Precision Medicine Initiative for Oncology Including Development of Improved Preclinical Cancer Models

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NIH NATIONAL CANCER INSTITUTE

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Precision Medicine Initiative

Proposed FY16 Support

Agency	$ Million
NIH	200
• *Cancer*	*70*
• *Cohort*	*130*
FDA	10
Office of the National Coordinator for Health Information Technology	5
TOTAL	$215

Precision Medicine Initiative: Oncology

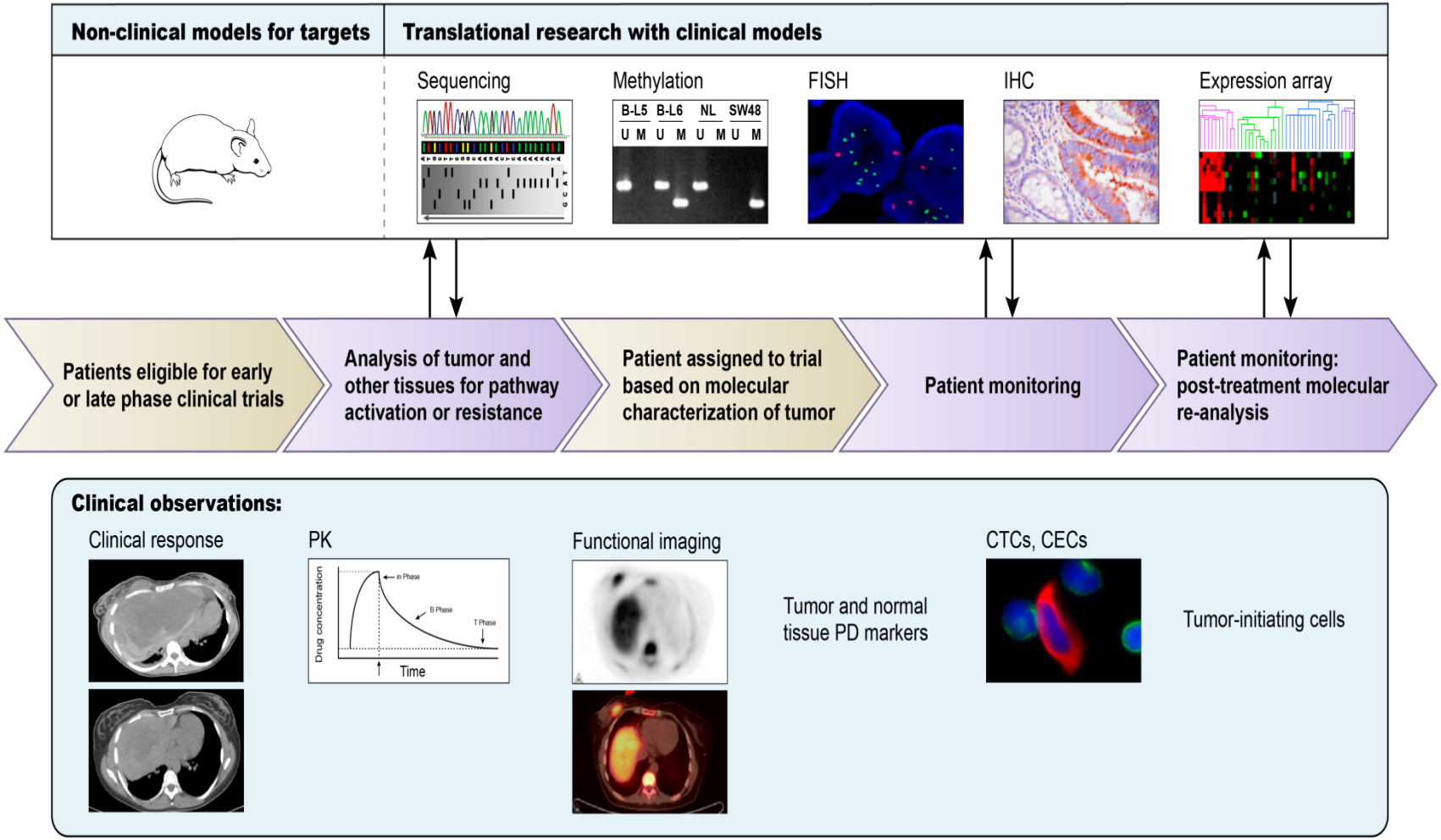
What Problems Are We Trying to Solve?

- 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

Precision Medicine/Oncology in Practice



Nature Rev. Clin. Oncol. 11: 649-662, 2014.

Precision Medicine Initiative: Oncology

Resources:
Scope
Speed
Scale

Goal: Increase Genomics-Based Clinical and Preclinical Studies of Cancer Treatment

1. Expand genomics-based clinical trials
2. Understand & overcome resistance to targeted drugs; drug combinations; and mechanistic understanding of immunotherapy
3. Build repository of patient-derived pre-clinical models for evaluating targeted therapeutics
4. Create 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

Pending:

- ALK Inhibitor
- MET Inhibitor
- Pediatric MATCH

Precision Oncology Trials: NCI-MATCH

NCI-MATCH: Features

[Molecular **A**nalysis for **Th**erapy **Ch**oice]

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

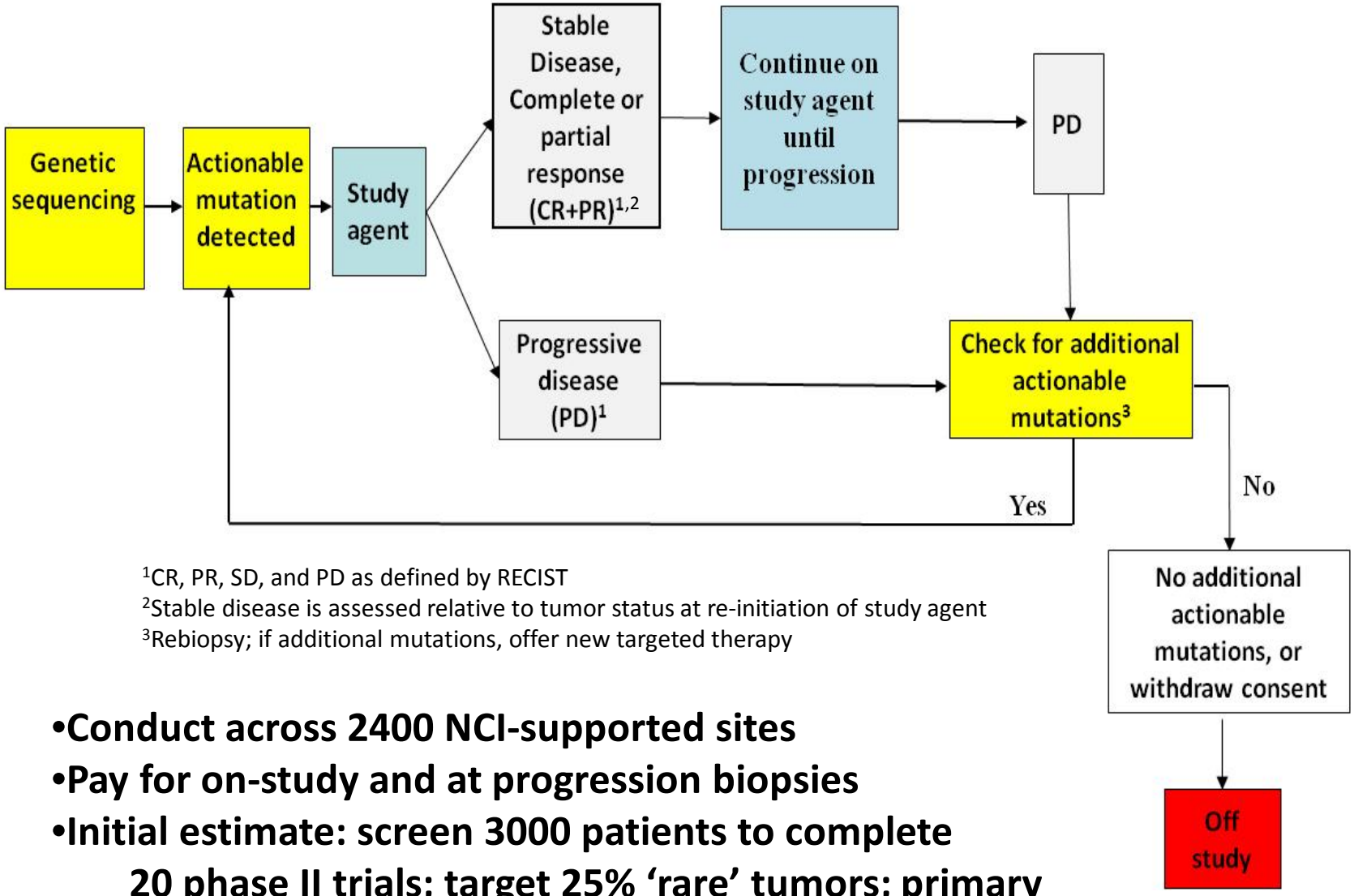
- Regulatory umbrella for phase II drugs/studies from > 20 companies; single agents or combinations

- Validated gene sequencing at 4 sites; >98% concordance for "locked down" analysis of mutations in 143 genes; fresh biopsies at study entry

- Available nationwide (2400 sites); CIRB

- Accrual began mid-August 2015; 160 patients accrued first 4 weeks

NCI MATCH



[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

- **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%**

NCI-MATCH: Initial Ten Studies

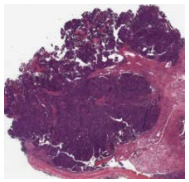
Agent(s)	Molecular Target(s)	Estimated Prevalence
Crizotinib	ALK Rearrangement (non-lung adenocarcinoma)	4%
Crizotinib	ROS1 Translocations (non-lung adenocarcinoma)	5%
Dabrafenib and Trametinib	BRAF V600E or V600K Mutations (non-melanoma)	7%
Trametinib	BRAF Fusions, or Non-V600E, Non-V600K BRAF Mutations (non-melanoma)	2.8%
Afatinib	EGFR Activating Mutations (non-lung adenoca)	1 – 4%
Afatinib	HER2 Activating Mutations (non-lung adenoca)	2 – 5%
AZD9291	EGFR T790M Mutations and Rare EGFR Activating Mutations (non-lung adenocarcinoma)	1 – 2%
TDM1	HER2 Amplification (non breast cancer)	5%
VS6063	NF2 Loss	2%
Sunitnib	cKIT Mutations (non GIST)	4%
		≈ 35%

Agents and targets below grey line are pending final regulatory review; economies of scale—larger number of agents/genes, fewer overall patients to screen

MATCH Assay: Workflow for 10-12 Day Turnaround

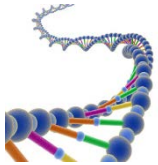
Biopsy Received at Quality Control Center

3-5 DAYS — **Tissue Fixation Path Review**



Tumor content >70%

1 DAY — **Nucleic Acid Extraction**



DNA/RNA yields >20 ng

1 DAY — **Library/Template Prep**

Library yield >20 pM

1 DAY — **Sequencing , QC Checks**

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

1 DAY — **Centralized Data Analysis**

aMOIs Identified

3 DAYS — **Clinical Laboratory aMOI Verification**

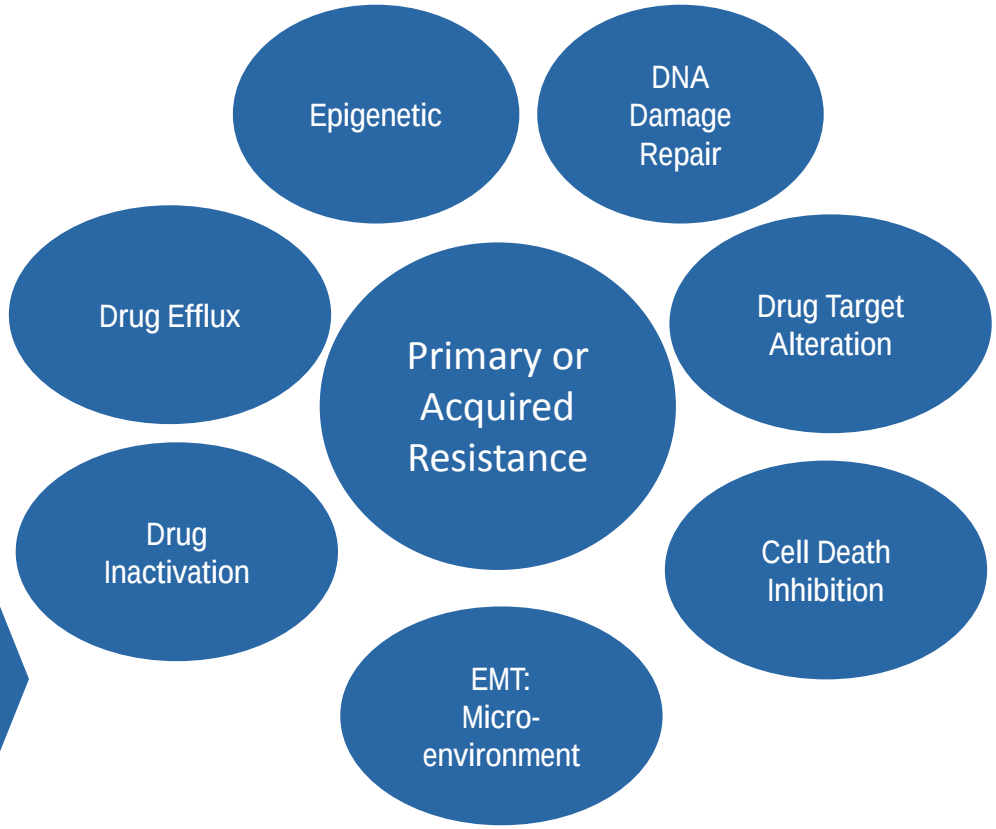
10-12 days

Rules Engine Treatment Selection

PMI-O: Expanding Genomically-Based Cancer Trials (FY16-FY20)

- 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



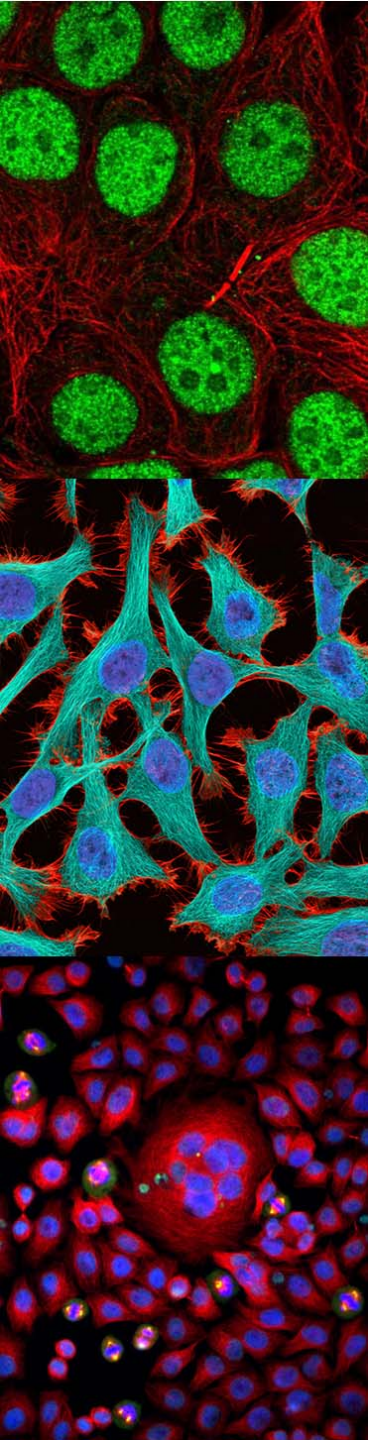
- Broad range of mechanisms
- Until recently, tools to interrogate possibilities *in vivo* quite limited
- Resistance to single agents inevitable: 1º or acquired; *requires combinations* but data to provide molecular rationale for the combination (both therapy & toxicity) not often available

PMI-O: Understanding and overcoming resistance to therapy (FY16-FY20)

- Create a repository of molecularly analyzed samples of resistant disease
- Expand the use of tumor profiling methods such as circulating tumor cells (CTCs) and fragments of tumor DNA in blood to understand and monitor disease progression
- Develop new cancer models to identify the heterogeneity of resistance mechanisms
- Use preclinical modeling to determine the effectiveness of new combinations of novel molecularly targeted investigational agents

PMI-O: Developing new models for preclinical studies (FY16-FY20)

- Launch the Human Cancer Models Initiative (HCMI) and develop representative human cancer model systems for the research community
- Expand the number and availability of novel human cell lines and patient-derived xenographs
- Enhance the ability to predict the success of immunotherapy through the examination of malignancies that have shown response to immune checkpoint therapy in novel model systems



Modeling the Diversity of Human Cancer: An Unmet Need

- Genetic analysis has identified recurrent genetic lesions in cancer that range in frequency from 1% - >50% of cases.
- Most cancer cell lines have not been directly compared to the primary tumor using current genomic methods.
- Existing cell line models of common cancer types are suspect biologically and genetically (e.g. prostate CA)
- Models of rare cancer subtypes may be nonexistent or underrepresented
- Models do not exist for many recurrent genetic lesions in human cancer, and for common combinations of lesions
- Existing models do not recapitulate hierarchical relationships of tumor subpopulations (i.e. tumor propagating cells, stroma)
- Baseline clinical data and response to treatment are typically not available for existing cancer cell lines

PMI-O: Developing a national cancer knowledge system to support precision medicine (FY16-FY20)

- Establish NCI's Genomic Data Commons (GDC) to facilitate the identification of subtypes of cancers and potential new drug targets
- Develop secure, flexible, meaningful, interoperable interfaces to provide for the analysis of large-scale cancer genomic and clinical data
- Establish a sustainable infrastructure for cancer genomic data to allow for the analysis of multiple data types, multi-scalar data, and temporal data

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
- GDC will be a single repository for all NCI cancer genomics data
  - ✓ Will include data from existing and new NCI cancer genomics efforts
  - ✓ Will allow researchers to upload, analyze, and share their own cancer genomic data
  - ✓ Store all data including raw data
  - ✓ Harmonize the data as appropriate
  - ✓ Will be the authoritative reference data set

Precision Medicine Initiative for Oncology: Extramural presentations and workshops

Recent & Ongoing Input from Extramural Community

- Joint meeting of NCI Board of Scientific Advisors & National Cancer Advisory Board., **June 2015**
- Organoids & Reprogrammed Cell Lines: Lou Staudt, M.D., Ph.D., **July 2015**
- Exceptional Responders Workshop—Next Steps: Barbara Conley, M.D., **March 2016**
- Immunotherapy—Combination Approaches and NGS: Helen Chen, M.D., **January 2016**
- PDX Models, Combination Therapy, and Drug Resistance: J. Doroshow, M.D. and Dinah Singer, Ph.D., **January 2016**
- Genomic Data Commons workshop: W. Kibbe, Ph.D. and Lou Staudt, M.D., Ph.D., **Fall, 2016**

Patient-Derived Models Repository to Support Cancer Discovery & Therapeutics Development

September 2015

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

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FNLCR Patient Derived Cancer Models Repository: Issues for Consideration

- Development of PDM Repository—update since February 2014
- Novel cancer models
- Considerations for future use

NCI Patient-Derived Models (PDM) Repository

- A national repository of PDMs to serve as a resource for academic discovery efforts and public-private partnerships for drug discovery 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,
- NCI to provide long-term home for >1000 PDX and PDC models each produced from tissues and blood supplied by NCI-designated Cancer Centers, NCTN & ETCTN
  - Target collections of tumors less prevalent in current resources (eg., Small Cell Lung, Pancreatic, Head/Neck, Ovarian & Bladder cancers; Prostate, Kidney, Sarcomas, Melanomas)
- Goals:
  - ✓ ~50 unique patient models (solid & derived tumor line) per disease (min) with sufficient size of each molecularly-characterized subgroup to power 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

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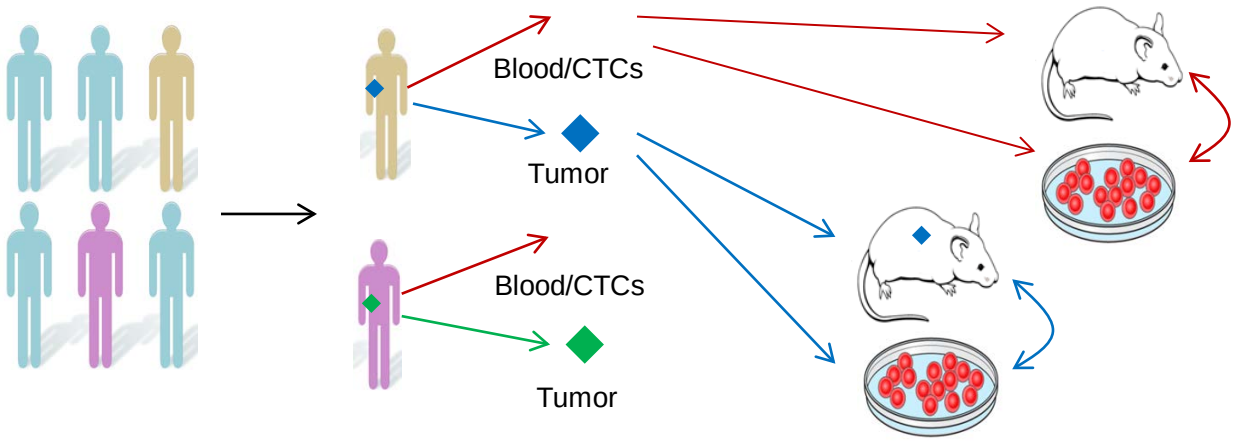
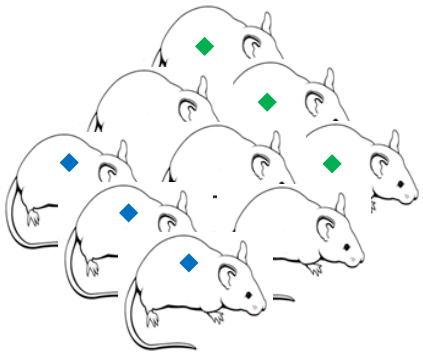
NCI Patient-Derived Models Repository: Multiple Avenues for Discovery

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

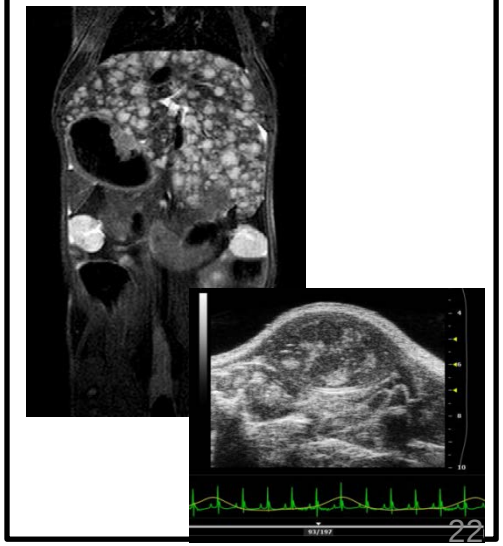


Tumor/Patient Heterogeneity

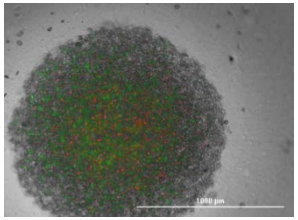


Preclinical Trial Modeling

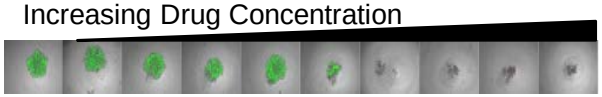
Live Tumor Imaging



3D Culture, 3D Pharmacodynamics



Increasing Drug Concentration



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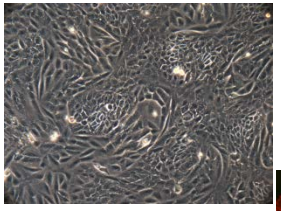
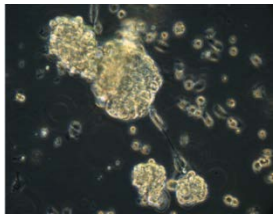
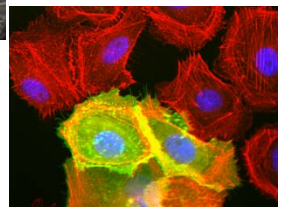
2D Culture, Spheroid growth

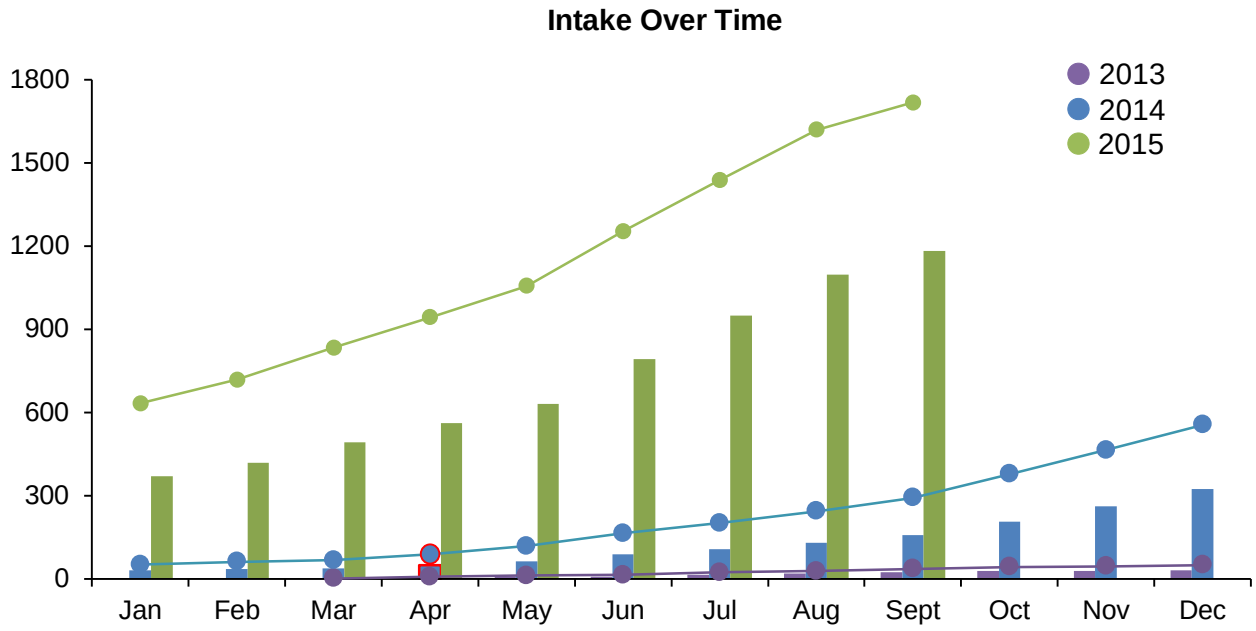






Specimen Acquisition for Model Development

- Currently receiving tissue (resections, biopsies) and blood samples for CTC enrichment from two separate tissue procurement protocols (06-C-0213 [NCI] and 9846 [CIRB])
- Clinical centers include 2 NCI clinics, 16 NCI comprehensive cancer centers, and 23 ETCTN/NCORP LAO/LPOs with >140 participating sites.



Lines Graph: Total Specimens
Bars Graph: Total Patients

Updated 9/21/2015

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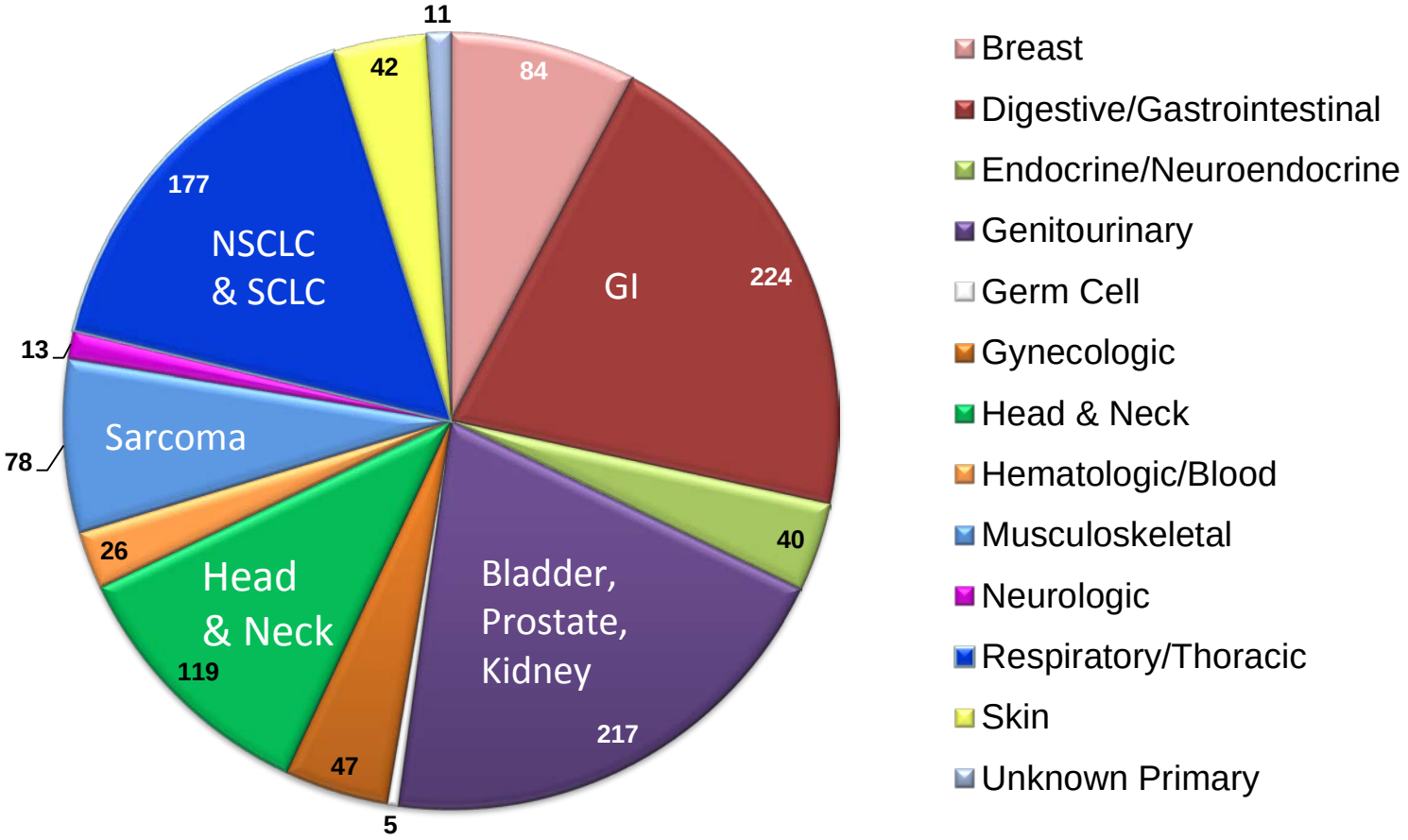
NCI Patient-Derived Models Repository Patient Tumor Types by Disease Location



As of Sept, 21 2015

Total Number of Specimens (tissue and blood) Received: 1502

Total Number of Patients: 1083

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PDX Take-Rate from Tumor Tissue Implantations

Body Location	Total Received	Total Assessable Specimens (>P0)	%Take-Rate of Assessable Specimens	Passageable Tumor*	Discontinued†	*Not Yet Assessable: P0 tumors*
Breast	16	3	0%	0	3	*13*
Digestive/ Gastrointestinal	103	59	78%	46	13	*44*
Endocrine/ Neuroendocrine	24	7	43%	3	4	*17*
Genitourinary	108	48	54%	26	22	*60*
Germ Cell	1	0		0	0	*1*
Gynecologic	23	18	50%	9	9	*5*
Head and Neck	97	70	79%	55	15	*27*
Hematologic/Blood	1	0		0	0	*1*
Musculoskeletal	86	31	58%	18	13	*55*
Neurologic	4	1	0%	0	1	*3*
Respiratory/Thoracic	44	25	80%	20	5	*19*
Skin	31	15	87%	13	2	*16*
Unknown Primary	8	4	50%	2	2	*4*
Totals	546	**281**	**68%**	**192**	89	*265*

*Passageable Tumor — Includes any PDX where a palpable tumor has been passaged to at least P1 as well as Distributable PDXs. One or more of QC steps for PDX confirmation are pending for earlier passages.

†Discontinued — (1) Did not successfully grow palpable tumor in P0 (monitored 300 days), (2) Passaged tumor failed to grow in subsequent passages, (3) Mouse found dead/tumor not passageable, (4) Palpable tumors were 100% murine content, (5) xenograft-associated lymphoproliferative disease (XALD: host-versus-graft disease or human lymphoma out-growth)

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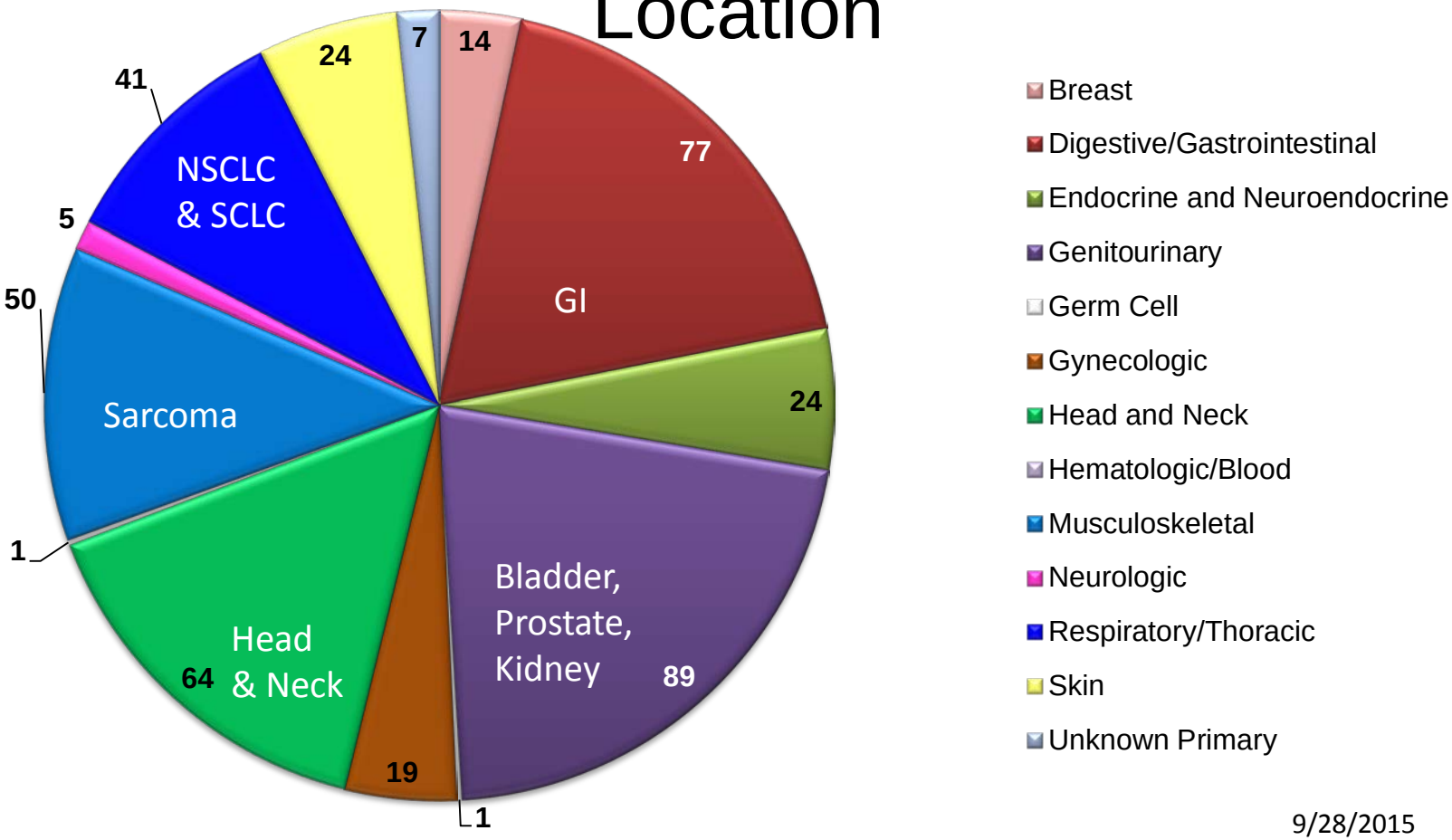
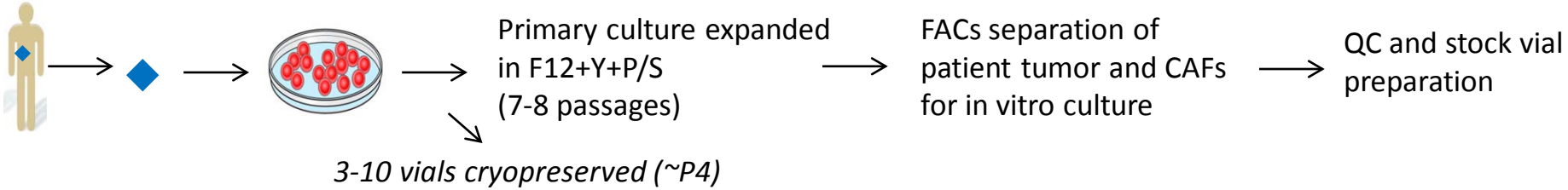
PDC Patient Tumor Types by Disease Location



Total number of cultures that have either been (1) Completed or are (2) In Progress for initial *in vitro* growth: **416**

Discontinued no-growth models not included in chart

In vitro Culture of Patient-Derived Tissue

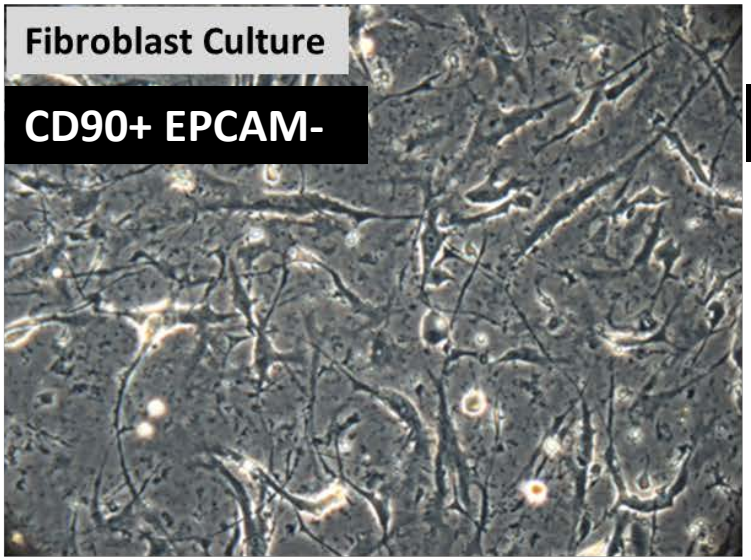


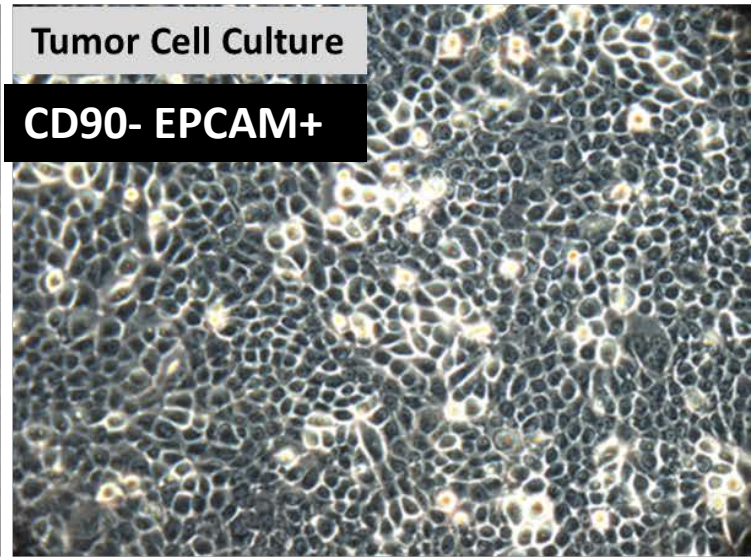
	Grown to P4	Tumor Material Present After FACs	CAFs Present After FACs
Total Attempted Cultures	578	341	341
#In Initial or Post-FACS Culture	52	69	33
Total Assessable Cultures	526	272	308
#Successful	341	--	--
#Discontinued (no growth)	185	79	30
#Discontinued (cell type not present)	--	118	87
Sorted, Tumor Cells Present*	--	75	N/A
Sorted, CAF Present*	--	N/A	191

- *After initial isolation of tumor cells or CAFs by FACs, cultures are expanded and may be resorted to achieve >**99%** pure cultures.
- Cultures then undergo final QC including: Genomic studies, Identifiler, karyotyping, tumorgenicity testing, growth rate assessment, and verification that distribution lots will grow for up to 20 passages from freeze.

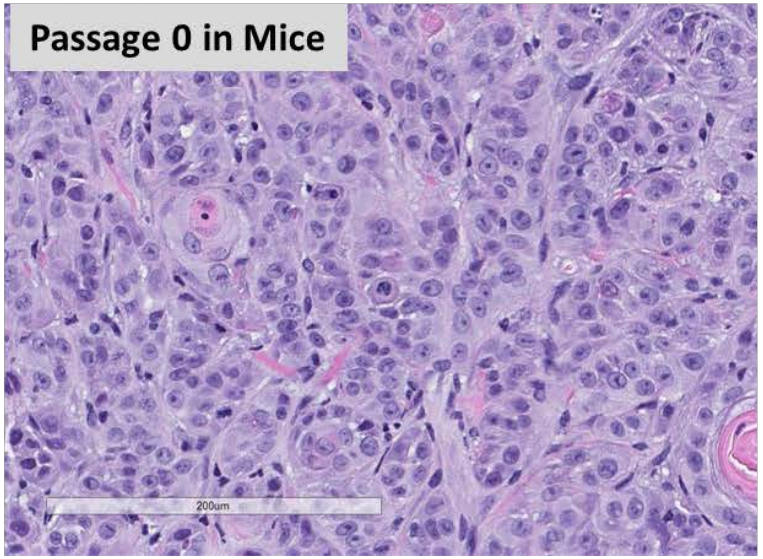
Salivary Gland Adenocarcinoma

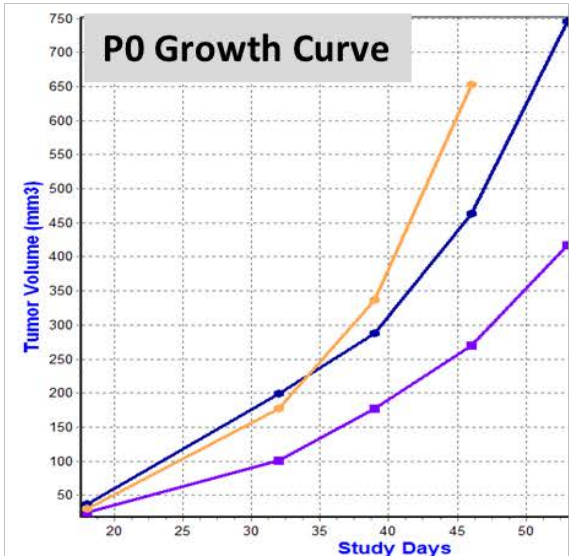
In vitro





In vivo





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PDM Quality Control Steps

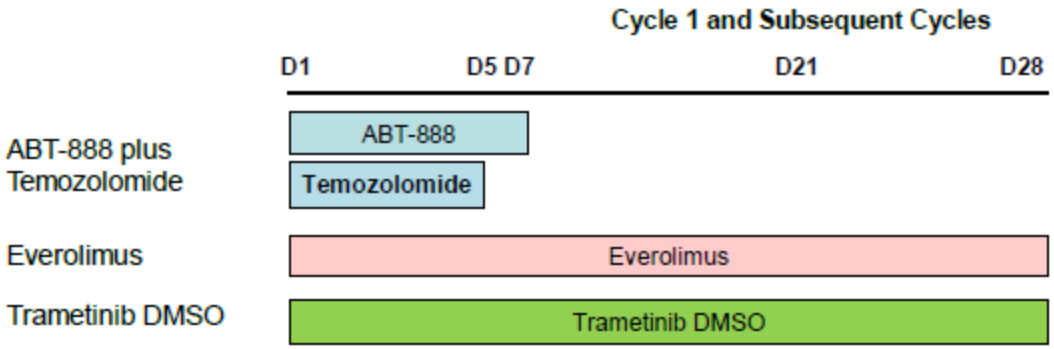
Patient-Derived Xenografts (PDX)

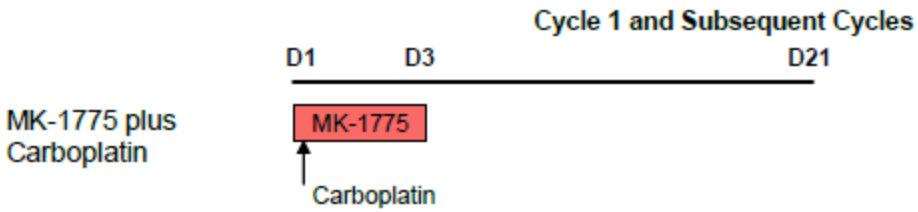
- **Initial QC**
  - Verify pathology matches patient diagnosis
  - Human:Mouse DNA ratio
- **Distribution Lot (DL) QC**
  - Verify pathology of all PDXs contributing to DL
  - Identifiler comparison to Passage 0
  - Whole Exome Sequencing , MPACT assay, and RNASeq of 6 PDXs performed; 1 deep sequence and 5 shallow sequence. Reviewed for concordance with primary and/or P0.
  - Verify regrowth of cryopreserved fragment

Patient-Derived Cell (PDC) Cultures

- **Initial QC**
  - Use FACs sorting to isolate tumor cultures and cancer-associated fibroblast cultures
  - Determine doubling time, and optimal growth conditions
  - Perform qRT-PCR for tumor versus fibroblast cell phenotype
  - Human:mouse DNA ratio if tumor cells originated from a PDX rather than directly from human donor
- **Distribution Lot (DL) QC**
  - FACS and qRT-PCR analysis to verify purity
  - Identifiler comparison to early passage in vitro culture, and when possible to PDX
  - Whole Exome Sequencing, MPACT assay, and RNASeq of 6 PDXs performed; 1 deep sequence and 5 shallow sequence. Reviewed for concordance with PDX
  - Karyotyping performed
  - Verify growth of cryopreserved vial for tumor lines and lack of growth for CAF lines as PDXs

Preclinical MPACT:
Modeling NCI-MPACT Clinical Trial 13-C-0105



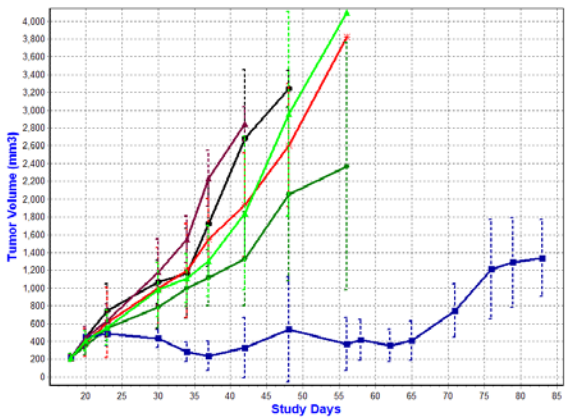


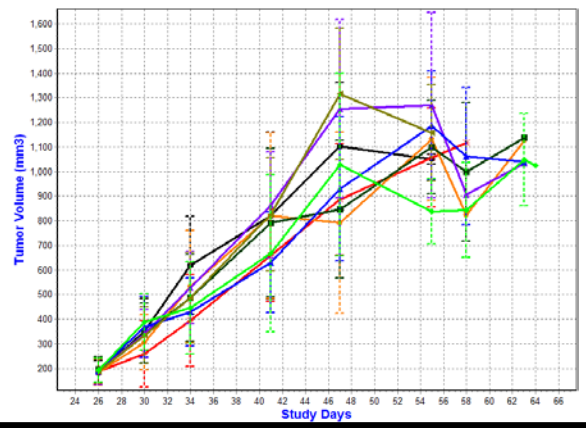
Preclinical trial dosing modeled after the <u>CLINICAL TRIAL</u>:

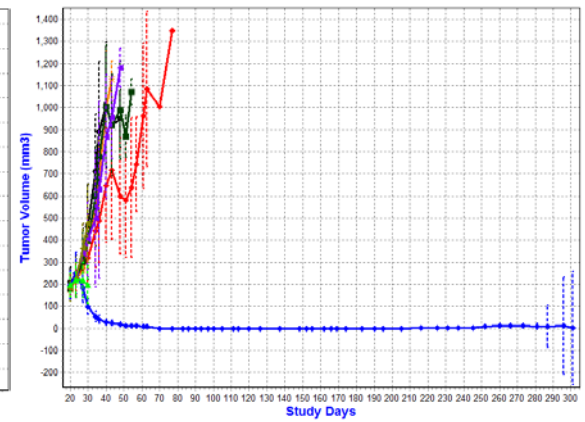
- Patients with specified mutations of interest will be assigned to receive **one** of the following study drugs or drug combinations at the assigned dose.
- **ABT-888** 40 mg orally BID qd days 1-7 plus **temozolomide** 150 mg/m2 orally qd days 1-5 (no food restrictions) in 28-day cycles
- **Everolimus** 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)

Preclinical MPACT Bladder Models

(Group) NSC	Drug
(G1)	vehicle
(G2) 733504	Everolimus
(G4) 758246	Trametinib
(G6) 752840	ABT-888
362856	Temazolomide
(G8) 754352	MK-1775
241240	Carboplatin







	BL0382	BL0269	BL0293
	Bladder Cancer, transitional cell ca	Bladder Cancer, invasive	Bladder Cancer, sarcomatoid differentiation
MPACT aMOI	TP53-E336 (stop codon)	PIK3C-H1074R	TP53-R248Q
Assign:	MK1775+Carboplatin	Everolimus	MK1775+Carboplatin
Of interest			BRCA2-R2034C (coseg-regated in a male breast ca family in the Dutch BRCA1/2 database)

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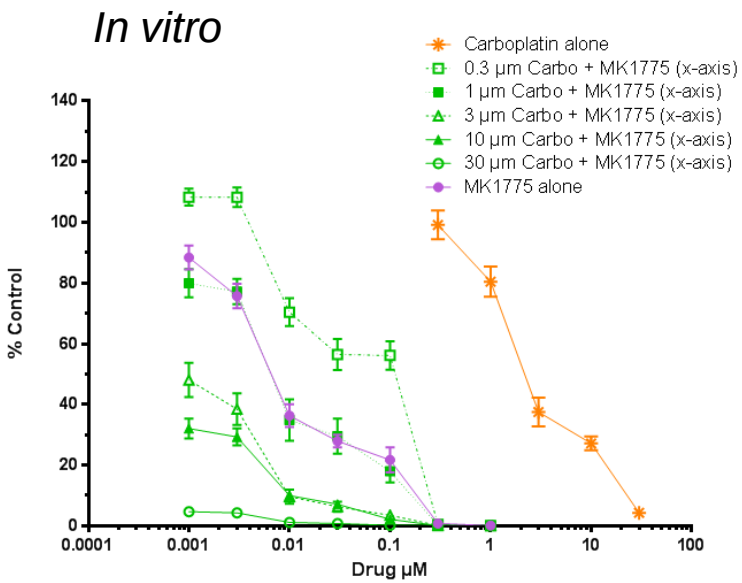
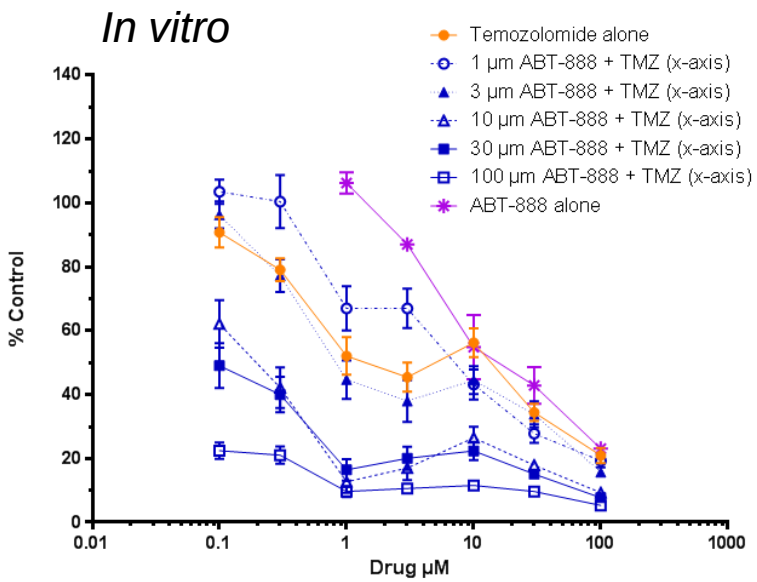
Planned Analysis of Preclinical MPACT

- To date 12 models have completed the Preclinical NCI-MPACT study, 3 are ongoing and an additional 7 models are in the queue for tumor growth and treatment.
- Whole exome sequencing and RNASeq are being performed at baseline and at pre-defined times during the study.
- In a PDX model, what correlates with response to drug? While complete regressions and no response can be categorized fairly easily; what is/can be called a drug response in between those two extremes can be difficult to define.
  - ✓ We currently evaluating different criteria for tumor doubling times and event-free survival to assign a numerical value for the relative survival of different treatment groups.
  - ✓ Once criteria have been established, comparison of RNASeq data for models that survive statistically longer than others within a treatment cohort will begin.

Bladder Model BL0293: *In Vitro* and *In Vivo* Response



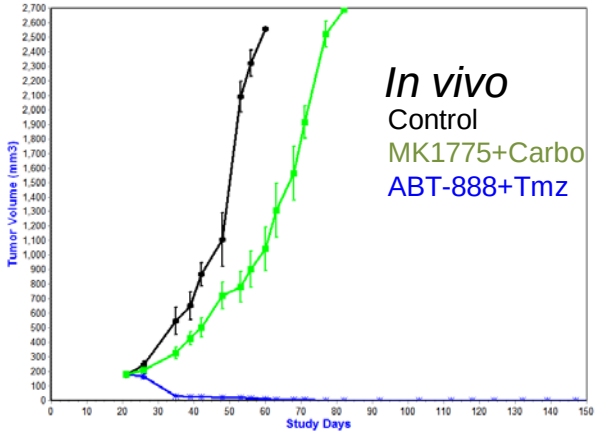


CI values: MK1775 + Carboplatin

ED50 3.52 = antagonistic

ED75 2.19 = antagonistic

ED90 1.4 = antagonistic



CI values: ABT-888 + Temozolomide

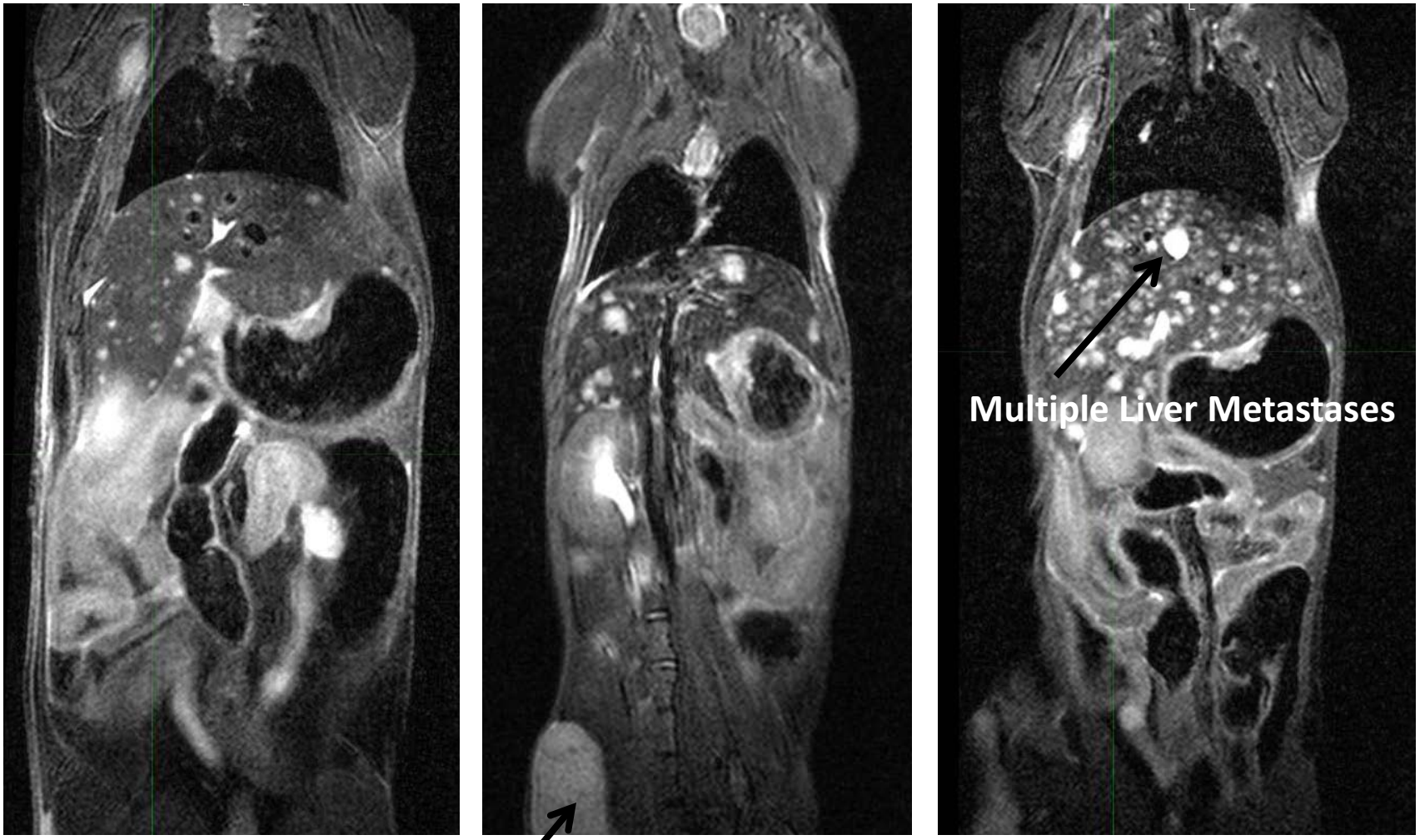
ED50 5.04 = antagonistic

ED75 0.65 = synergistic

ED90 0.47 = synergistic

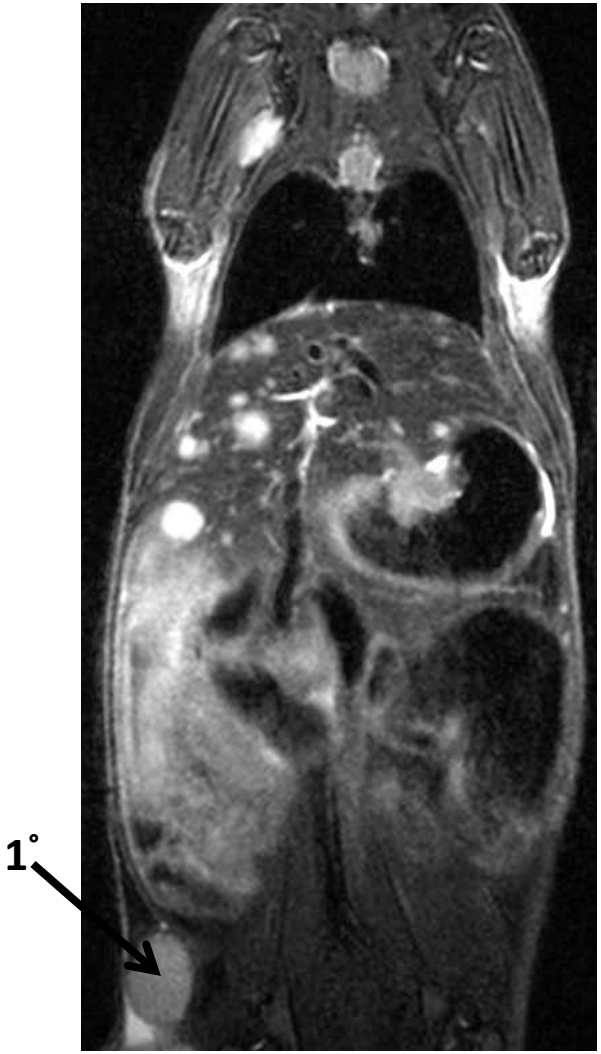
In vitro data confirmed that BL0293 was more sensitive to ABT-888 + Temozolomide than MK1775 + Carboplatin

BL-0293 Bladder PDX Implanted in 3 NSG mice on 6/8/2015
MRI 7/30/2015

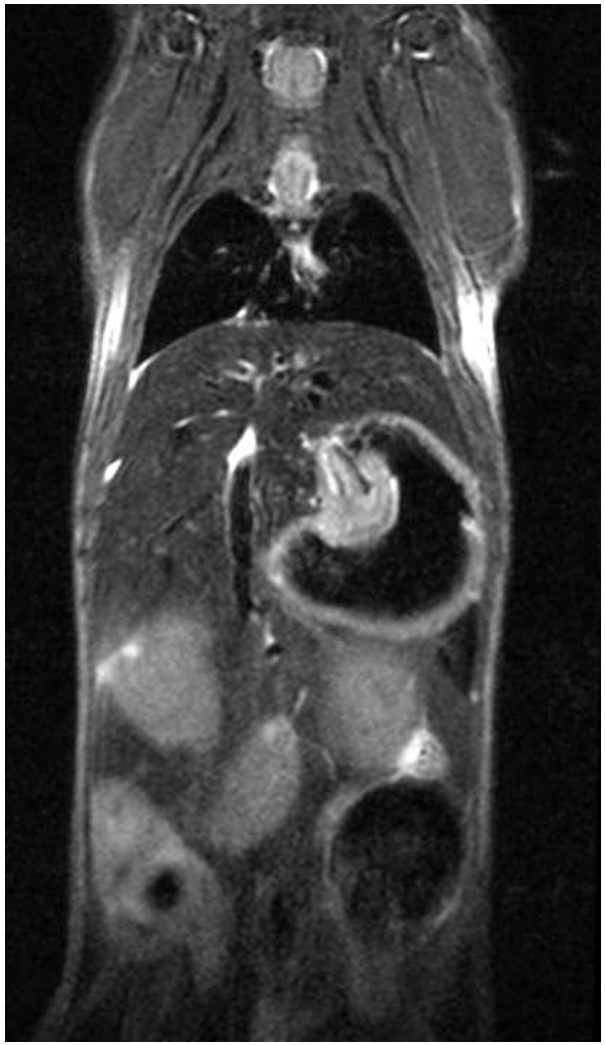


T2 Image of Primary In Place

BL-0293 Bladder Tumor:
Single Cycle of ABT-888 + TMZ Begun 8/12/2015 (Daily X 5d)



8/12/2015: Pre-Dose



8/27/2015: CR

9/04/2015: CR

Nude Rat PDXs: Implanted from Human PDXs Grown in NSG Mice

PDX ID	CTEP SDC Diagnosis	Growth in Rat (Passageable tumor)
172845-121-B	Adenocarcinoma - colon	No Growth
CN0330F216	Adenocarcinoma - colon	No Growth
CN0375F725	Adenocarcinoma - colon	Yes
CN0428F1126	Adenocarcinoma - colon	No Growth
CN0446F447	Adenocarcinoma - colon	Yes
466732-252-T	Adenocarcinoma - small intest.	Yes
ST0110F1568	GIST, poorly differentiated	No Growth
295223-140-R	H & N squamous cell car.	Yes
SA0426F1136	Leiomyosarcoma - not uterine	Yes
692163-330-T	Leiomyosarcoma - uterus	Yes
941425-263-T	Mesothelioma	Yes
LG0904F1496	Neuroendocrine cancer	Yes
LG0703F948	NSCLC, Adenocarcinoma	No Growth
LG0807F1297	NSCLC, Adenocarcinoma	Yes
LG1189F1952	NSCLC, Adenocarcinoma	Yes
114551-080-T	Salivary gland cancer, acinic	No Growth
275155-148-R	Salivary gland cancer, adenocarcinoma	Yes
LG0520F434	Squamous cell lung carcinoma	No Growth
LG0830F1385	Squamous cell lung carcinoma	Yes
416634-122-T	Transitional cell car. - uroth.	Yes
BL0269F402	Urothelial/bladder cancer	Yes
BL0293F563	Urothelial/bladder cancer	Yes
BL0382F1232	Urothelial/bladder cancer	Yes
BL0470F1820	Urothelial/bladder cancer	Yes
SA0350F605	Uterine cancer, undifferentiated sarcoma	Yes

A total of 54 models have been implanted into nude rats

- Of the 25 assessable models (table) there is a 72% success rate growing PDXs.
- 29 additional models are still in P0 growth
- Possible now to assess CTCs

Of interest: Previous less successful attempts to grow traditional xenografts in nude rats have been started from in vitro culture and required a larger cell number implanted than normal to grow a xenograft.

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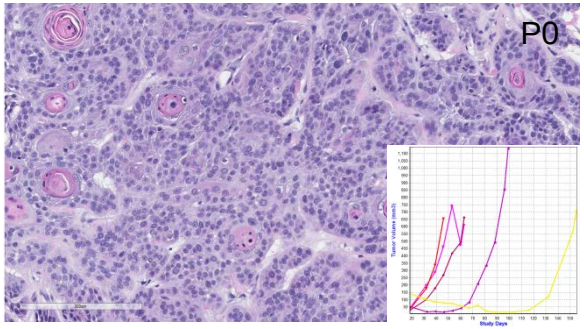
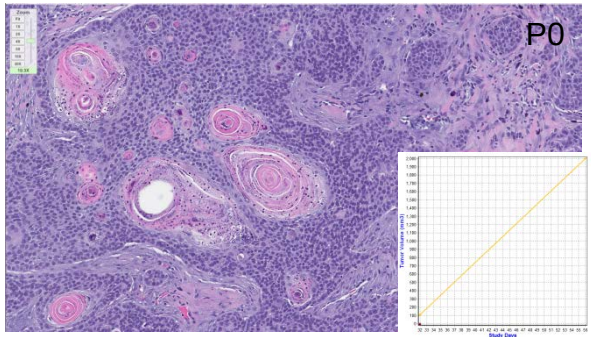
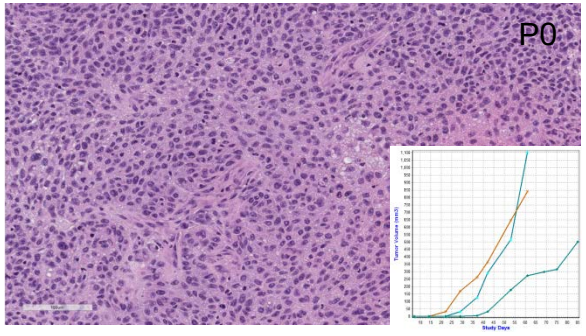
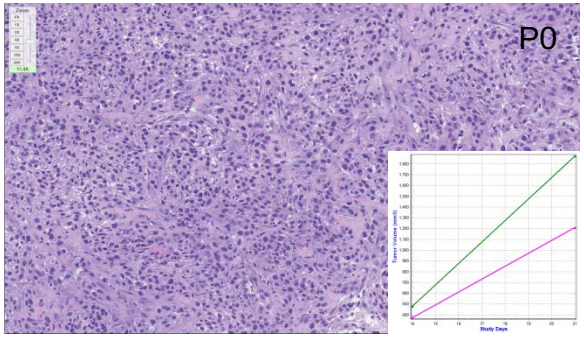
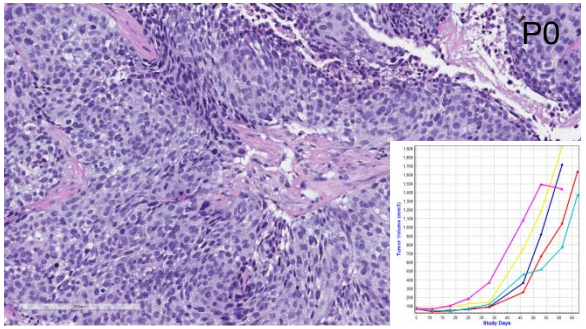
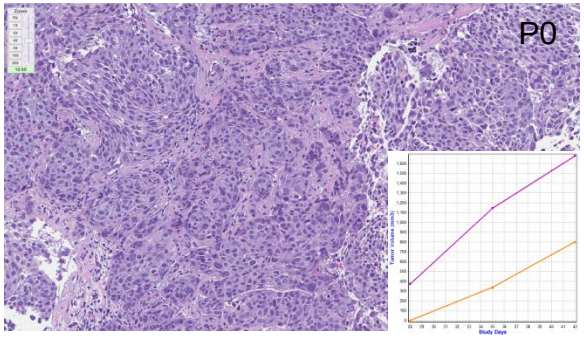
Similar Pathology in Mouse and Rat PDXs

	Mouse PDX	Rat PDX
275155-148-R Salivary Gland adenocarcinoma		
LG0904-F1496 Neuroendocrine carcinoma		
295223-140-R H & N squamous cell carcinoma		

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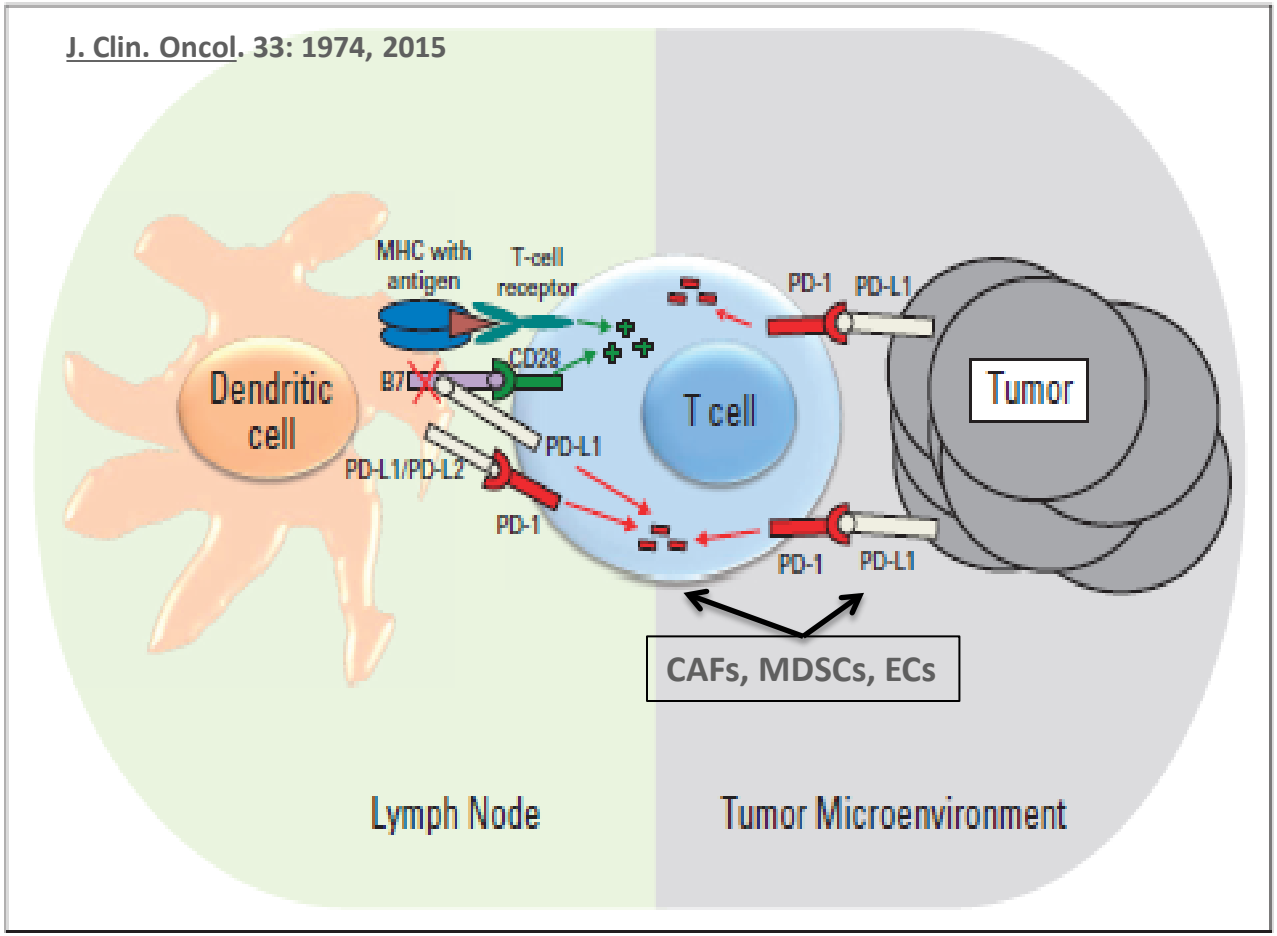
Enhancing Immunotherapy Models



- **Develop complementary models of spontaneous tumors amenable to pre-clinical tissue sampling and clinical trials: COTC**
- **For pre-clinical modeling of immunotherapy combinations using species specific reagents**

NCI Patient-Derived Models Repository (Expected Launch, Early Spring 2016)

National Cancer Institute | U.S. National Institutes of Health | www.cancer.gov

PDM Patient-Derived Models Repository

DCTD Division of Cancer Treatment and Diagnosis

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NCI Patient-Derived Models Repository

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- About the Repository
- PDM Team/Core Facilities
- Contributing Institutions
- Contact Us

About the NCI Patient-Derived Models Repository

Background

The National Cancer Institute (NCI) is developing a national repository of Patient-Derived Models (PDMs) comprised of patient-derived xenografts (PDXs) and in vitro patient-derived cell cultures (PDCs), including mixed cell populations, clonal cell lines, and fibroblast cell lines, to serve as a resource for public-private partnerships and for academic drug discovery efforts. These PDMs will be clinically-annotated with molecular information available in an ea

Home | Patient | Patient Specimen | Sample (PDX) | Genomic Analysis | Advanced Search

Find Specimen

Go | Reports 1. Primary Report | Rows 15 | Actions | Export

1 - 15 of 20

View	Patient ID	Specimen ID	Tissue Type	MedDRA Code	MedDRA Code Description	Disease Body Location	Collection Date	Biopsy Site	Growth Curve Avail
	114551	048-080-T	Tumor Biopsy	10039397	Salivary gland cancer	Head and Neck	03/21/2013	Right pleura	Yes
	172845	064-121-B	Blood	10009951	Adenocarcinoma - colon	Digestive/Gastrointestinal	05/01/2013	Blood	Yes
	172845	064-121-T	Tumor Biopsy	10009951	Adenocarcinoma - colon	Digestive/Gastrointestinal	05/01/2013	Liver	Yes
	172845	064-142-T	Tumor Biopsy	10009951	Adenocarcinoma - colon	Digestive/Gastrointestinal	05/22/2013	Liver	Yes
	172845	064-288-R	Resection	10009951	Adenocarcinoma - colon	Digestive/Gastrointestinal	10/15/2013	Left adrenal	Yes
	692163	035-330-T	Tumor Biopsy	10046799	Leiomyosarcoma - uterus	Gynecologic	11/26/2013	Abdomen	Yes
	941425	003-263-T	Tumor Biopsy	10027410	Mesothelioma	Unknown Primary	09/20/2013	Retroperitoneal mass - right	Yes

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FNLCR Patient Derived Cancer Models Repository: Future Possibilities

- Distribution of models: PDXs, conditionally-reprogrammed cell lines, DNA, RNA, whole cell lysates first quarter 2016
- Use as core resource in support of extramural SCLC consortium
- Support development of extramural early phase pre-clinical clinical trials consortium
- Novel models to develop immunotherapy combinations and PD, for example in comparative oncology trials
- Support extramural studies that require in vivo use of investigational agents—performed at FNLCR with PI

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