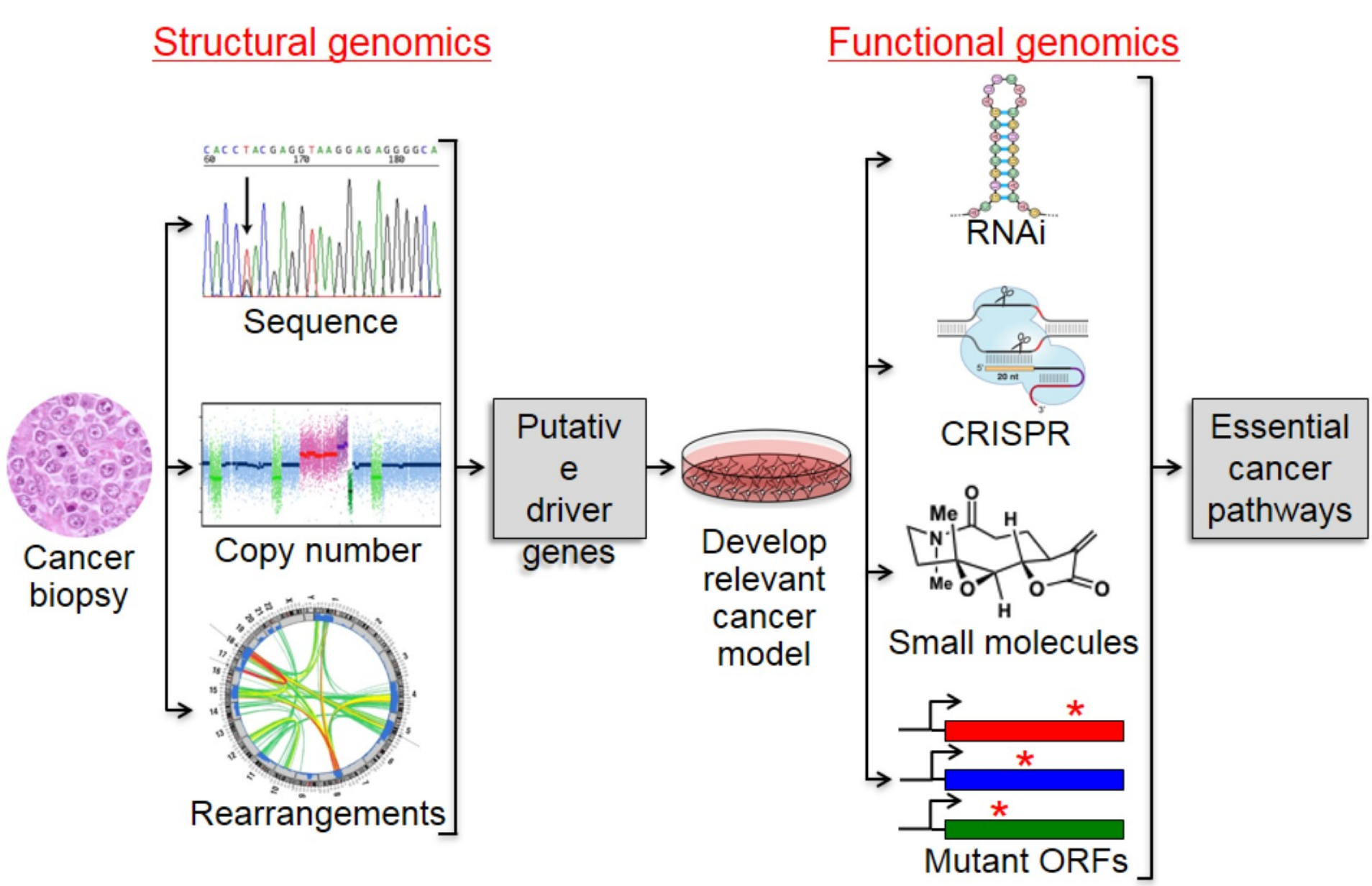
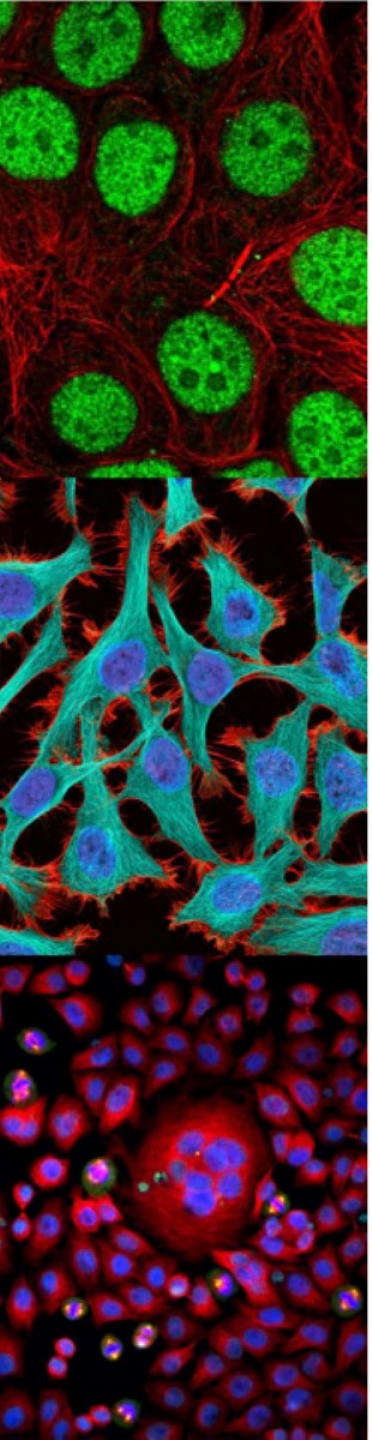
Development of Representative Human Cancer Model Systems Is Key to Identifying Essential Cancer Pathways



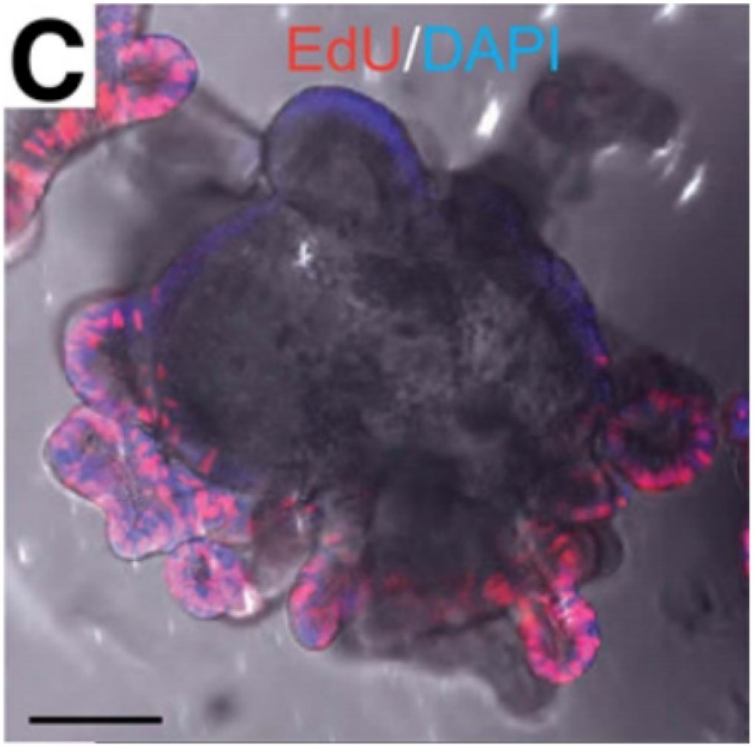


Modeling the Diversity of Human Cancer: An Unmet Need

- 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)

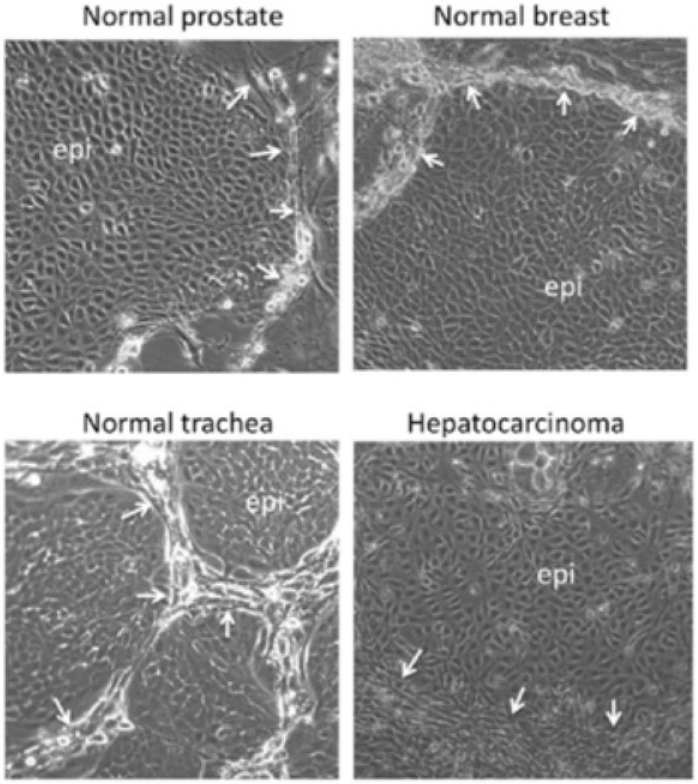
New Cell Culture Technologies Enable the Propagation of Normal and Malignant Epithelial Cells

Organoid cultures



Clevers laboratory
Sato et al. Gastroenterology 2011 141:1762

Conditionally reprogrammed cells (CRCs)

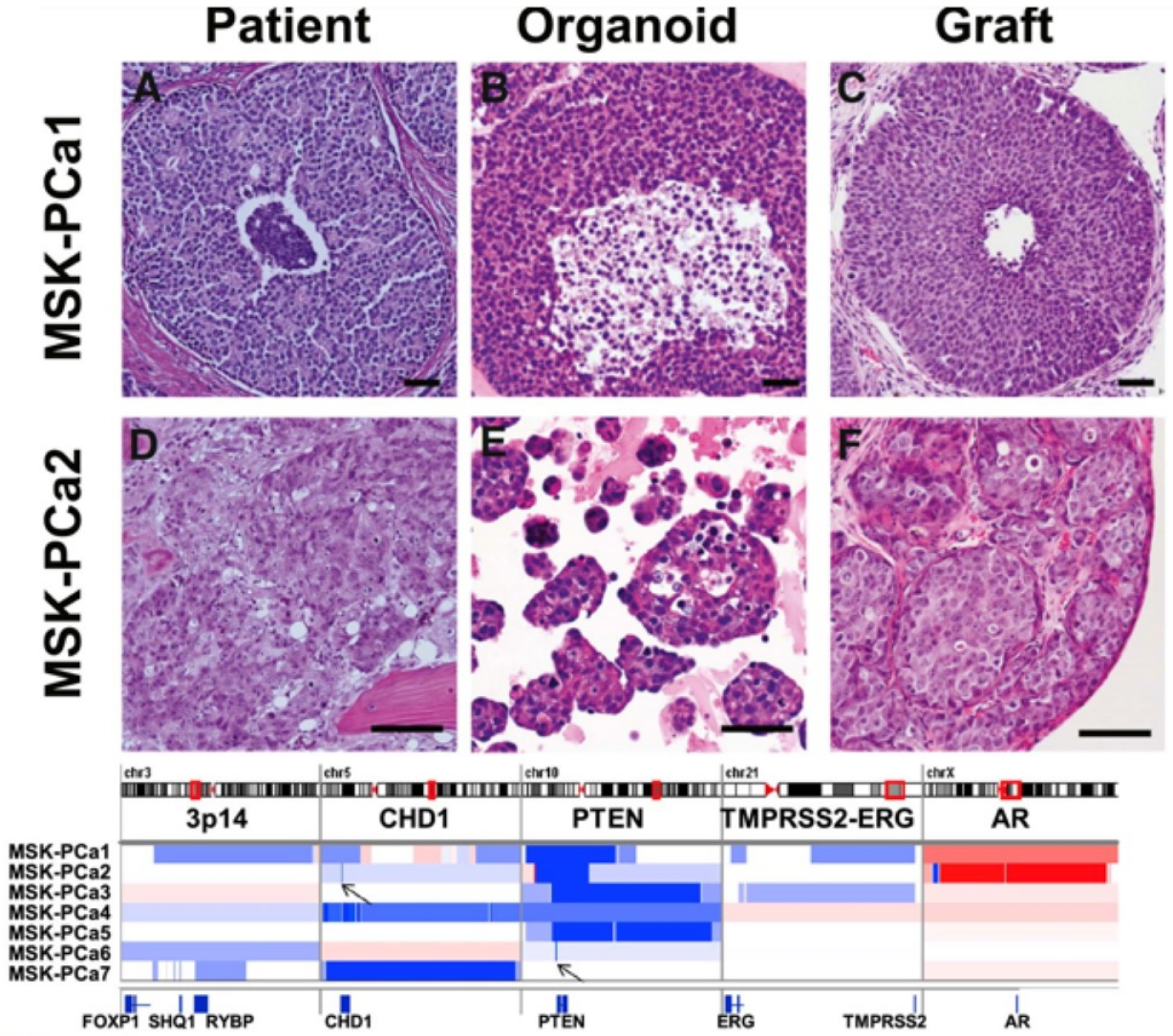


Schlegel laboratory
Liu et al. American J Pathol 2012 180:599

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
Gao et al. Cell 2014 159:176

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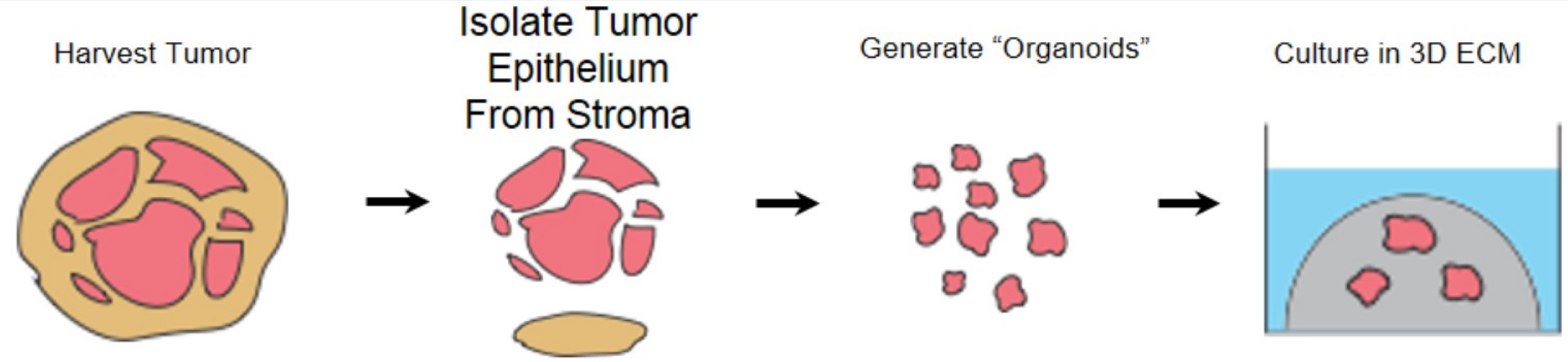
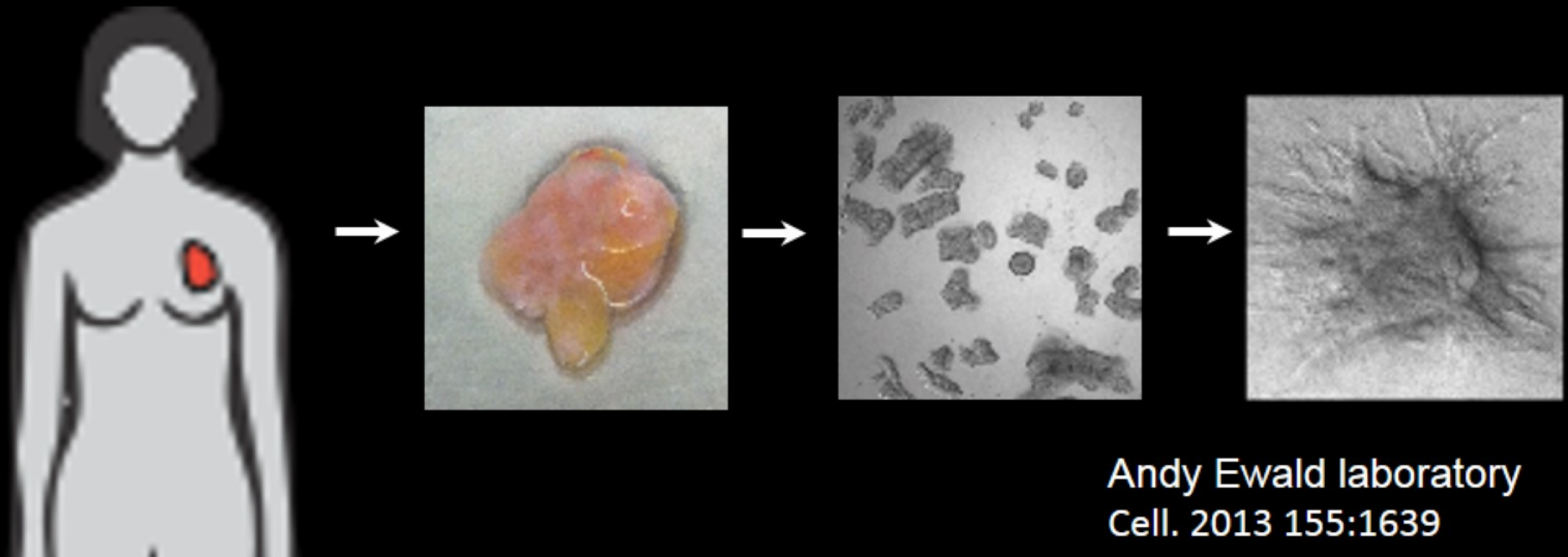
- Cancer biology
  - Models that recapitulate human cancer phenotypes
    - Dependencies on stroma
    - Metastatic propensity

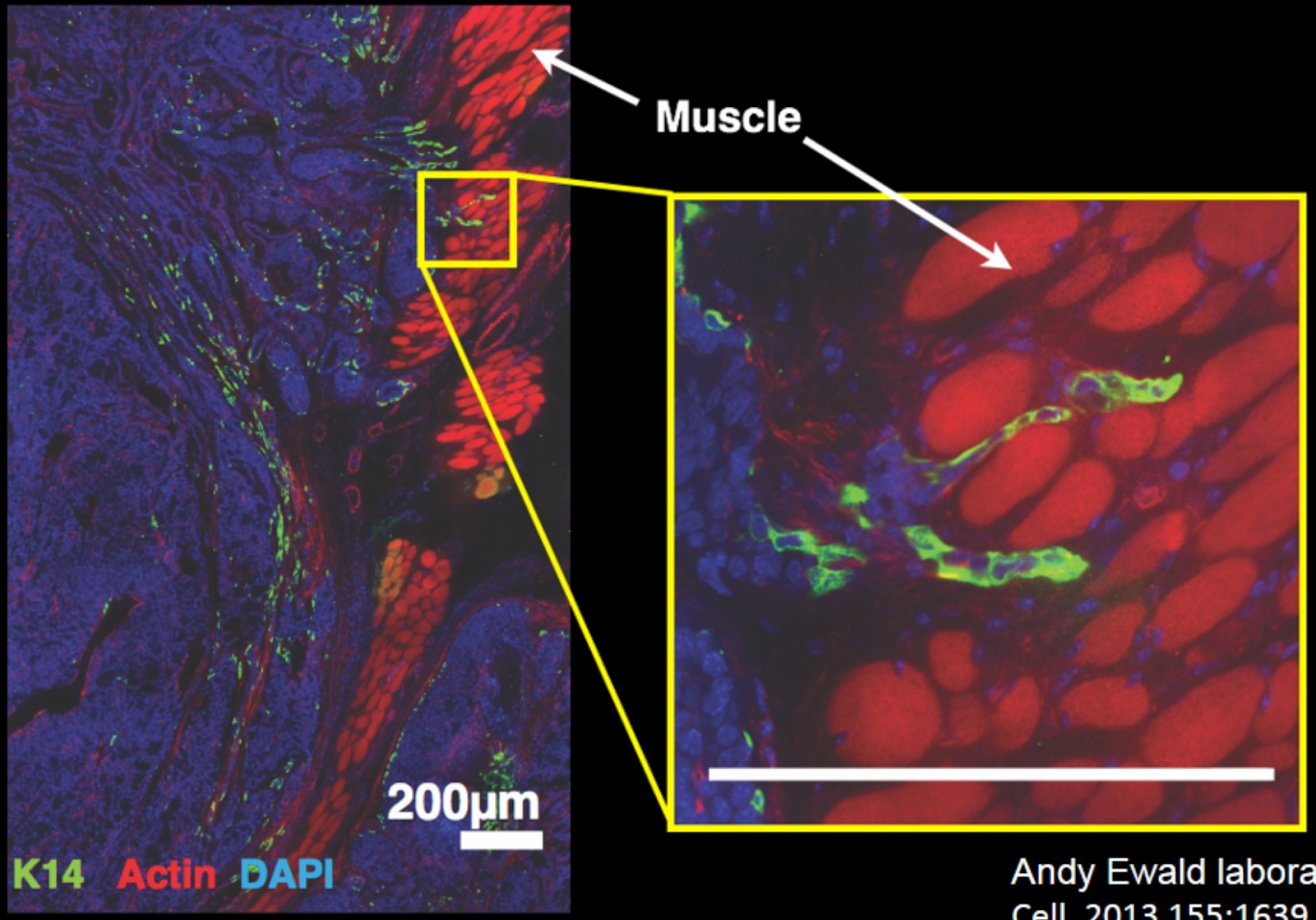
Generation of Tumor Organoids From Primary Human Breast Tumors





Andy Ewald laboratory
Cell. 2013 155:1639

K14+ Cells Constitute 1.5% Of Tumor Cells And Lead 90% Of Invasion Events In Vivo



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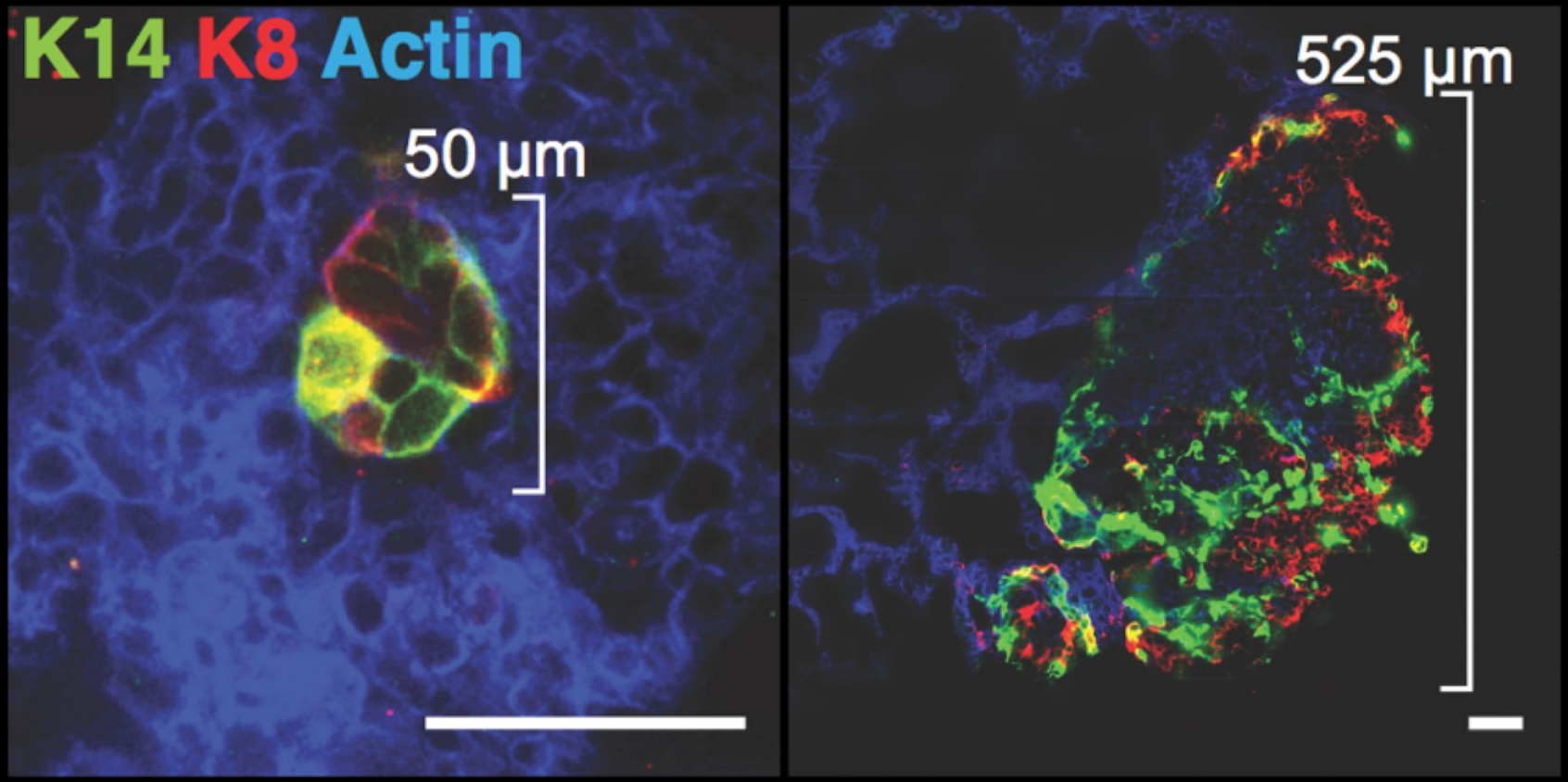

n=187 metastases, 3 mice, $p < 0.002$

Andy Ewald laboratory
Cell. 2013 155:1639

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- Cancer biology
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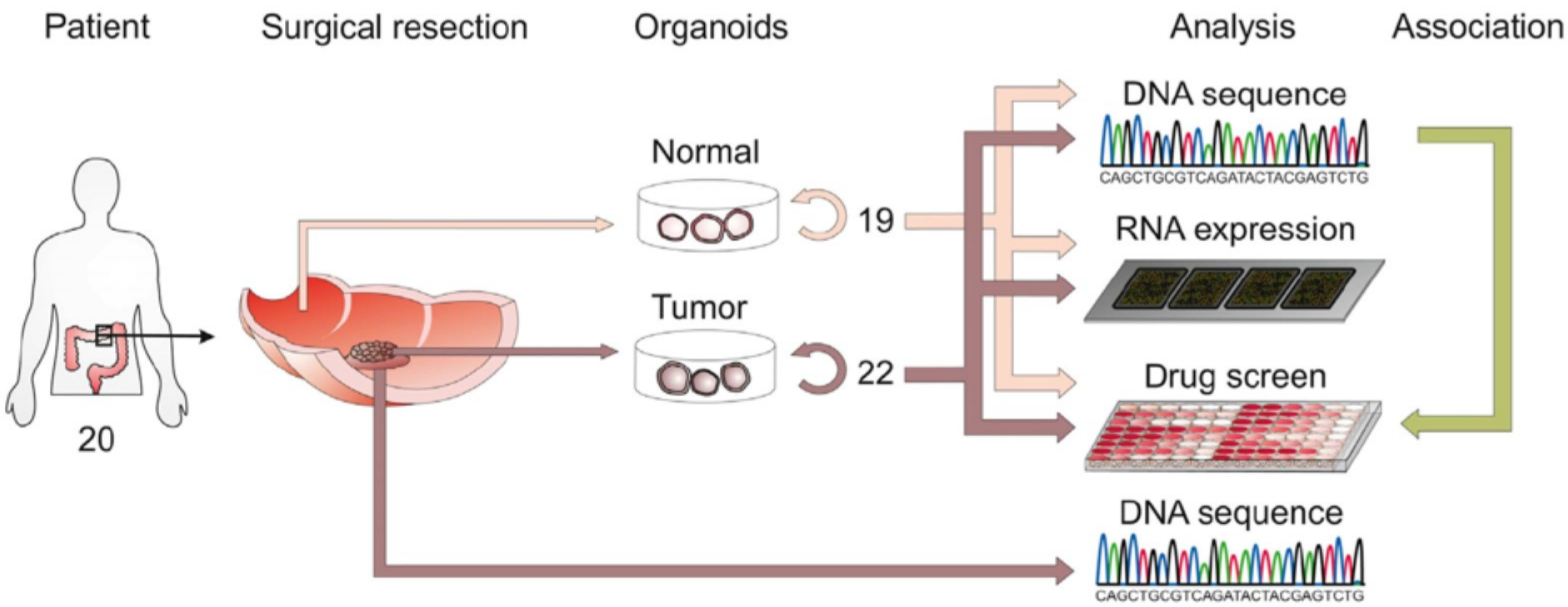
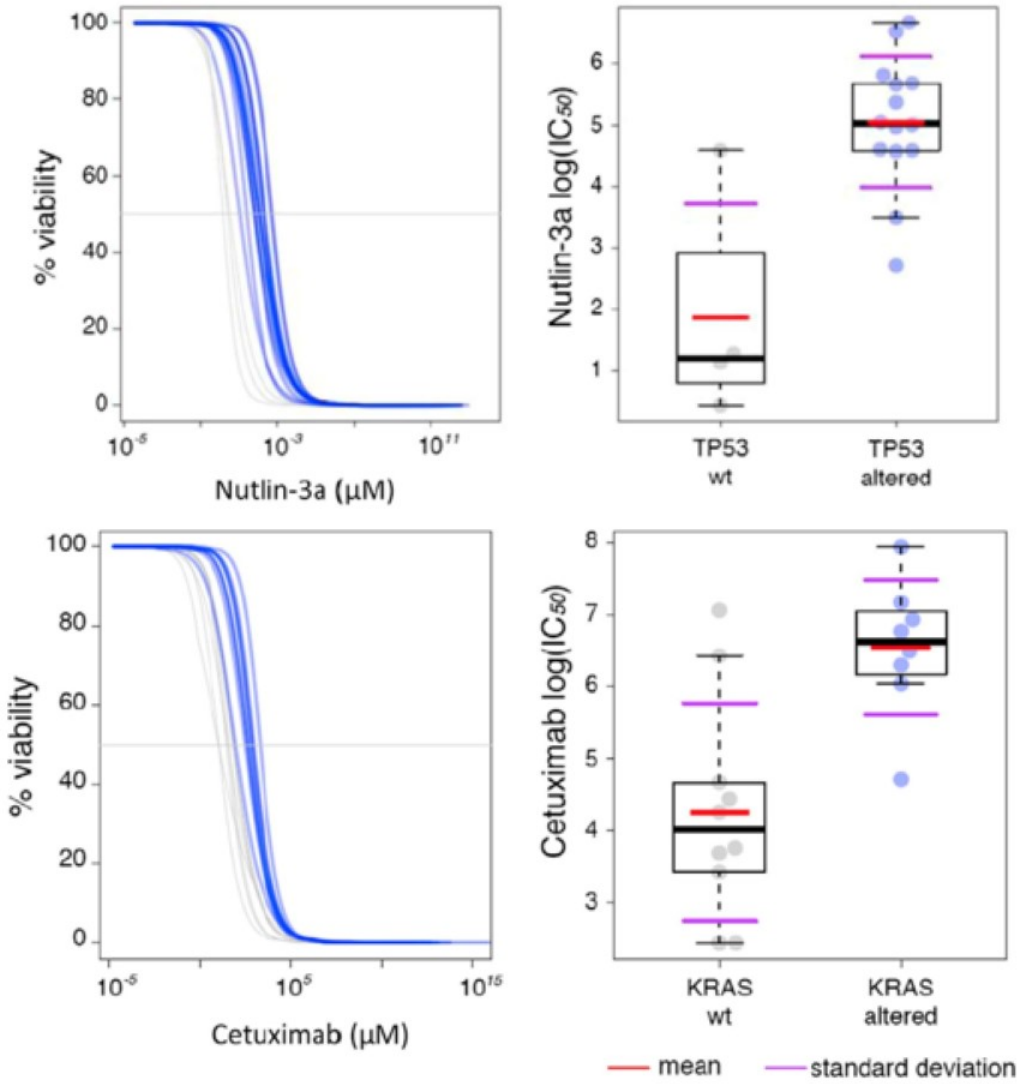
    - Dependencies on stroma
    - Metastatic propensity
- Cancer treatment
  - Models representative of common cancer genotypes/phenotypes that can be used to develop multi-drug combination therapies
  - Models that can predict therapeutic response for an individual patient
  - High-throughput small molecule screening of human cancer models

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



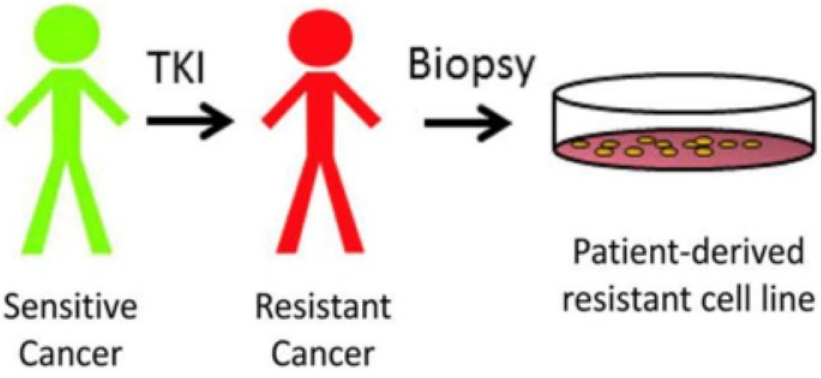
Van de Wetering et al. Cell 2015 161:933

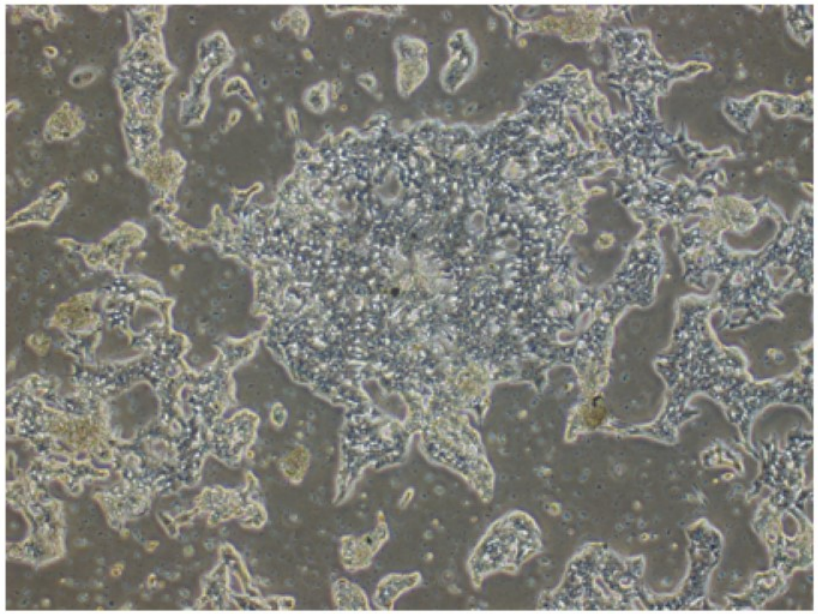
Using Next Generation Cancer Models to Develop Therapies: Colon Cancer Organoids

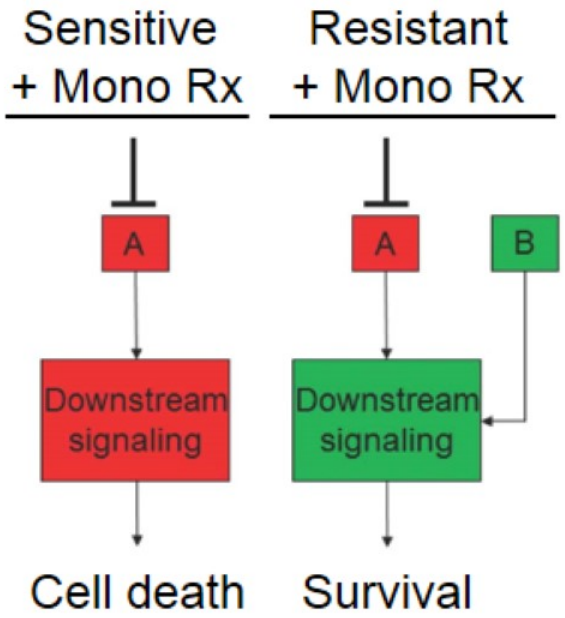


Van de Wetering et al. Cell 2015 161:933

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



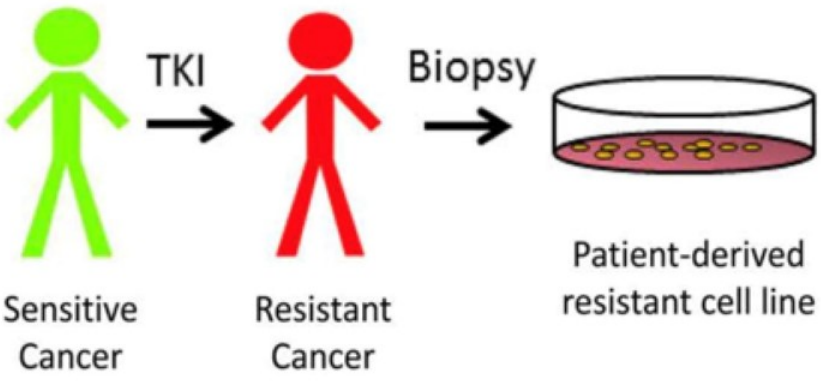


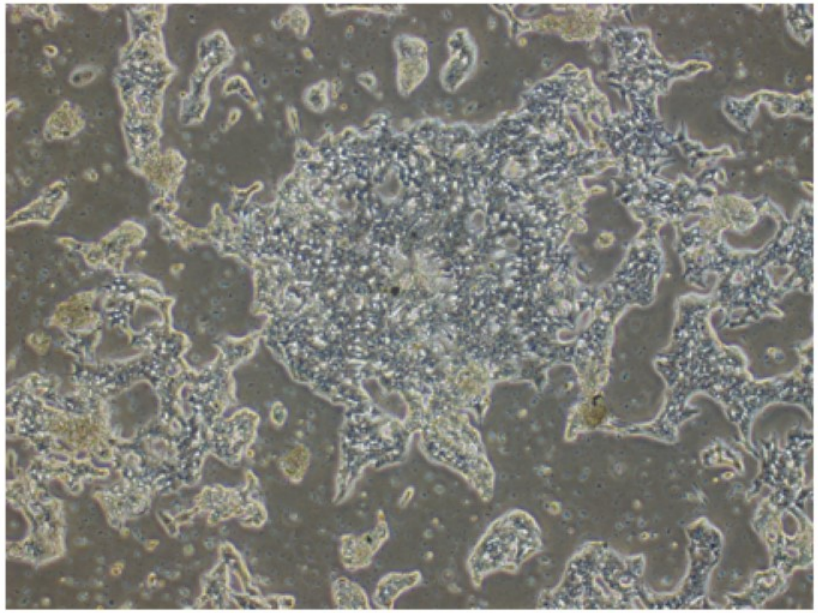


Engelman laboratory

Crystal et al. Science 2014 346:1480

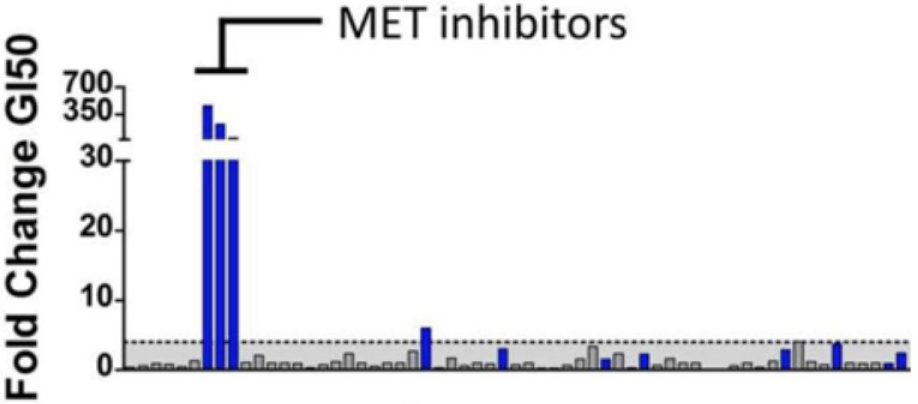
Using Next Generation Cancer Models to Develop Therapies: Lung Adenocarcinoma Conditional Reprogrammed Cells

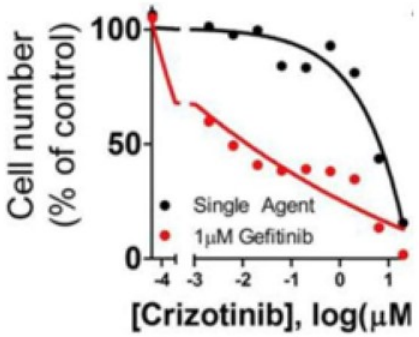




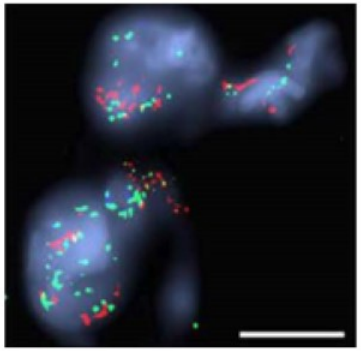
Engelman laboratory
Crystal et al. Science 2014 346:1480

Combo drug screen with Gefitinib

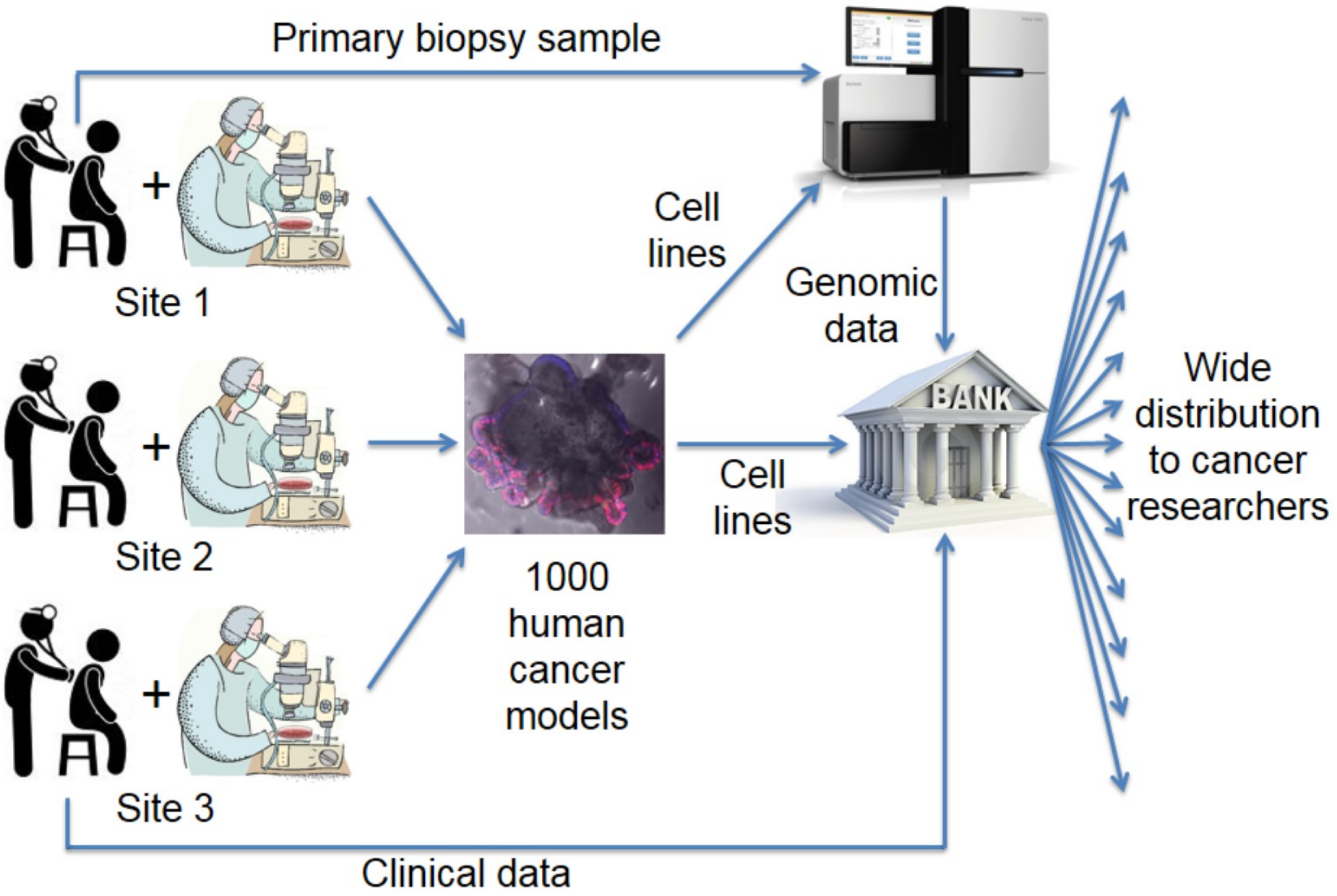




High level MET amp



Human Cancer Model Initiative (HCMI): Pilot Phase



Human Cancer Model Initiative Pilot
Scientific Considerations

- Does the genetic / epigenetic nature of the primary tumor influence its ability to be established or propagated *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