Preclinical Models Repository to Support Cancer Discovery & Therapeutics Development

**Goal:** Develop a program attractive to academia and industry to create and produce clinically-annotated, patient-derived mouse and cell-based model systems for cancer discovery and therapeutics development in support of extramural investigators.

James H. Doroshow, M.D.
FNL Advisory Board
September 24, 2013
Emerging Human-Centered Preclinical Strategies in Drug Discovery/Development

- Patient-Derived Xenografts (PDX) & Conditionally Reprogrammed Cell Lines
- GEM-Derived Allografts (GDA)
- Genetically-Engineered Mice (GEM)

Molecularly characterize, treat/screen mice bearing transplants & cells with relevant drugs

“Pre-clinical clinical trials: Mouse Hospital”

- Tumorigenesis
- Transplantation into NSG mice
- Create reprogrammed cell lines

Tumor/patient heterogeneity

Transplantation into syngeneic immunocompetent mice

Treat with best available drugs

Made in wild type mice or using the Collaborative Cross

Tumorigenesis
Preclinical Models Repository: Why?

- Large expense
  - Drug development failures require improved preclinical models
  - Developing/maintaining patient derived xenograft (PDX) library with clinical and ‘omic annotation

- Need to interrogate models from both primary tumors and metastases, particularly from patients on clinical trials

- Preclinical models for development of therapeutics
  - Critical need to enhance reproducibility and transparency of preclinical data, and to justify (or not) investment in animal models used for preclinical therapeutics
  - Clarify the role of PDXs in target qualification
  - Need for development of models allowing comparative assessment of molecular predictors of drug efficacy: PDXs, conventional xenografts, conditionally-reprogrammed lines, and organoids
  - Establishment of predictive genomic signatures and/or proof of mechanism PD

**Goal:** Enhance ability of preclinical systems to predict success in the clinic in a timely fashion; facilitate extramural access to annotated models
Preclinical Models Repository: Why NCI?

- Large network of early phase academic trial sites currently funded to supply tumor samples. Over 5000 accruals/year and >100 active INDs
- Clinical annotation of specimens for patients on therapeutic trials are integral to NCI studies
- Facilities at FNL
  - Major facilities exist for animal production,
  - tumor model development,
  - tumor cell repository,
  - genomic characterization of human tumor biopsy specimens,
  - cell line screening
Preclinical Models Repository: What?

- Establish a quality-controlled repository of PDX models at NCI that have undergone detailed molecular characterization (>1000 models—initial goal)
  - Develop models from patients with recurrent disease; include complete clinical annotation; include pre-treatment and at-progression biopsies from patients at NCI-supported clinical trial sites
  - Obtain primary models, usually surgical samples (particularly of rare diseases) from NCI-designated Cancer Centers
  - Obtain established PDX models from Pharma partners, as available
  - Share SOPs for development, monitoring, and maintenance of reproducible models

- Co-develop conditionally-reprogrammed lines (tumor and adjacent ‘normal’ tissue) from same patient samples used for PDX models

- Share molecular characterization data and models with extramural community
  - Molecular characterization data to be made publicly available according to NIH policy
  - Available to all academic and Pharma partners
Patient-Derived Xenograft (PDX) Repository

- NCI to provide long-term home for \textit{>400-500 models} produced from primary tissues and blood supplied by \textit{NCI designated Cancer Centers} or already developed at those sites; in negotiation with several \textit{companies} that have indicated their willingness to share models with the NCI; additional \textit{400-500 models} to be developed from \textit{NCI-supported clinical trials}

- **Repository size** - should include sufficient number of biologically- and clinically-annotated models to reflect genetic diversity and effects of therapy for application in:
  - Target qualification
  - PD assay and predictive marker development
  - ‘Preclinical’ clinical trials

- **Goals**
  - >1000 clinically-annotated PDXs with 25% from pre- and post-treatment biopsies from the same patient
  - ~75-100 unique patient samples (solid tumor and tumor lines) per common disease 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 where data not available

- **Publicly-available repository**
  - Molecular information in an easily accessible database
  - PDX models supplied to the extramural community at modest cost
  - Serve as a resource for public-private partnerships and for academic drug discovery efforts
  - Establish extramural group to provide input for optimal use of repository
NCI’s M-PACT Clinical Trial: Study Design

- Fresh tumor biopsy on-study and at progression
- Primary endpoint response (CR + PR) and 4-month PFS improved for agents chosen on the basis of specific mutations
- Crossover from Arm B (non-mutation–directed) to Arm A (mutation-directed) treatment at progression
- Trial open across NCI’s Phase I/II network (>30 NCI-designated Cancer Centers)
- Accrual expected to begin Q1-2014
Patients with specified mutations of interest will be assigned to receive one of the following study drugs or drug combinations at the assigned dose. Cycle length is +/- 1 day for scheduling:

- **ABT-888** 40 mg orally BID qd days 1-7 plus temozolomide 150 mg/m² orally qd days 1-5 (no food restrictions) in 28-day cycles
- **Everolimus** 10 mg orally each day (no food restrictions) in 28-day cycles
- **Trametinib DMSO**: 2 mg orally each day either one hour before or two hours after a meal in 28-day cycles
- **MK-1775** 225 mg orally BID for 5 doses either at least two hours before or two hours after a meal plus carboplatin (AUC 5) IV on day 1 every 3 weeks (21-day cycle)
# MPACT Assay

4 Drug Protocols, 3 Pathways, 22 Targeted Genes (aMOI)

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Treatment Protocol</th>
<th>Gain of Function Mutations</th>
<th>Loss of Function Mutations</th>
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Tissue Outputs from M-PACT Trial

**PDX Models**

- Prospective collection of ~1000 clinically-annotated *on-study tissue biopsies* from sites of recurrence (not primary tumors), and *blood samples for CTCs* in context of clinical trial
  - Characterize mutational status with CLIA-approved panel
  - Available for whole exome sequencing
- Biopsies at disease progression for patients treated on study (~200 pts) with whole exome analysis
- Both on-study and at progression samples used for establishment of PDX models

**Conditionally-Reprogrammed Lines**

- Biopsies (3 passes) split by pathologist at time of acquisition for:
  - Genomics
  - PDX models
  - Initiation of conditionally-reprogrammed lines (J2 murine fibroblast co-culture with Rho-kinase inhibitor; Am. J. Pathol. 180: 599-607, 2012), and for frozen reserve specimen
Dielectrophoretic Field-Flow Fractionation (DEP-FFF): Viable Circulating Tumor Cell Capture

Cells are injected from the chamber bottom so they do not need to settle.

Differential DEP forces cause different cell types to traverse the channel at different heights.

DEP levitation + hydrodynamic lift forces

Sedimentation force

Cells at different heights in the flow are separated by skimming them using ports with precisely controlled exit flow rates.

• DEP-FFF utilizes balance of physical forces in a laminar flow chamber to isolate CTCs from blood cells.

• Throughput is high compared to other systems; 1 ml of blood can be processed in <30 minutes.
Cancer Cell Separation from Blood Cells using DEP-FFF

- MDA-435 tumor cells isolated from blood cells with high purity and 2000-fold enrichment as observed by Wright staining.

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Specificity of Non-Small Cell Lung Cancer CTC Isolation by DEP-FFF

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<th>NSCLC</th>
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<th>DEP-FFF Count (CK+/CD45−/DAPI+) per 7.5 ml blood</th>
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<table>
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<th>Normal Donor Blood</th>
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<tr>
<td>Normal Donor Blood 2</td>
<td>3</td>
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</table>

Low number of false-positive CK+/CD45−/DAPI+ CTCs are recovered from normal donor blood by DEP-FFF isolation method
- PDX initiation
- Single cell sequencing
- Molecular characterization
### PDX Research Challenges

#### Pros
- patient-derived tumors
- pre & post therapy samples possible
- clinical annotation
- experimental replicates
- some human stroma

#### Cons
- lacks immunobiology
- mouse/human stroma
- bypasses initiation/progression
- change possible with passage
Conditionally-Reprogrammed Cell Lines (‘Georgetown Technique’)

**Pros**
- potential to grow tumor & associated ‘normal’ tissue from same biopsy samples
- pre & post therapy samples
- clinical annotation
- potential to expand limited tumor resources to allow broader molecular characterization
- amenable to drug sensitivity/resistance testing

**Cons**
- technology just getting started
- long-term stability of lines unknown
- only preliminary evidence of clinical correlation
- changes in culture possible
PDX Models: Initial Progress

- **Tissue/Model Acquisition:**
  - 16 NCI-Designated Cancer Centers just reviewed and funded to each supply 20 tumor and 20 matched blood samples with clinical annotation in FY14; focus on less common malignancies: small cell lung cancer; head and neck cancer; sarcoma; thymic carcinoma; bladder cancer; melanoma; prostate cancer:
  - Total $\approx$ 300 tumors & 300 blood samples for CTCs
  - Offered existing Cancer Center collections (>25 unique PDX models each ovary and breast)
  - Total 50 (so far)
  - >300 unique PDXs from Pharma/Biotech: in negotiation
  - $\approx$ 1000 tumor biopsies from NCI MPACT Trial: starts Q1 2014

- **PDX tumors in hand:**
  - 27 GBMs
  - 31 Lung (adenosquamous; 3 sclc’s)
  - 7 Bladder
  - 5 Colon
  - 5 Sarcoma
  - 3 Head & Neck
  - 1 NHL
  - Take rate:
    - 70% for 18 gauge needle biopsies
    - 7/21 implants directly from CTCs growing as PDXs
Histology Over Multiple Generations: 172845, Colorectal Cancer

- PDX Sample obtained from DTC clinic (06-C-0213)
- Considered a “PDX tumor model” as a sample has not yet been frozen and re-established in mice
- In vitro cell culture with Rho Kinase inhibitor and fibroblast-conditioned F-media, not on mouse feeder layer.

172845-Patient
No H&E
Patient not delinked

P0, Biopsy Material
Biopsy Date: 5/1/2013
Biopsy Date: 5/22/2013

P0, CTC Material
Blood Draw Date: 5/1/2013

In Vitro Growth: Primary Cell, Mixed Population Cultures
Biopsy Date: 5/1/2013
Blood Draw Date: 5/1/2013
Growth Over Multiple Generations: 172845, Colorectal Cancer

Study Number: PDX 172845-64-121-T
## MPACT Assay v1.0 Gene Panel

### 63 Gene Panel

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<td>EGFR</td>
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<td>NOTCH1</td>
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### Actionable Mutations for the MPACT Trial

**Pathways:**
- RAS/RAF/MEK
- AKT/PI3K
- DNA Repair
Histology Over Multiple Generations: CN0330F, Colon Cancer

- PDX Sample obtained from Jackson Laboratories (P1). NCI generations start with P2.
- Considered a “PDX xenoline” as tumor material was frozen and the ability to establish a new tumor was seen with P2.
- MPACT aMOI include AKT-1 (E17K) and KRAS (G13D) gain of function mutations. Mutations also called through Jackson Lab ONCARTA screen.

CN0330F-Patient

P0

- CN0330F-216P0

P1

- CN0330F-216P1

P2

- CN0330F-216M517

P3 (4th mouse generation)

- CN0330F-216M519M102
- CN0330F-216M519M106
- CN0330F-216M519M107
Variability Across 3 Generations: BL0269 (Bladder Cancer)

- High degree of overall gene expression similarity between BL0269F-402M601 initial in vivo passage (P1) at NCI, P2, and P3
  - One P3 tumor (of 6) began to over-express members of the GAGE/MAGE and SSX gene families located on the X-chromosome. Both of these gene families have been previously linked to increased aggressiveness or drug resistance.
  - Other X-linked genes do not show similar increased expression levels in M251’s gene expression profile, suggesting its unique gene expression is not due to grand chromosome level abnormalities (ie duplications).

- If the tumors from the BL0269F-402M601-M633-M251 lineage are to be used in further experiments, the altered gene expression of GAGE/MAGE and SSX fusion genes verified by protein blots and drug resistance tendencies should be monitored.
### Glioblastoma PDX Project (UAB)

<table>
<thead>
<tr>
<th>PDX ID</th>
<th>Diagnosis</th>
<th>Passages Received</th>
<th>Original Date Implanted</th>
<th>TMZ sensitivity, flank xenografts</th>
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Aliquots over several passages currently undergoing testing for transmissible spongiform encephalopathies (TSEs, aka prion disease) before growth in mice at FNLCR is initiated. Analysis being performed through collaboration with Andy Hughson (NIH/NIAID Rocky Mountain Laboratories).
Kinomic profiling of xenolines: 27 GBM tumors PTK and STK PamChip kinomic profiles were performed and the most highly variable substrates (var>0.3) were selected for hierarchical clustering displayed as a heatmap with phosphosubstrates indicated on the Y-axis and GBM xenoline name on the X-axis.

Heatmap of significantly different phospho-substrates from three different GBM PDXs with resistance, intermediate response or sensitivity to a specific JAK2 small molecule inhibitor.
Project Deliverables

Technology/Tools
• Together, develop a repository of reliable and relevant graft (PDX) models, methods, and SOPs optimized to inform future clinical trials. Bank tissues, fluids, and nucleic acids for future-use
• Tissue biomarker validation
• Clinical/preclinical database with positive and negative data

Preclinical Science
• Develop consensus with Cancer Centers and Pharma on the value of new preclinical models in directing successful clinical trial designs
• Genomic and network analysis of PDXs at baseline and following therapy to identify new targets
• Development of conditionally-reprogrammed lines from biopsies and PDXs
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<th>Service Description</th>
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<th>Full Work-up</th>
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<td>Human pathogen testing</td>
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<td>$500</td>
</tr>
<tr>
<td>5 Mice/PDX: passage 2</td>
<td>$200</td>
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</tr>
<tr>
<td>Identifiler</td>
<td>$45</td>
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</tr>
<tr>
<td>Vial freeze (80 vials)</td>
<td>$120</td>
<td>$120</td>
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<tr>
<td>Labor</td>
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</tr>
<tr>
<td>MPACT Panel &amp; Whole exome sequencing; microarray?</td>
<td></td>
<td>$1,350</td>
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<tr>
<td>Histopathology</td>
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<tr>
<td>Mouse pathogen testing</td>
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Estimate for 1 PDX Model

$4,325

$8,025

Approximate NCI Initial Investment (500 Models)

$2,162,500

$4,012,500
Summary

• Develop a PDX repository to support a national program to provide clinically-annotated, molecularly-characterized PDX models in multiple tumor types to extramural investigators

• Intellectual input from academia and Pharma colleagues

• Obtain both solid and liquid tissues primarily from NCI-designated Cancer Centers and NCI intramural clinics for new models; and currently-available PDX models from: Pharma/Biotech and Cancer Centers

• Ensure access to models and baseline molecular and clinical data for extramural community

• Longer-term goals:
  – Compare PDX, conditionally-reprogrammed lines, and other new culture systems to current xenograft models to optimize drug development across several histologies/genotypes
  – Understand mechanisms of drug resistance in patients using multiple model systems that allow comparison with actual clinical trial outcomes
Acknowledgements

Harold Varmus
Edward Harlow
Terry van Dyke
Robert Wiltrout
Joseph E. Tomaszewski
Sheila Prindiville
Raymond Petryshyn
Melinda Hollingshead
Glenn Merlino
Zoe Weaver-Ohler
Serguei Kozlov
Linda Weiss