Next Gen Technology for Next Gen Cancer Models

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

NCI Board of Scientific Advisers

March, 2019

Daniela S. Gerhard, Ph.D.

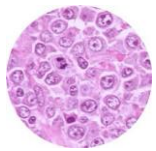
Director, Office of Cancer Genomics, CCG

"The Big Picture"

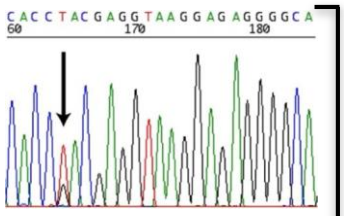
Existing technology

HCMI program

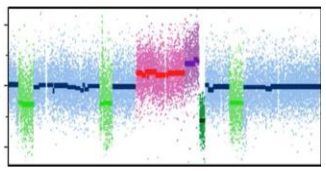
Proposed RFA



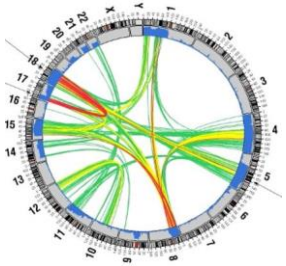
Cancer biopsy



SNVs, indels

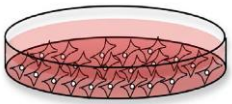


Copy number

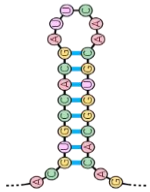


Rearrangements

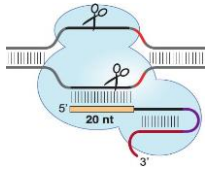
Putative driver genes



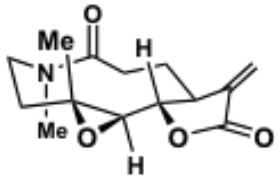
Relevant cancer models



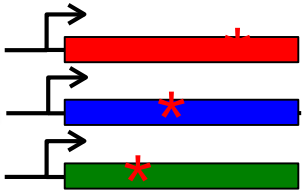
RNAi



CRISPR



Small molecules



Mutant ORFs

Essential cancer pathways

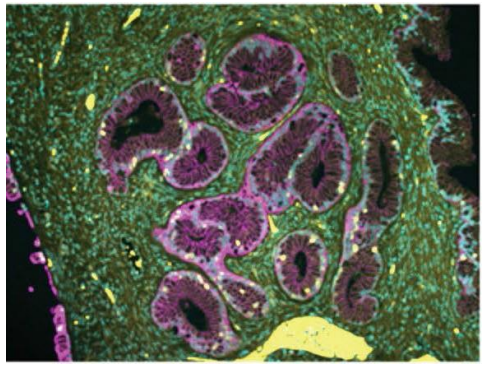
Presentation Outline

- Background
  - Human Cancer Models Initiative (HCMI)
- Concept
  - Rationale, Scope and Examples of the Funding Opportunity Concept (FOA)
- Additional Information
  - Advantages
  - Budget
  - Changes per BSA input
- Questions

Human Cancer Models Initiative (HCMI)

- International consortium: ~1000 “next generation human cancer models” (**NGCM**) with clinical and molecular data
  - NCI (Moonshot initiative)
  - Wellcome Sanger Institute
  - Hubrecht Organoid Technology

- Technologies for model development:
  - Organoids
  - Conditionally Reprogrammed Cells
  - Others



C. Kuo

HCMI is Active

- Community Resource
- Distribution by ATCC to academic and commercial entities
- Genomes and transcriptomes of each model, case-matched normal and “parent” tissue are sequenced
  - Epigenomes will be analyzed
- Data is deposited to NCI’s Genomic Data Commons
- All protocols used to expand the models are shared through https://ocg.cancer.gov/programs/hcmi/resources
- Status: ~214 U.S. models have been established
  - 22 Asian or African American
  - 143 White
- HCMI updates: https://ocg.cancer.gov/programs/HCMI

HCMI: Cancers

- Adult tumors
  - Breast
  - Colorectal
  - Gastroesophageal
  - Glioblastoma
  - Lung
  - Pancreatic
  - Rare
- Pediatric tumors
  - Ewings sarcoma
  - Neuroblastoma
  - Rhabdomyosarcoma
  - Wilms
- "On deck"
  - Melanoma
  - Head and Neck
  - Renal
  - Ovarian
  - Relapsed or metastatic

- Number of cancers types and populations represented is expanding, e.g. tissues and clinical data from
  - Under-represented minorities through Center to Reduce Cancer Health Disparities supplements
  - Children from GAIN Consortium

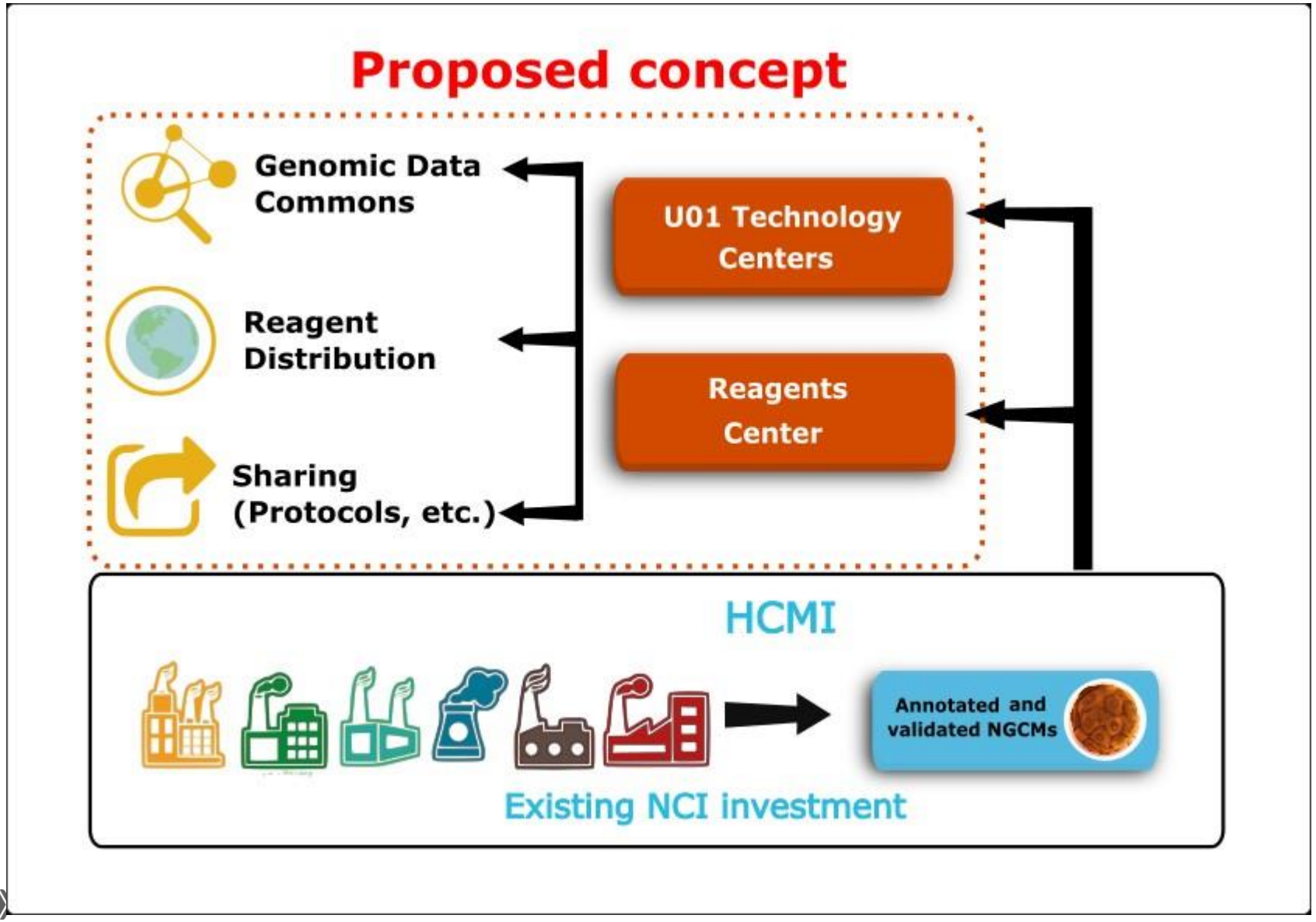
Presentation Outline

- Background
  - Human Cancer Models Initiative (HCMI)
- Concept
  - Rationale, Scope and Examples of the Funding Opportunity Concept (FOA)
- Additional Information
  - Advantages
  - Budget
  - Changes per BSA input
- Questions

Concept Rationale

- Challenge: Functional genomic technologies are not optimized for efficient use in next-gen cancer models
- Opportunity: Successful completion of this concept will fill gaps, e.g.:
  - What is the impact of cellular polarity in 3D structures on the results from perturbagen screens?
    - Does topology (e.g. 3D organoids) change the effect of gene(s) essentiality in cancer?
  - How to adapt pertubagens that were developed for classical cancer cell lines to function in other cancer models?
  - What transduction technologies should be optimized for 3D and 2D NGCM?
    - E. g. can diffusion work efficiently for cells that are within (internal) an organoid?

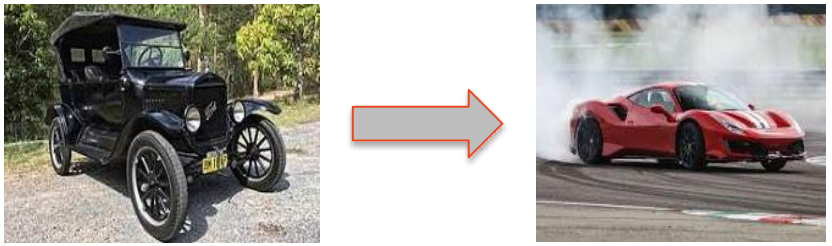
The Concept Will Use HCMI Models



Goals

- The NGCMs represent a powerful tool for precision oncology
  - Clinical data, including response to treatment of donor patient
  - Genomic characterization upfront

- This FOA aims to accelerate functional genomics using the HCMI models in screens using:
  - Cas9/gRNA (CRISPR)
  - RNAi
  - Open reading frame (ORF) cDNA
  - Small molecule



Goals and Future Applications

- This concept will address the technical challenges of using NGCM in functional genomics experiments and applications by:
  - Development of robust protocols and conditions when using molecular perturbagens (e.g. Cas9/gRNAs, small molecules, cDNAs) with NGCMs and
  - Rapid sharing of all data and reagents

Enabling 60,000' level:

- The methods, data and reagents generated under the FOA will enable researchers to gain insight into essential pathways in cancer.
- This preclinical knowledge base will support precision oncology by identifying new drug targets and mechanisms of therapeutic resistance.

Examples of a Few FOA Topics - 1

- Platforms and applications
  - Develop methods for high throughput screening using NGCMs
    - Optimize growth conditions for NGCMs
    - Reduce volumes for 384-1536 well screening
  - Define experimental parameters which influence screening results
    - Role of extracellular matrix used (Matrigel, collagen II, other)
    - Influence of 2D vs. 3D cell growth
    - Effect of stromal and immune cells interactions, e.g. cancer associated fibroblasts

- Proof-of-concept of methodologies in medium sized screens to demonstrate the validity and extensibility of the techniques developed
  - Small molecule screen with 1,000 + targeted compounds in 30-100 organoid or other HCMI models
  - Cas9/gRNA screen oof 1,000+ genes in 30-100 HCMI models

Examples of a Few FOA Topics - 2

- Development of standardized Cas9/gRNA reagents for use in NGCMs
  - Develop the methods to efficiently engineer the model genomes
    - Develop and optimize a single construct to express both Cas9 and gRNA
    - Identify two gRNA/gene with efficient CRISPR cutting to enable whole genome screens using manageable cell numbers

- Development of alternate cellular assays of Cas9/gRNA-induced phenotypes for use in pooled “CRISPR” screens
  - Novel apoptosis censors
  - Reporters of gene expression (e.g. “knock-in” of fluorescent proteins into endogenous loci)
  - Reporters of signaling/regulatory pathways (e.g. PIK3 kinase, NF-κb)

Expected Outcomes: U01s

- Each Center would address a subset, e.g two to three, topics in RFA
- The U01s will be selected based on proposal quality, approach, validation and benchmarking experiments
  - The criteria will include an approach to achieve the programmatic goals (i.e. minimize overlap, maximize diversity)
- Share data, tools and protocols through GDC and OCG web sites, e.g. https://ocg.cancer.gov/programs/hcmi/resources
- Participate in monthly steering committee calls to discuss results and evaluate progress

.

Reagent Development: FYI

- Define quality parameters and efficacy data for Cas9/gRNA reagents

- Develop whole genome “CRISPR” Cas9-gRNA/gene constructs
  - Develop and validate the efficacy of two guide RNAs per gene
  - Distribute through a 3rd party to research community at reasonable cost, e.g. AddGene

- Participate in steering committee meetings with the U01 Centers

Presentation Outline

- Background
  - Human Cancer Models Initiative (HCMI)
- Concept
  - Rationale, Scope and Examples of the Funding Opportunity Concept (FOA)
- Additional Information
  - Advantages
  - Budget
  - Changes per BSA input
- Questions

Advantages of RFA Consortium

- The grant awardees will use NGCMs developed through NCI's investment in the HCMI program
- Research in the cooperative U01 setting will:
  - Reduce excessive redundancy, thereby ensure cost efficiency
  - Promote sharing of reagents and communication
  - Standardize methods
  - Provide standardized reagents
  - Make all data publicly available
- The contract mechanism requires deliverables and oversight
- A single steering committee allows real-time sharing of results between the U01 Centers and contractor

Funding

Three year Funding Period: FY 2020-2022

- **U01 Technology Centers**
  - ~3 Centers
  - Estimated cost: $3.3M/year

- **Standardized Reagent Developer (Contract)**
  - CRISPR reagents development and distribution
    - Budget ~700k/year

Total costs: $4M /year, $12M

Changes Made in Response to BSA's Comments

Comments

- Simplified and clarified the goals of the concept
  - Removed mentions of precision oncology
  - Refocused the Scientific Goals
    - ✓Added emphasis on technology development
    - ✓Emphasized that HCMI is an already ongoing project and source of the NGCM to be used in this research
  - Removed the Matrigel production in Y1

Summary

- Will enable rapid, cost-effective functional genomics experiments whose results will apply new cancer knowledge base and improve future patient outcomes

Thank you

Questions?