NCI’s Integrated Precision Oncology Networks

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National Cancer Institute, NIH
Precision Oncology in Theory

<table>
<thead>
<tr>
<th>Non-clinical models for targets</th>
<th>Translational research with clinical models</th>
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<tbody>
<tr>
<td></td>
<td>Sequencing</td>
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<tr>
<td></td>
<td>Methylation</td>
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<td>FISH</td>
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<td>IHC</td>
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<td>Expression array</td>
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</tbody>
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- 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
- Tumor and normal tissue PD markers
- CTCs, CECs
- Tumor-initiating cells

Challenges to Precision Oncology in Practice

- **Inadequate preclinical modeling for:**
  - Molecularly targeted agents
  - Immuno-oncology
  - Combination therapy

- Imprecise measurements of target engagement and downstream effectors of therapeutic response

- Inexact predictors of activity/response to immunotherapy

- Insufficient support for standardization of data collection, tissue acquisition, & critical correlatives of sensitivity and resistance

- **NCI initiatives resourced by NIH precision medicine program**
Combination Therapy: Unresolved Issues

Drug A → Drug B: Sequential targeting
Drug A + B: Concurrent targeting
Drug B → Drug C: Sequential targeting
Drug B + C: Complementary targeting

Independent action: Greater than additive/synergy

Cell 171: 1476-1478, 2017
NCI Patient-Derived Models Repository (PDMR)

Develop PDX Models and PDC (Tumor & Fibroblast) Lines
DNA, RNA, Protein, WES, RNASeq, Targeted Sequencing

Tumor/Patient Heterogeneity

3D Culture, 3D Pharmacodynamics

Increasing Drug Concentration

2D and Organoid Cultures

Preclinical Trial Modeling

Live Tumor Imaging
NCI Patient-Derived Models Repository

• Currently have **154 PDX models available** for request (cryo-material) through the public website (pdmr.cancer.gov)

• **> 300 PDX** models to be released in next 6-9 months; ≈ 50 low prevalence tumor models

• Every model has:
  ✓ Patient limited medical history
  ✓ Representative PDX histology images
  ✓ STR Profile
  ✓ Human Pathogen Status
  ✓ WES (FASTQ, vcf) and RNASeq (FASTQ, TPM) from 4-6 representative PDXs
  ✓ Genetic ancestry assessment

• All data are publicly accessible and available for download for metadata analysis and model selection

• Specimens are from patients with both primary and metastatic disease from treatment naïve to heavily pre-treated.
Patient-Derived Models Network (PDXNet): PDX Preclinical Trials in Support of NCI’s Early Phase Clinical Trials

PDXNet:

PDX Development and Trial Centers (PDTC)

PDX Data Commons and Coordinating Center (PDCCC)

NCI PDM Repository (PDMR) at FNLCR

Perform preclinical trials of single agents and combinations using IND drugs to be examined by NCI/CTEP’s Experimental Therapeutics Clinical Trials Network (ETCTN)

PDX models screening pipeline
Canine Precision Medicine Consortium: Evaluation of Targeted Agents and Immunotherapy in Spontaneous Malignancies

Randomized phase I trial of novel top1 inhibitors in spontaneous canine lymphomas
- Selected optimal agent
- DDR biomarker panel validated
- Basis for recently initiated phase I


Canine Consortium
- Academic sites and NCI’s comparative oncology clinical trials network
- Screen small molecules
- I/O trials with novel canine therapeutic agents, biomarker development, NGS, data commons
- Supported by Moonshot initiative
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NCI’s Re-imagined Early Phase Clinical Trials Network

- 10 lead organizations
- ~30-40 enrolling sites
- Centralized trial support
- New specimen collection & centralized PK resources
- Addition of shared data environment for correlative studies
- New clinical lab network for genomics and PD assays
- Preclinical modeling for sensitivity and resistance & immune monitoring network
# Biomarkers of DNA Damage & Repair in NCI Early Phase Trials

<table>
<thead>
<tr>
<th>Pathway Target</th>
<th>Molecular Target</th>
<th>CTEP Therapeutic Agents</th>
<th>DDR PD Biomarker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single/Double Strand Break Induction</td>
<td>multiple TOP1i</td>
<td>any chemoRx agents irinotecan, topotecan, indenoisoquinolines, AZD1775 (Wee1i)</td>
<td>pNBS1, γH2Ax, RAD51, ERCC1 γH2Ax w/Casp3 (apoptosis)</td>
</tr>
<tr>
<td>Single Strand Break Response: BER</td>
<td>PARP1/2i</td>
<td>veliparib, olaparib, talazoparib</td>
<td>PAR polymer</td>
</tr>
<tr>
<td></td>
<td>APE blockade w/TOP2 sensitivity</td>
<td>TRC102 (methoxyamine)</td>
<td>Late DNA damage (pNBS1, γH2Ax, RAD51)</td>
</tr>
<tr>
<td>Single Strand Break Response: TMB, MSI</td>
<td>PD1/L1 blockade</td>
<td>pembrolizumab nivolumab, durvalumab, atezolizumab</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
</tr>
<tr>
<td>DDR Sensors</td>
<td>ATRi</td>
<td>M6620 (formerly VX-970)</td>
<td>pS1989 autophosphorylation</td>
</tr>
<tr>
<td></td>
<td>DNA-PKi</td>
<td>M3814 M9831 (aka VX-984)</td>
<td>γH2Ax, pKAP1 (recent project plan)</td>
</tr>
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A Cancer Moonshot Initiative: Network to provide a standing infrastructure of Laboratories and Data Commons for correlative studies in NCI-sponsored trials involving immunotherapies

- **4 CIMACs**: to perform biomarker assays and analysis, using state of the art, consistent methodologies
- **A CIDC** to provide the data repository of assay results and an informatics platform for integrative and correlative analysis across studies

**Goals:**

- **Immediate** - Enhancing the translational outcomes of a wide range of immunotherapy trials across NCI clinical trials networks
- **Longer term** - Building a framework that would allow for evolution of the Data Commons into a sustainable I-O data resource serving the larger research community
- **Collectively**, in concert with efforts from academia, industry, NGO partners, the ultimate goal is to identify biomarkers with a translational potential for optimizing the therapeutic strategies for patients

Cancer Immune Monitoring and Analysis Centers (CIMACs)
Cancer Immunologic Data Commons (CIDC)
Cancer Immune Monitoring and Analysis Centers (CIMACs)
Cancer Immunologic Data Commons (CIDC): Organization & Assays

- Each CIMAC will be in a Primary Alignment with 1-2 trial Networks - Standing relationship for collaboration in scientific planning, Biobank interactions
- ALL CIMACs will also work outside the primary alignment as determined by LCC, e.g.
  - Provide unique assay capabilities for the entire network
  - Work on other network trials to balance the workload across CIMACs

<table>
<thead>
<tr>
<th>Tissue Imaging</th>
<th>Dana-Farber</th>
<th>MD Anderson</th>
<th>Mt Sinai</th>
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<tbody>
<tr>
<td>Conventional immunohistochemistry</td>
<td>Dana-Farber</td>
<td>MD Anderson</td>
<td>Mt Sinai</td>
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<tr>
<td>Multiplexed ion-Beam Imaging (MIBI)</td>
<td>Mt Sinai (soon)</td>
<td>Stanford</td>
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<tr>
<th>Cell Profiling</th>
<th>Dana-Farber</th>
<th>MD Anderson</th>
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<tr>
<td>Mass Cytometry (CyTOF)</td>
<td>Dana-Farber</td>
<td>MD Anderson</td>
<td>Mt Sinai</td>
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<td>High-dimensional flow cytometry</td>
<td>Dana-Farber</td>
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<td>ELISpot</td>
<td>MD Anderson</td>
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<td>Whole Exome Sequencing</td>
<td>Dana-Farber</td>
<td>MD Anderson</td>
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<td>TCR/BCR clonality</td>
<td>Dana-Farber</td>
<td>MD Anderson</td>
<td>Mt Sinai</td>
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<td>Single-cell TCRseq</td>
<td>Dana-Farber</td>
<td>MD Anderson</td>
<td>Mt Sinai</td>
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<td>HLA-Seq; Epitope prediction</td>
<td>Dana-Farber</td>
<td>MD Anderson</td>
<td>Mt Sinai</td>
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<td>ISH DNA/RNA</td>
<td>Dana-Farber</td>
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<td>Neoantigen Prediction</td>
<td>Dana-Farber</td>
<td>Mt Sinai</td>
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<td>Cell-free DNA (circulating tumor DNA)</td>
<td>Dana-Farber</td>
<td>MD Anderson</td>
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<td>Epigenomics (ATAC-Seq)</td>
<td>MD Anderson</td>
<td>Mt Sinai</td>
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<td>HTQ-EdgeSeq (gene expression)</td>
<td>MD Anderson</td>
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<td>Microbiome (16S Deep Sequencing)</td>
<td>MD Anderson</td>
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<td>Single-cell transcriptome</td>
<td>Dana-Farber</td>
<td>Mt Sinai</td>
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<th>Dana-Farber</th>
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<th>Mt Sinai</th>
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<tr>
<td>O-link serum cytokine analysis</td>
<td>Mt Sinai</td>
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<tr>
<td>Luminex</td>
<td>MD Anderson</td>
<td>Mt Sinai</td>
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<td>Seromics-ELISA/Grand serology</td>
<td>Mt Sinai</td>
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<tr>
<td>Mesoscale Discovery</td>
<td>MD Anderson</td>
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Developing Novel Immuno-Pharmacodynamic Assays

Conventional PD

Baseline

Tumor cell
Apoptosis

Drug target

1° effect

Drug

2° effect

Apoptosis

Altered tumor cell pathways

3° effect

Tumor cell apoptosis

Cellular immunoPD (e.g., immune checkpoint blockade)

Baseline

Tumor cell
Drug targets

MHC I

CD8

TCR

Suppressed T cell

Proximal tumor cell

1° effect

Drug

Inhibition released

2° effect

Altered T cell pathways

3° effect

Tumor cell apoptosis

Release of tumor-killing molecules

Challenges to Precision Oncology in Practice

• Inadequate preclinical modeling for:
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• NCI initiatives resourced by NIH precision medicine program
NCI Clinical Trials Data Archive and NCI Navigator

**ARCHIVE—Launched 2017**
- Centralized database of patient-level data from phase III NCTN studies
- Initially for studies published after January 1, 2015—22 trials
- Prospectively de-identified patient-level data must be submitted within six months of publication
- Legacy trials case-by-case
- NCINCTNDATAarchive@mail.nih.gov

**NCI Navigator—Launched 4/2018**
- NCTN trial specimens (tumor and blood)
- >850,000 specimens, >60,000 patients, 98 trials
- Associated clinical annotation
- Specimens available to investigators who submit proposals to an extramural review committee
- navigatorcontact@imsweb.com
Cancer Moonshot Biobank

- Establish a national cancer biobank containing **longitudinally-accrued** biospecimens (blood & tumor) from both newly diagnosed patients and those with recurrent disease.

- Provide high quality, clinically-annotated specimens to support the following communities:
  - Cancer atlas initiative
  - Drug sensitivity and resistance initiative
  - Immunotherapy response initiative
  - Patient derived models repository

- **Pilot** program for 150 matched pretreatment, post-treatment, and at progression specimens:
  - Focused on specimen acquisition in the community (NCORP sites; underserved populations)
  - Patients treated with specific, FDA-approved standard of care targeted and I/O agents
  - Phase 1: Prostate, Lung, Colon, and AML patients
  - Standardized tissue acquisition procedures (validated kits), central repository and sample Q/C, NGS sequencing
  - Development of patient portal and public database

- If successful, expand to 1000 patients
Drug Resistance and Sensitivity Network (DRSN)

NCI Resources:
- Non-clinical agents
- Patient-Derived Models Repository (PDMR)
- PADIS (PD assays)
- PDXNet
- Cancer Systems Biology Consortium (CSBC)
- Cooperative Human Tissue Network (CHTN)
- NCI Genomic Data Commons (GDC)
- Moonshot Biobank
- Experimental Therapeutics Clinical Trials Network (ETCTN) investigators
Challenges/Updates to Precision Oncology in Practice

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• NCI clinical initiatives resourced by NIH precision medicine program
Precision Oncology Clinical Trial Designs

- Lung Map

- NCI MATCH
- NCI/COG Pediatric MATCH

JNCI 107(4): djv003, 2015
NCI-MATCH: Pearls

- Registered to screening (Aug 2015 through May 2017): 6396
- Biopsies submitted: 5963
- Biopsies profiled: 5550 (93% of biopsies submitted)
- Accrual demographics: 60% female; Median age 62; 85% white; 10% black; 4% asian
- 63% patients with less common cancers (not CRC, breast, NSCLC, Prostate—far higher than goal of 25%); tumor gene variants occurred less frequently than expected
- Managing protocol amendments, IRB approvals, and issues related to building the study (with 30 arms) into EHR was a major undertaking
- Phase II trials
  - ✓ 14 arms completed; 2 arms administratively closed (1 for lack of accrual, 1 for lack of drug)
  - ✓ 14 arms accruing with different entry procedure
  - ✓ 5 additional subprotocols expected to activate in June
- Able to accrue to trials where the prevalence of the molecular abnormality was over 1.5%.
- Screening for rare variants (prevalence < 1.5%) from clinical NGS results – 4 outside labs enrolled 129 pts with 88% assigned to therapy
DCTD
Division of Cancer Treatment and Diagnosis

- Developmental Therapeutics Program
  Jerry Collins
  Melinda Hollingshead
  Ralph Parchment
  Robert Kinders
  Bev Teicher
  Tony Navas
  Deborah Wilsker
  Apurva Srivastava
  Alice Chen
  Naoko Takebe
  Geraldine O’Sullivan-Coyne
  Rose Aurigemma
  Shivaani Kummar (Stanford)
  Khan Do (DFCI)

- Center for Cancer Research
  Yves Pommier
  Bill Dahut
  Peter Choyke

- DCTD OD
  Toby Hecht
  Jason Cristofaro
  Barbara Mrochowski
  Michael Difilippantonio
  Yvonne Evrard

- CTEP, Biometrics, & Cancer Imaging Program
  Jeff Moscow
  Meg Mooney
  Jeff Abrams
  Paula Jacobs
  Larry Rubinstein
  Helen Chen
  Percy Ivy
  Lisa McShane

- Cancer Diagnosis Program
  Lyndsay Harris
  Barbara Conley
  Mickey Williams
  Tracy Lively
  Magdalena Thurin