Development of Representative Human Cancer Model Systems Is Key to Identifying Essential Cancer Pathways

**Structural genomics**

- Cancer biopsy
- Copy number
- Rearrangements

- Sequence
- Putative driver genes
- Develop relevant cancer model

**Functional genomics**

- RNAi
- CRISPR
- Small molecules

- Essential cancer pathways

- Mutant ORFs
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)
New Cell Culture Technologies Enable the Propagation of Normal and Malignant Epithelial Cells

Organoid cultures

Conditionally reprogrammed cells (CRCs)

Clevers laboratory
Sato et al. Gastroenterology 2011 141:1762

Schlegel laboratory
Human Cancer Model Initiative Endpoints

- Cancer genetics
  - Models that represent known driver lesions
  - Models that recapitulate pathway dependencies
  - Models that can be manipulated to address genetic contribution to the malignant phenotype
Organoids Capture Recurrent Genetic Lesions in Human Prostate Cancer

Chen, Sawyers laboratory
Human Cancer Model Initiative Endpoints

- Cancer genetics
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- Cancer biology
  - Models that recapitulate human cancer phenotypes
    - Dependencies on stroma
    - Metastatic propensity
Generation of Tumor Organoids From Primary Human Breast Tumors

Harvest Tumor

Isolate Tumor Epithelium From Stroma

Generate “Organoids”

Culture in 3D ECM

Andy Ewald laboratory
Cell. 2013 155:1639
K14+ Cells Constitute 1.5% of Tumor Cells and Lead 90% of Invasion Events In Vivo
K14+ Cells Constitute 1.5% Of Primary Tumor Cells And Are Present In 90% Of Metastases In Vivo

n=187 metastases, 3 mice, p < 0.002

Andy Ewald laboratory
Cell. 2013 155:1639
Human Cancer Model Initiative Endpoints

- **Cancer genetics**
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- **Cancer biology**
  - Models that recapitulate human cancer phenotypes
    - Dependencies on stroma
    - Metastatic propensity

- **Cancer treatment**
  - Models representative of common cancer genotypes/phenotypes that can be used to develop multi-drug combination therapies
  - Models that can predict therapeutic response for an individual patient
  - High-throughput small molecule screening of human cancer models
Using Next Generation Cancer Models to Develop Therapies: Colon Cancer Organoids

Using Next Generation Cancer Models to Develop Therapies: Colon Cancer Organoids

Using Next Generation Cancer Models to Develop Therapies: Lung Adenocarcinoma Conditional Reprogrammed Cells

Engelman laboratory
Crystal et al. Science 2014 346:1480
Using Next Generation Cancer Models to Develop Therapies: Lung Adenocarcinoma Conditional Reprogrammed Cells

Engelman laboratory
Crystal et al. Science 2014 346:1480
Human Cancer Model Initiative (HCMI): Pilot Phase

Primary biopsy sample

Site 1

Site 2

Site 3

Clinical data

1000 human cancer models

Cell lines

Genomic data

Cell lines

Wide distribution to cancer researchers

BANK
Human Cancer Model Initiative Pilot
Scientific Considerations

- Does the genetic / epigenetic nature of the primary tumor influence its ability to be established or propagated \textit{in vitro}?  
- Do the various culture methodologies favor different genetic/epigenetic subpopulations within the primary tumor?  
  Is the subclonal heterogeneity of the primary tumor maintained?  
- Can conditions be found to favor growth of malignant epithelium over normal epithelium and vice versa?  
  Is the presence of non-malignant cells a feature or a bug?  
- What experimental manipulations are possible?  
  Retroviral/lentiviral transduction?  siRNA transfection?  CRISPR/Cas9?
Human Cancer Model Initiative Pilot
Methodological Considerations

- Can procedures to establish and propagate models be adopted easily by new laboratories?
  Are proprietary reagents used that have batch variability?
- Do culture conditions need to be optimized for every organ / tumor type?
- How sensitive are the techniques to variation in surgery / post-surgery handling of tumor?
- Is expansion of cultures limited by time / doublings?
- Does the cellular composition / molecular signature of cultures drift over time?
- Could a third-party distributor provide these cancer models to the research community and ensure reproducibility?
Human Cancer Model Initiative Pilot
Ethical / Regulatory / Procedural Considerations

- Are there barriers to sharing patient cell lines broadly – can privacy and consent issues be handled appropriately?
- Can diagnostic and treatment data be shared?
  - Should the tissue source institution retain a key to patient identity?
- How to adequately protect genomic data from cell lines?
  - What restrictions should apply to cell line resequencing?
- Should drug sensitivity of a patient-derived cancer model be shared with the patient?
  - What would CLIA approval require?
- Are there institutional impediments to sharing methodology and derived cell lines broadly and at an affordable cost?
Human Cancer Model Initiative Pilot Development Plan

- Collaboration established between NCI, Sanger Center (Mike Stratton) and the Hubrecht Institute (Hans Clevers)
  - All three institutions will provide funding and expertise
- Meeting at NCI in July 2015 to discuss operational details
- RFP for contracts to support Human Cancer Model Development Centers in late 2015
- 2 year funding to create ~1000 new human cancer cell lines