale systematic combinatorial drug screens, and resistance mechanism analysis
- On-study/at progression biopsies of NCI early phase trial patient cohort with resistant disease for molecular characterization (>500 pts/year); blood for CTC’s, cfDNA, cfRNA, exosomes (liquid biopsies)

TUMOR MICROENVIRONMENT

- Develop complementary Patient-Derived Models: clinically-annotated PDXs from drug-resistant tumors
- Use for pre-clinical modeling of molecularly targeted combinations and for co-clinical trials of NCI-IND agents
- Genomic underpinnings of immunotherapeutic checkpoint control
The NCI Genomic Data Commons (GDC): Rationale

- The Cancer Genome Atlas (TCGA) project and many other NCI funded cancer genomics projects each currently have their own data coordinating center
  - Raw data and results stored in many different repositories; confusing to users, inefficient, barrier to research

- New GDC will be single repository for all NCI cancer genomics data
  - Will include new, upcoming NCI cancer genomics efforts
  - Store all data including raw data
  - Harmonize the data as appropriate
  - Will be the authoritative reference data set
Precision Medicine Initiative: Opportunities for Therapeutic Oncology

Developing Input from Extramural Community

- Organoids & Reprogrammed Cell Lines: Lou Staudt, M.D., July 2015
- Exceptional Responders Workshop—Next Steps: Barbara Conley, M.D., Fall 2015
- Immunotherapy—Combination Approaches and NGS: Helen Chen, M.D., Fall 2015
- PDX Models, Combination Therapy, and Drug Resistance: J. Doroshow, M.D. and Dinah Singer, Ph.D., Fall 2015
- Genomic Data Commons workshop: W. Kibbe, Ph.D., Fall 2015