Technologies for Use in Next Gen Cancer Models Experiments to Accelerate our Understanding of Cancer and Facilitate the Transition to Individualized Therapy Strategies (Precision Oncology)

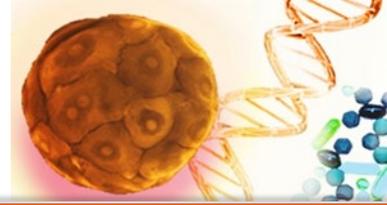## Concept in Response to the Recommendations by MS Develop New Cancer Technologies Blue Ribbon Panel

NCI Board of Scientific Advisors

December 5, 2018

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Director, Office of Cancer Genomics, CCG

Center for Cancer Genomics

Concept Summary 1/2

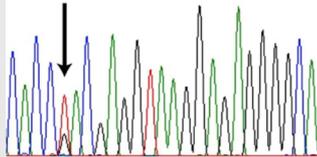Ongoing: Human Cancer Models Initiative aims to generate ~1000 next generation cancer models by end of 2020

➢ Address the Cancer Moonshot overarching goals

❖ Accelerate progress in cancer research

❖ Encourage collaboration

❖ Efficiently share data through publication and data portals

➢ Address the Blue Ribbon panel recommendations

❖ Address the urgent need for robust methods and reagents for high-throughput genetic and chemical screens

  ▪ The outcome would accelerate our knowledge of cancer initiation, progression, metastasis and resistance, and

  ▪ Teach the community how to use the models and resources to accurately predict treatment success in patients
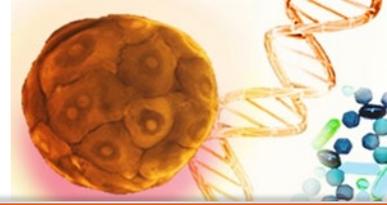
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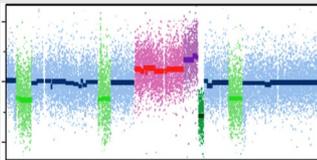
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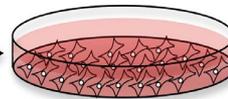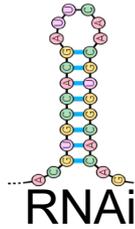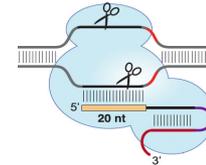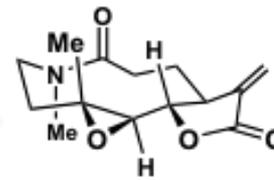
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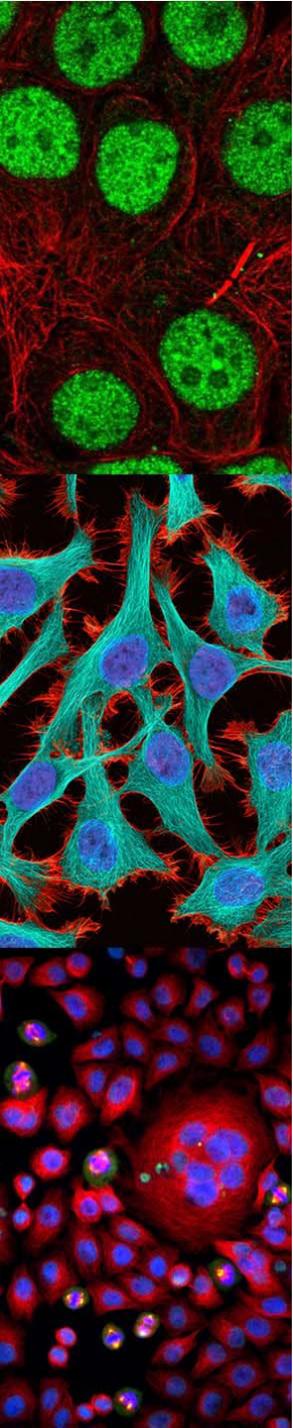
Diversity of Human Cancer Models: <u>Was</u> an Unmet Need

Genetic analysis of tumor tissues has identified recurrent genetic lesions in cancer that range in frequency from 1% - >50% of cases

➤ Models do not exist for many recurrent genetic lesions in human cancer, and even for common combinations of lesions

❖ The same for cancers from underrepresented populations and children

➤ Models of rare cancer subtypes may be nonexistent or underrepresented

➤ Some existing cell lines of common cancer types are suspect biologically and genetically (e.g. prostate CA)

➤ Most cancer cell lines have not been directly compared to the primary tumor using current genomic methods

➤ Existing models do not recapitulate hierarchical relationships of tumor subpopulations (i.e. tumor propagating cells, stroma)

modified from L.M. Staudt

New Cell Culture Technologies Enable the Propagation of Normal and Malignant Epithelial Cells

Organoid cultures

EdU/DAPI
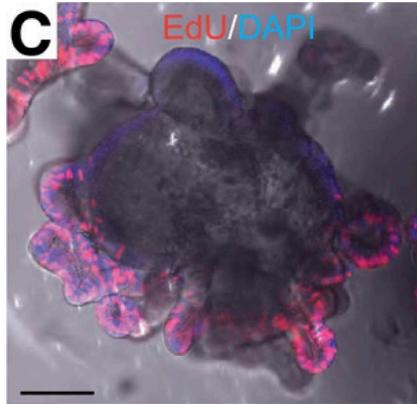
Clevers laboratory, Sato et al.
Gastroenterology 2011 141:1762

Optimized growth condition cultures

Tumor

vs.

Cell Line

ORIGINAL TUMOR

OCI-C5x

Keratin 7
PAX-8
DAPI
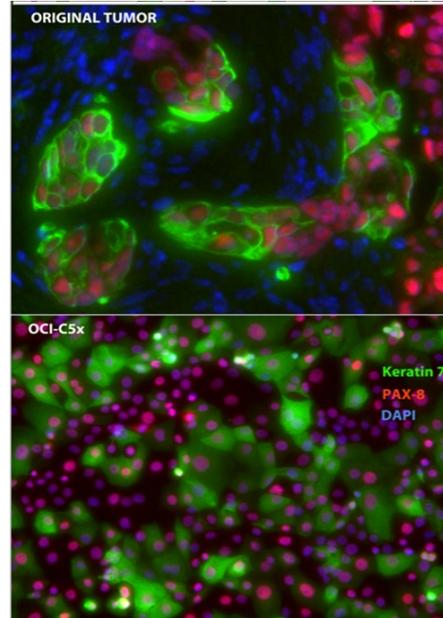
Ince et al.
Nat Comm. 2015 6:7419

Conditionally reprogrammed cells (CRCs)

Normal prostate   Normal breast

epi   epi

Normal trachea   Hepatocarcinoma

epi

epi
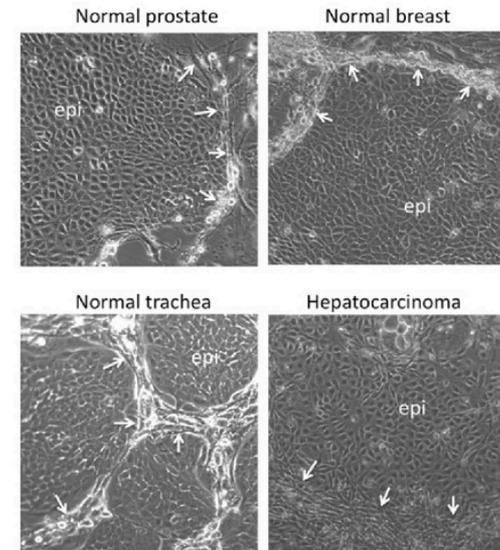
Schlegel laboratory, Liu et al.
American J Pathol 2012 180:599

modified from L.M. Staudt

Example of Organoid Models:
Capture Recurrent Genetic Lesions in Human Prostate Cancer

Chen, Sawyers laboratory
Gao et al. Cell 2014 159:176
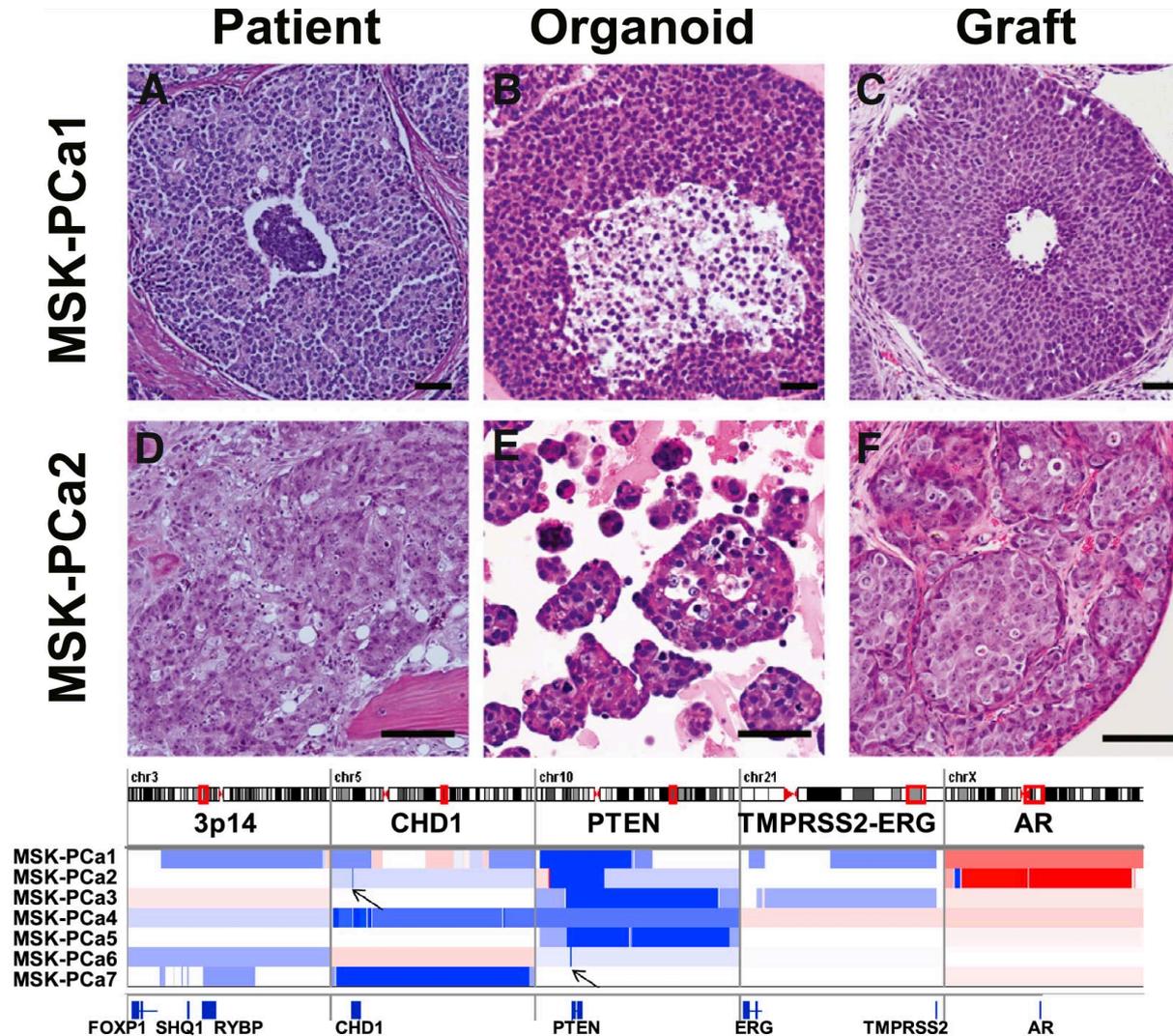
L.M. Staudt

Lung Adenocarcinoma Conditional Reprogrammed Cells: Used to Develop Therapies
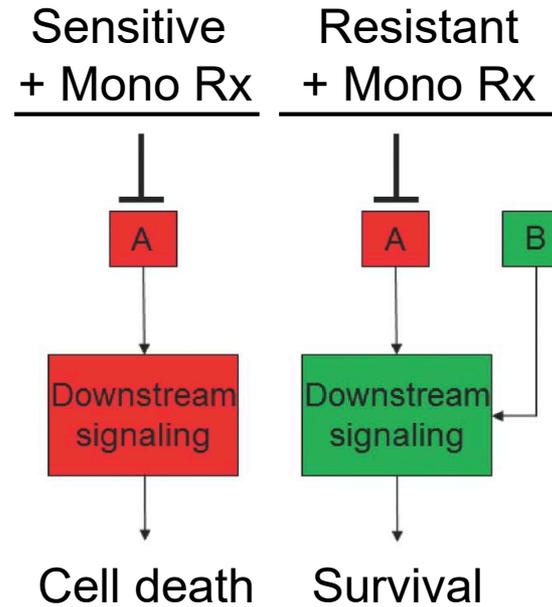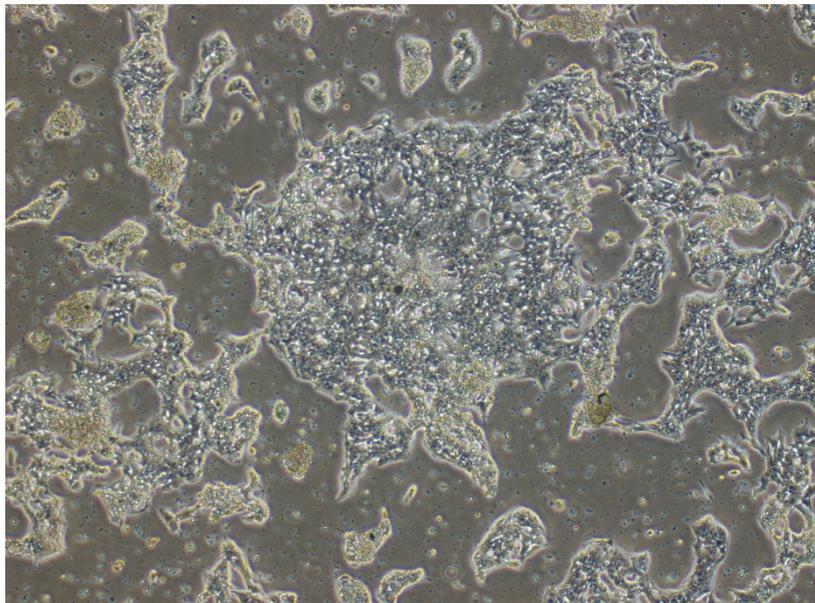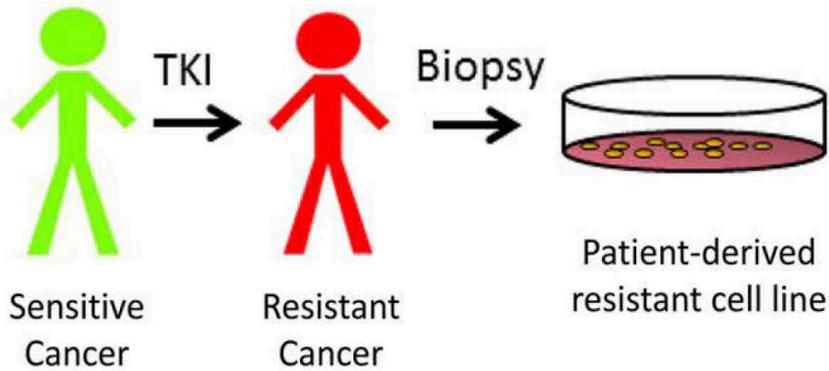
Engelman laboratory
Crystal et al. Science 2014 346:1480

L.M. Staudt

Lung Adenocarcinoma Conditional Reprogrammed Cells: Used to Develop Therapies
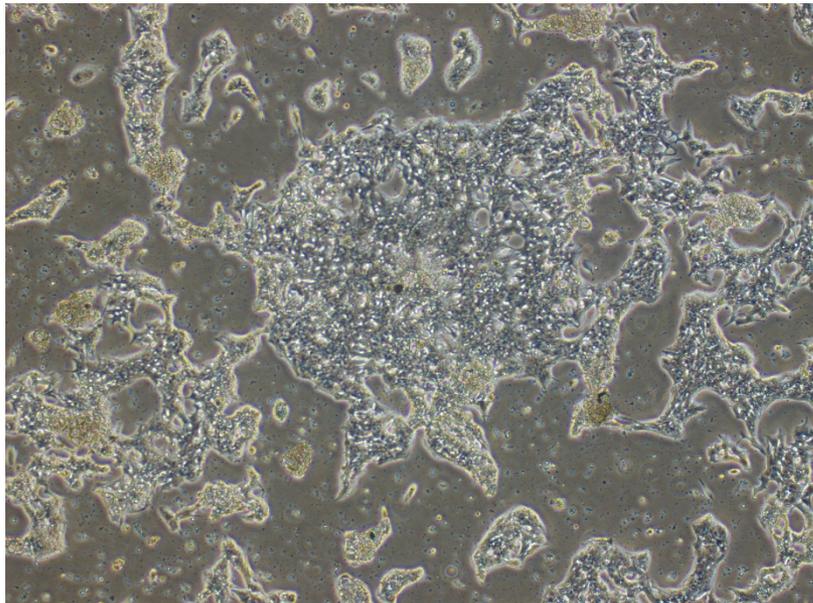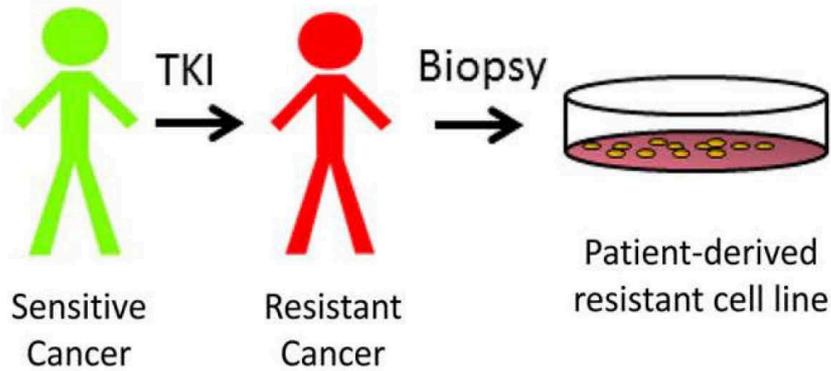
Combo drug screen with Gefitinib
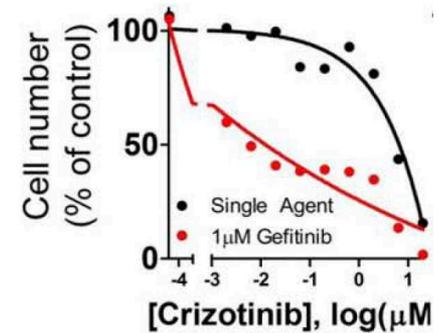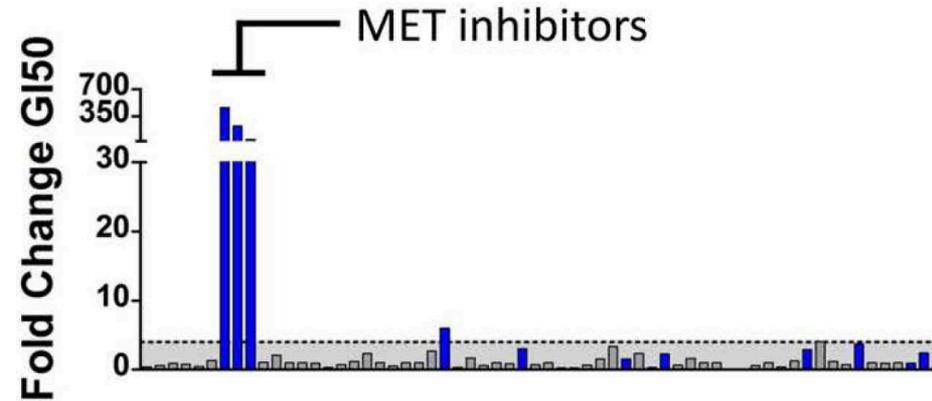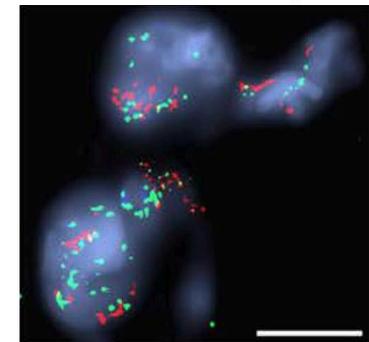
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Human Cancer Models Initiative (HCMI)
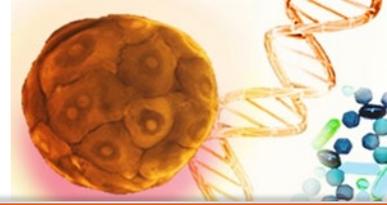
➢ The HCMI was established prior to the publication of the BRP MS recommendations yet they identified a need for

    ❖ Investment in new tumor models such as organoids and other patient-derived tissue models ………to accelerate the testing of therapies and characterization of tumors

➢ The aligned and the NCI leadership selected the project for MS

Human Cancer Models Initiative is an International Consortium

Wellcome Sanger Institute
Hinxton, United Kingdom

Hubrecht Organoid Technology
Utrecht, Netherlands

Cancer Research UK
London, United Kingdom

National Cancer Institute
Bethesda, MD, USA

➢ The consortium goal is to develop ~ 1000 fully characterized and annotated cancer models within 2-3 years

➢ NCI Funds 2 Cancer Models Development Centers

HCMI
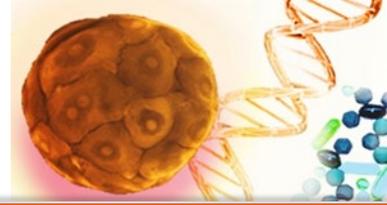
➢ Development of "next generation human cancer models" (NGCM) is in progress

❖ Organoids

❖ Conditionally Reprogrammed Cells

❖ Others

➢ Community Resource

➢ Distribution by a not-for-profit entity to academic and commercial entities

❖ Reasonable Material Deposition requirements

❖ Reasonable Material Transfer Agreements

➢ All protocols used to establish and expand the models to be shared as they are developed through the OCG web site
https://ocg.cancer.gov/programs/hcmi/resources

➢ First lot of U.S. models were submitted for expansion and molecular characterization

❖ Aim to start distribution in early 2019

Cancer Model Development & QC Processes
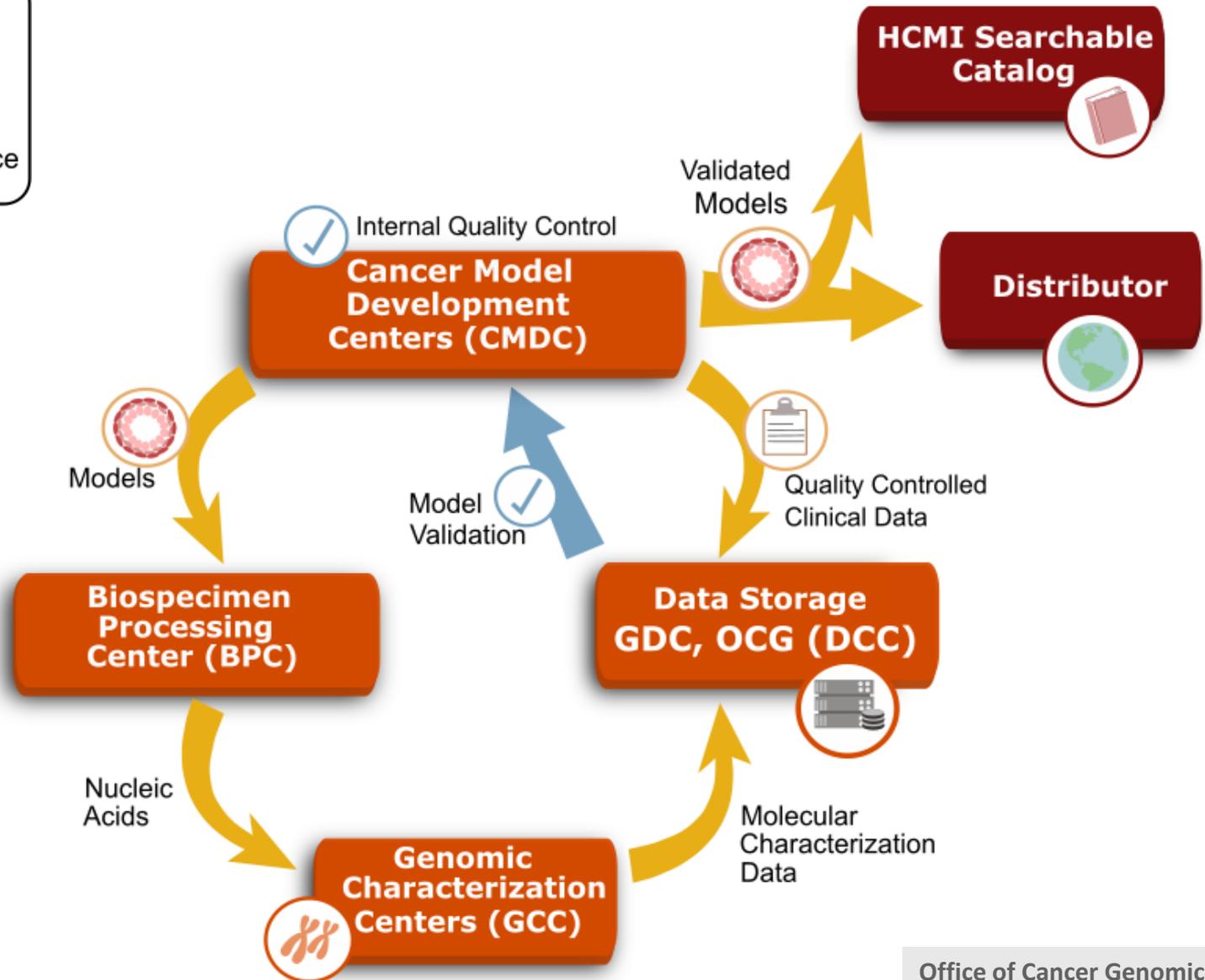
HCMI Pilot: Cancers
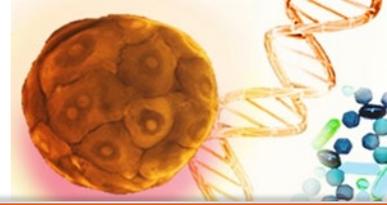
➢ Breast, Colorectal, Esophageal, Gastroesophageal, Glioblastoma, Lung Cancer, Pancreatic, Pediatric, Rare Cancers, Upper GI

❖ Melanoma, Head and Neck, Renal and Ovarian cancers are "on base"

➢ List of cancers types and populations represented is expanding, e.g.

❖ Tissues and clinical data from under-represented minorities will be through four CRCHD supplements and hospitals already working with each CMDC

❖ GAIN Consortium is providing tissues from pediatric cancers and clinical data

➢ HCMI updates: https://ocg.cancer.gov/programs/HCMI
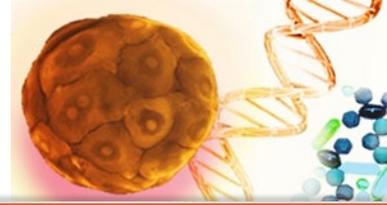
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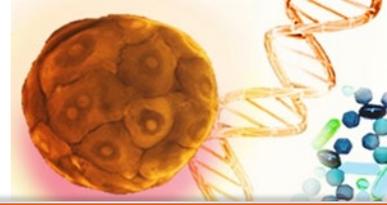   ❖ Budget

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Concept Rationale
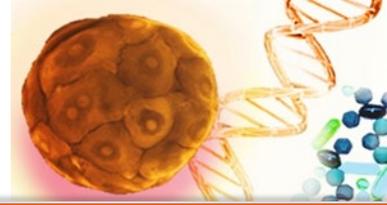
➤ The NGCMs are in their infancy

➤ The concept aims to accelerate

 ❖ Development of technologies

 ❖ Tools and reagents

 ❖ Analytical methods

 ❖ Transition into clinical applications, e.g. Precision Oncology

to make future experiments using the NGCMs more reproducible and interpretable and reduce the need for every laboratory to develop standard methods

➤ *The outcome will allow easier sharing and validation of results using the NGCMs by the basic and clinical oncology communities*

Goals

➢ This FOA aims to remedy the lack of *efficient and vetted* technologies and reagents for use in experiments or applications using NGCMs by:

  ❖ Development of robust protocols and conditions when using molecular perturbagens (e.g. CRISPRs, small molecules, cDNAs) with NGCMs <u>and</u>

  ❖ Ensure that the knowledge and materials developed are available broadly and expeditiously with researchers and clinicians world-wide

  ❖ Development of robust reagents for high-content, high-value screens

    ▪ To translate molecular data into pre-clinical knowledge and then to clinical applications

  ❖ Development of novel analytical methods to interpret results

The Concept Will Use HCMI Models
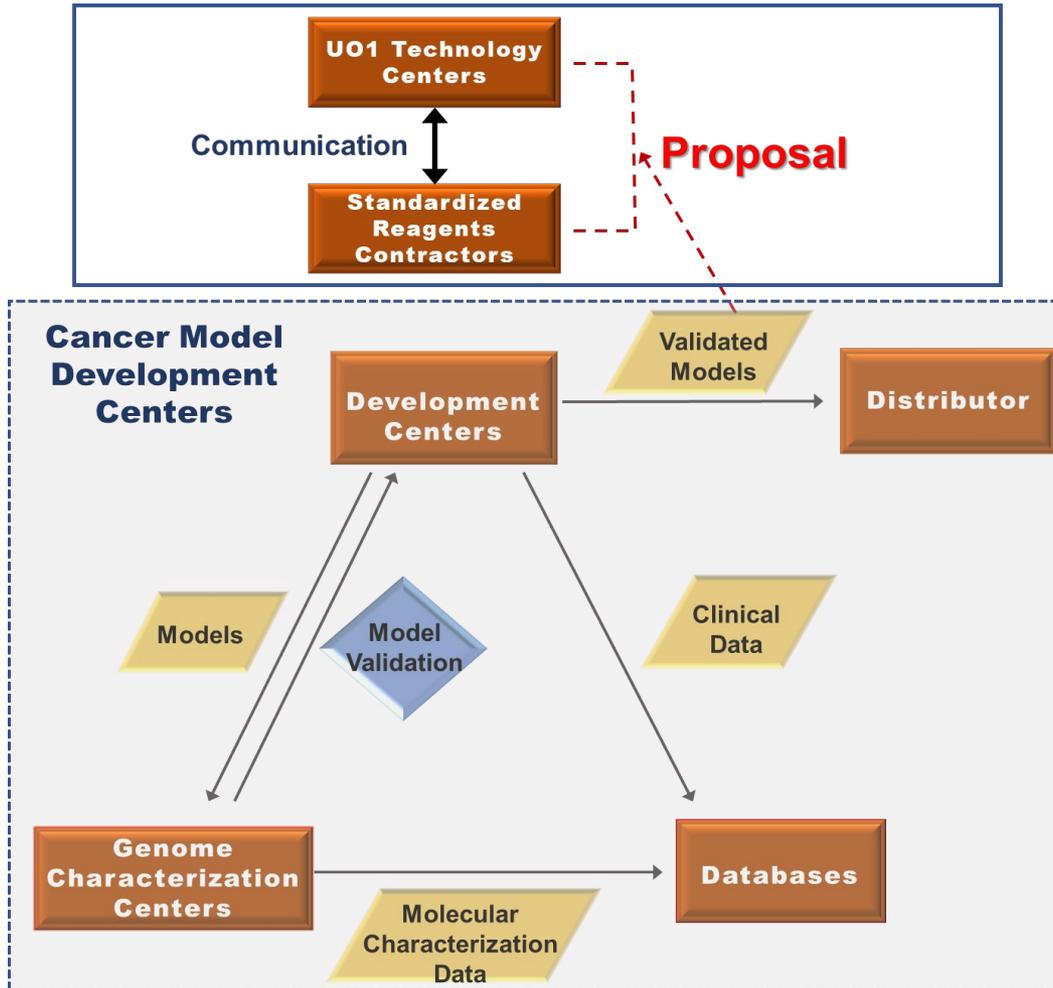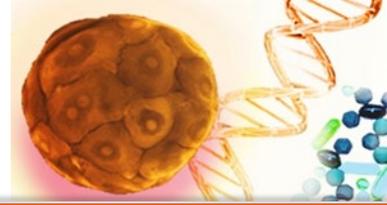
Examples of a Few FOA Topics - 1
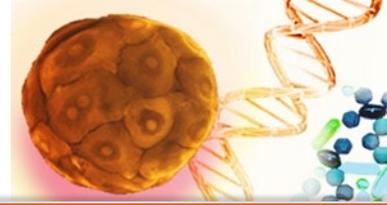
➢ **Develop platforms, technologies and applications**

❖ To utilize the NGCMs in high-content/throughput screening:

- How to grow NGCMs in a manner as similar as possible but without altering their molecular character from those of its parent tumor

- How to reduce variation in growth conditions

- How do biophysical parameters impact drug screens, whole genome screens etc.
  - ✓ Optimize throughput with use of 384 and 1536 well experiments

❖ Determine how to perform and interpret drug and genetic perturbation experiments

- Role of the extracellular matrix

- If different cancer models are established with different methodologies, e.g. 2D vs. 3D

- 3D vs. 2D comparisons in the same model

- Function of microenvironment, including immune cell interactions

- How to decrease the time needed to interpret results from CRISPR screens

Examples of a Few FOA Topics - 2
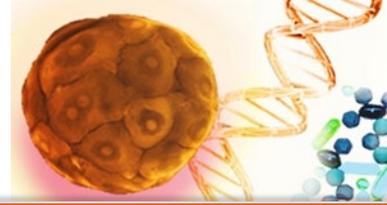
➢ Development of standardized CRISPR reagents

Challenge: The "usual" CRISPR screens require two expression constructs in each cell, the Cas9 and the gRNA. Screening experiments are done in two phases, cells are first transfected by the Cas9, its expression selected for and then the gRNAs for LoF or GoF determination is performed. At present, it is an expensive experiment in a high-throughput "discovery" protocol, though not impossible.

❖ Test Cas9s from different bacteria for their cutting and/or inhibiting/activating activity

▪ Interact with the U01s and other CRISPR experts to

✓ Identify a Cas9 which could be used a single Cas9/gRNA construct which is robustly expressed in most cellular contexts

✓ Define two gRNAs/gene for genome-wide CRISPR screens for cutting

▪ Two guides would provide for small redundancy, but not as many as are used currently which require extensive model expansion and NGCMs are more expensive to work with

✓ Define two gRNAs/gene for activating CRISPRs

❖ If the preliminary experiments indicate that a single Cas9/gRNA construct is not possible by the start of the 2nd year of funding, most highly functioning Cas9 construct will be selected, one each inhibiting or activating, and the corresponding two gRNAs/gene will be produced.

Expected Outcomes: U01s
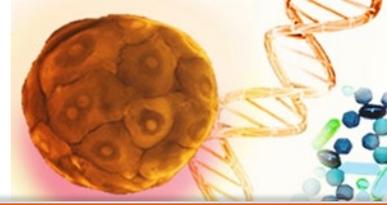
➢ Each Center would address a subset, e.g two to three topics enumerated in the RFA

 ❖ The U01s would be selected based on the quality of the proposals, approach to validation, benchmarking and to comprehensiveness of FOA topics are covered to minimize redundancies

 ❖ The Centers will develop collaborations as is expected of cooperative awards; OCG has a strong track record to facilitate them

➢ *Validation* and *benchmarking* are important components of the research. In addition

 ❖ The results, protocols and tools will be shared through OCG web site using framework developed for other projects https://ocg.cancer.gov/programs/hcmi/resources.

Expected Outcomes: Reagents
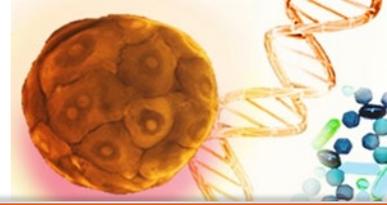
➢ Y1: Contractor #1 will generate QC'ed Matrigel for use in organoid experiments, participate in SC meetings

  ❖ Aliquots will be used for benchmarking in NCI programs (it is perishable, will not be permanent resource)

➢ Y2-3: Contractor #2 will develop CRISPR reagents and participate in SC meetings with the U01 Centers. In Y1 they would carry out initial QC experiments.

  ❖ The reagents and constructs will be shared through distributors, e.g. AddGene, ASU etc.

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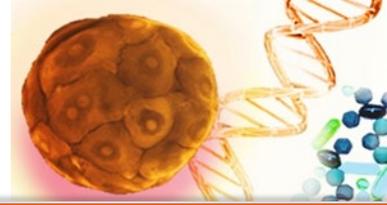
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Advantages of the Concept's Approach

➢ The grant awardees would be using NGCMs developed through NCI funding and the proposed research in the cooperative setting would:

   ❖ Reduce excessive redundancy

   ❖ Allow flexibility in the development of the technologies, reagents and tools based on results obtained within the network

   ❖ Ensure quality of the technologies discovered, reagents and tools developed

   ❖ Allow for the interpretability of future experiments which use the reagents developed since all information will be freely available

   ❖ Cost efficiency, i.e. the reagents would not need to be developed by individual laboratories, rather would be available from distributor(s) for purchase

➢ The contract mechanism requires deliverables and oversight

➢ A single steering committee that would allow real-time sharing of results between the Centers (U01s) and contractors
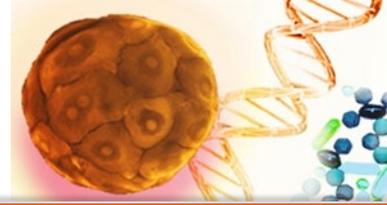
Funding

Funding Period: FY 2019-2021

➢ **U01 Technology Centers**

　❖ ~3 Centers

　❖ Estimated cost: $3.3M/year

➢ **Standardized Reagent Developer (Contract (s))**

　❖ Year 1: Investigate various CRISPR construct options and either generate or QC large lot of Matrigel, ~500k total budget

　❖ Years 1-3 CRISPR reagents development and distribution

　　▪ Year 1 budget ~$200k for testing, Y2-3 ~700k/year

Questions?