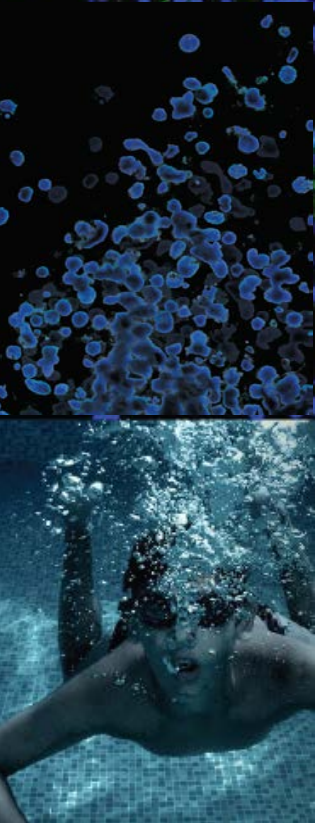




# Next-generation cancer models from the Human Cancer Models Initiative

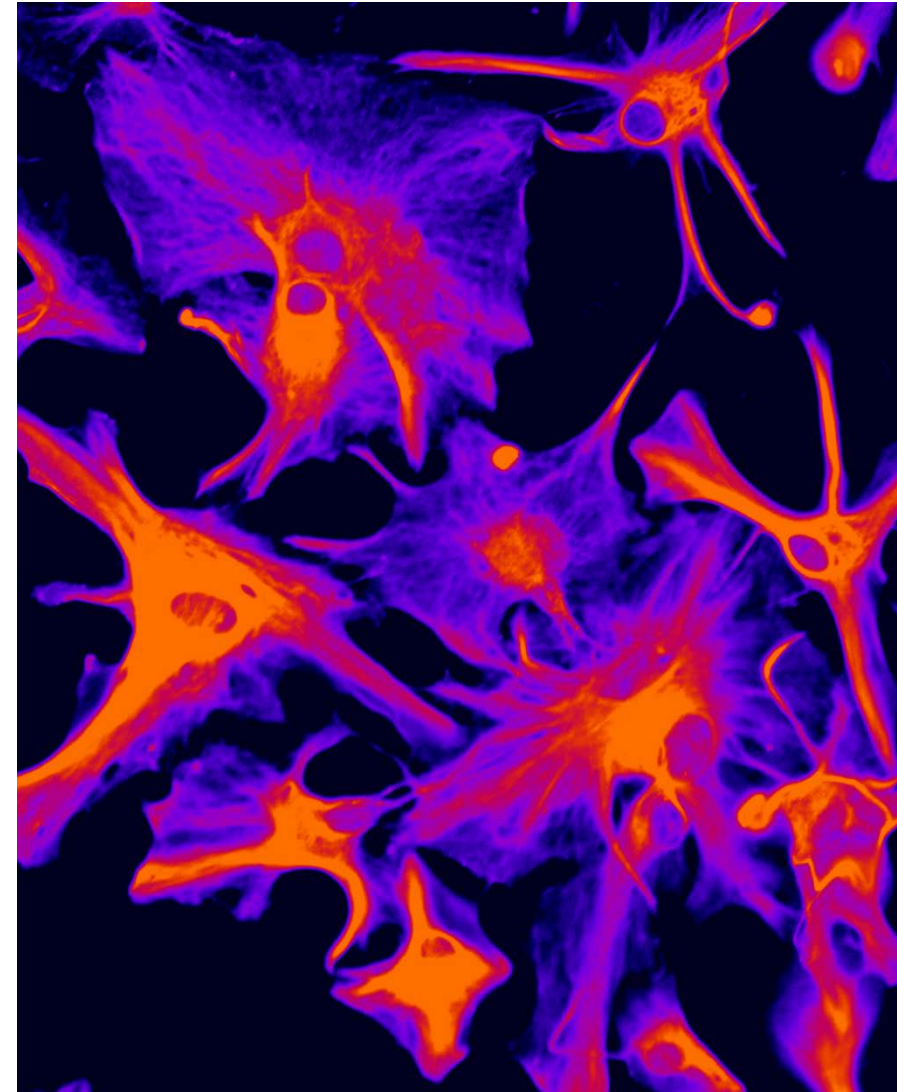
James M. Clinton, Ph.D.  
Senior Scientist, ATCC Cell Systems

Credible Leads to Incredible™



# Outline

- What is Human Cancer Models Initiative?
- What are next-generation cancer models?
- Resources to learn more about the HCMI and the models at ATCC
- HCMI models available
- Summary



# The unmet need

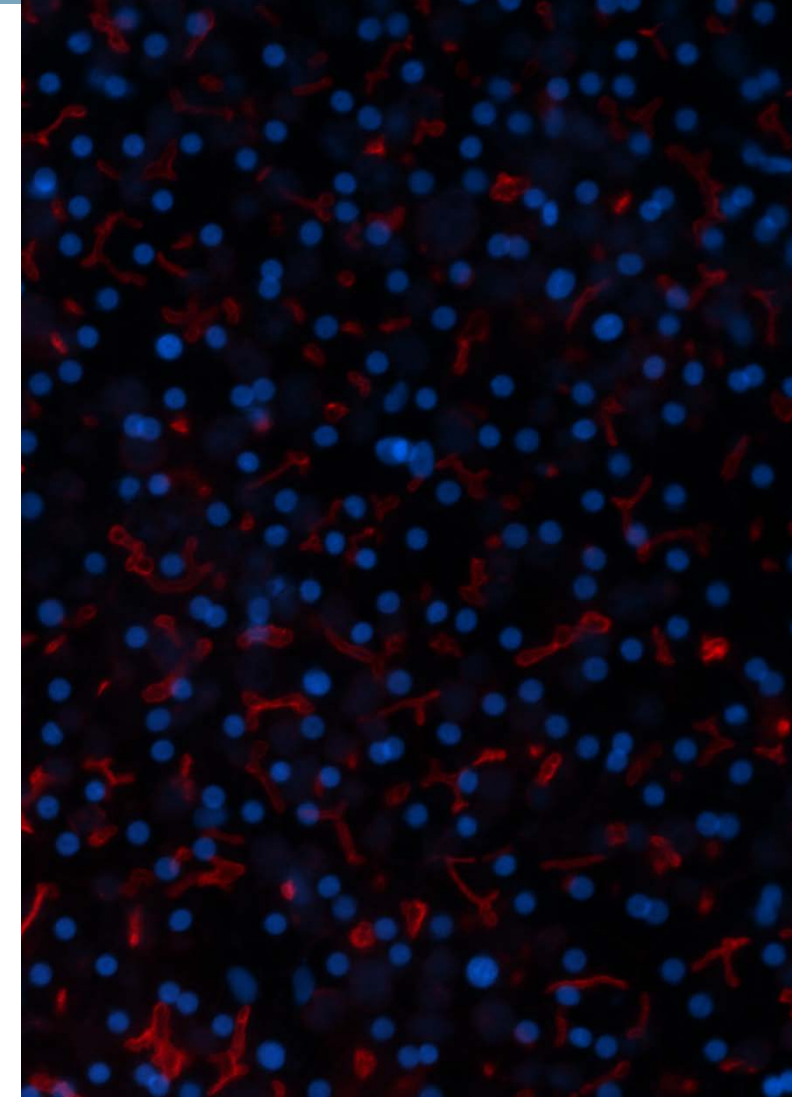
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- Patients do not respond to treatments as predicted, despite huge advances in genomic analysis of primary tumors and new drug targets.

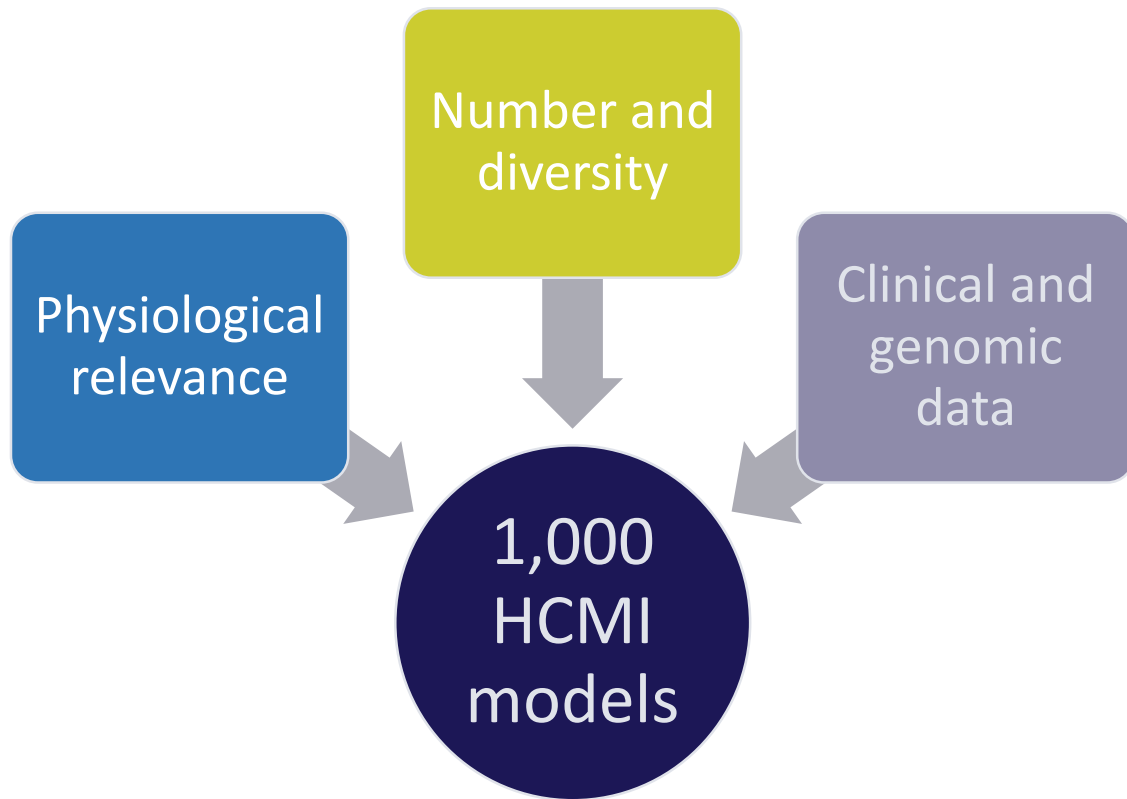
**There is a need for better preclinical models to predict therapeutic outcomes.**

# Why are new models needed?

- Poor representation of some cancer types/subtypes
- Lack of patient and clinical outcome data, model history
- Lack of comparison to normal reference sample and/or directly compared to primary tumor
- Insufficient to capture the genetic diversity of cancer
- Existing lines may not be biologically/genetically representative of *in vivo* tumor



# HCMI approach and core principles



- Models as a “community resource”
- Awareness of IP issues
- Permissive informed consent language permitting broad use
- Global distribution to ensure wide availability
- Open protocols

# Diversity of models from the HCMI

- Glioblastoma
- Gastric adenocarcinoma
- Melanoma
- Lung sarcoma
- Wilms Tumor
- Brain metastases
- Chordoma
- Esophageal carcinoma
- Neuroblastoma
- Ewing sarcoma
- Renal medullary carcinoma
- Spindle cell sarcoma
- Osteosarcoma
- Kidney renal clear cell carcinoma
- Rhabdomyosarcoma
- Pancreatic adenocarcinoma
- Mammary triple negative ER+
- Pancreatic adenosquamous carcinoma
- Lung carcinoid
- Primary pancreatic ductal carcinoma
- Colorectal cancer
- Cholangiocarcinoma
- BRCA mutant
- Barrett's esophagus
- Esophageal adenocarcinoma
- Lung adenocarcinoma
- Desmoid Tumor
- Lung Squamous cell carcinoma

*Not a comprehensive list.*

# Overview of HCMI and ATCC

## Founders

- National Cancer Institute
- Cancer Research UK
- Hubrect Organoid Technology Foundation
- Wellcome Sanger Institute

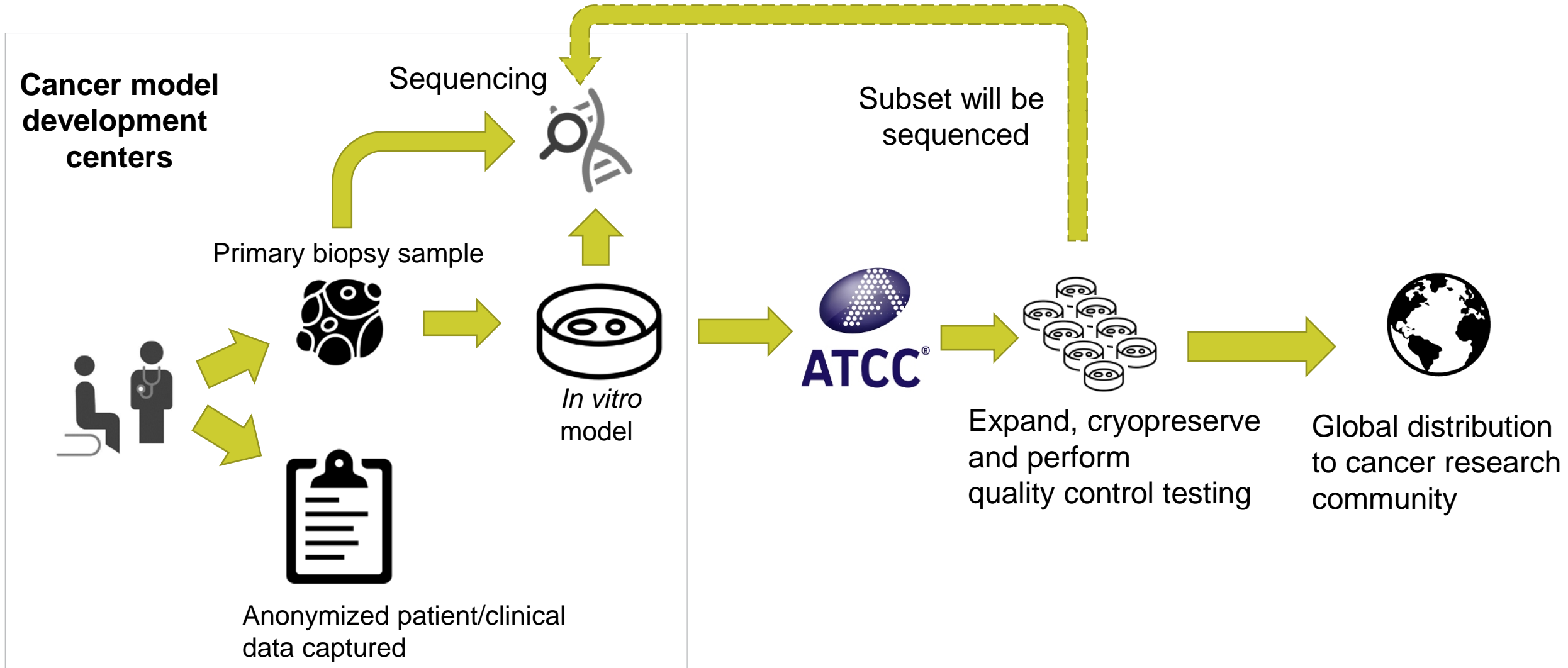
## Model Development

- Broad Institute
- Cold Spring Harbor Laboratory
- Wellcome Sanger Institute
- Hubert Organoid Technology Foundation
- University of Verona
- Hubrecht Institute
- Stanford University
- Weill Cornell Medical College

## Distribution



# Generation and distribution of HCMI models





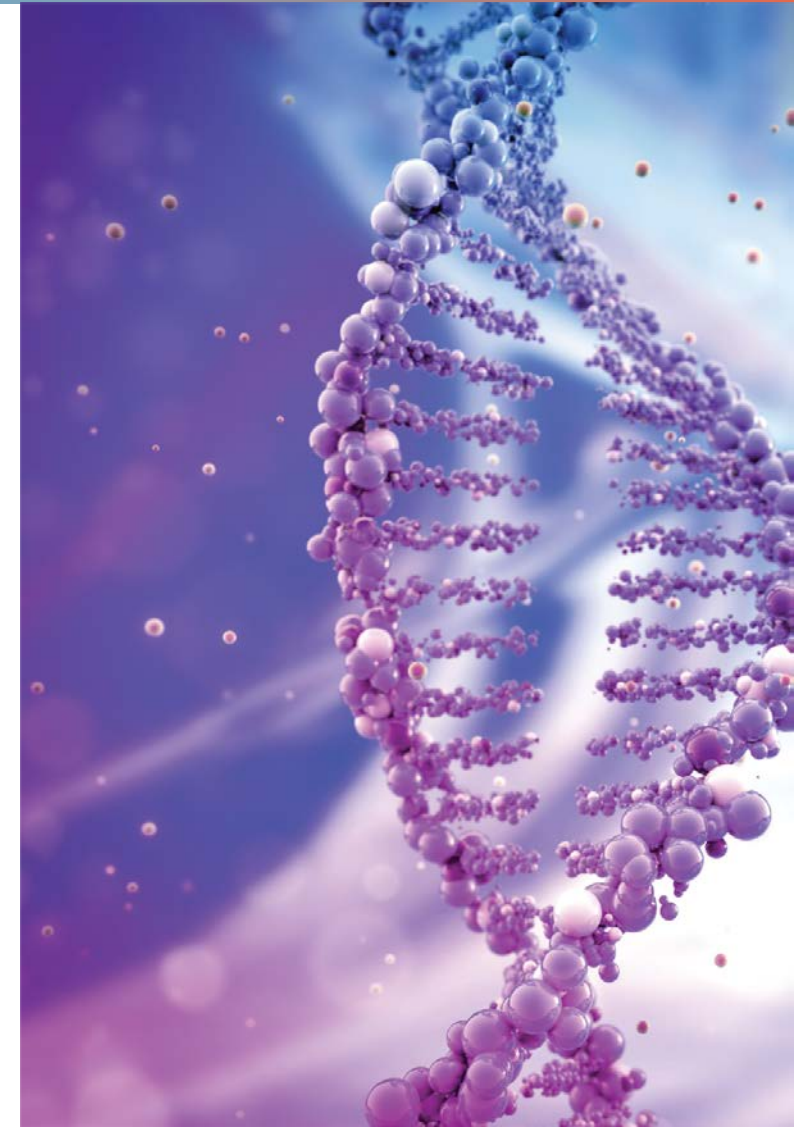
# Characterization of models

## Molecular

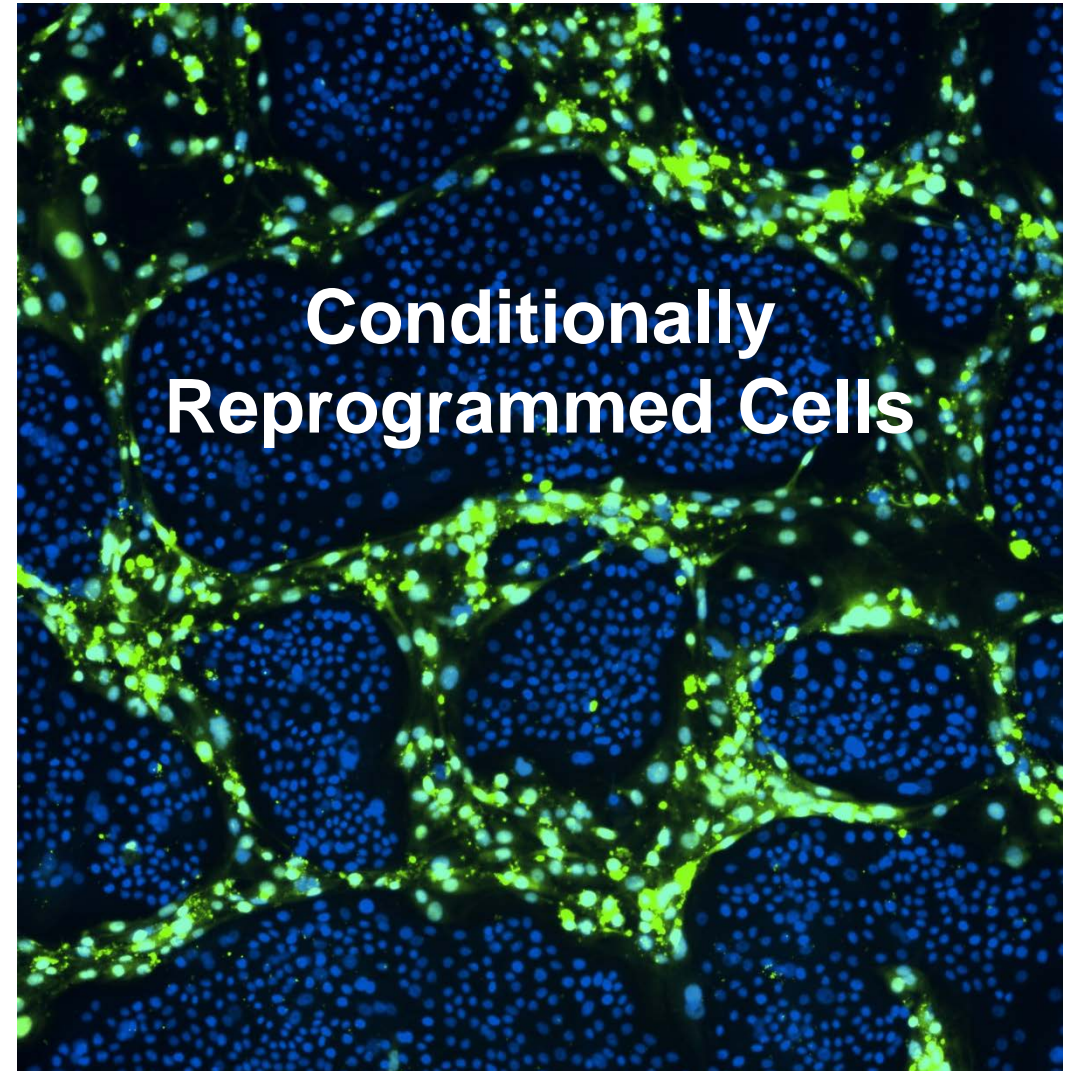
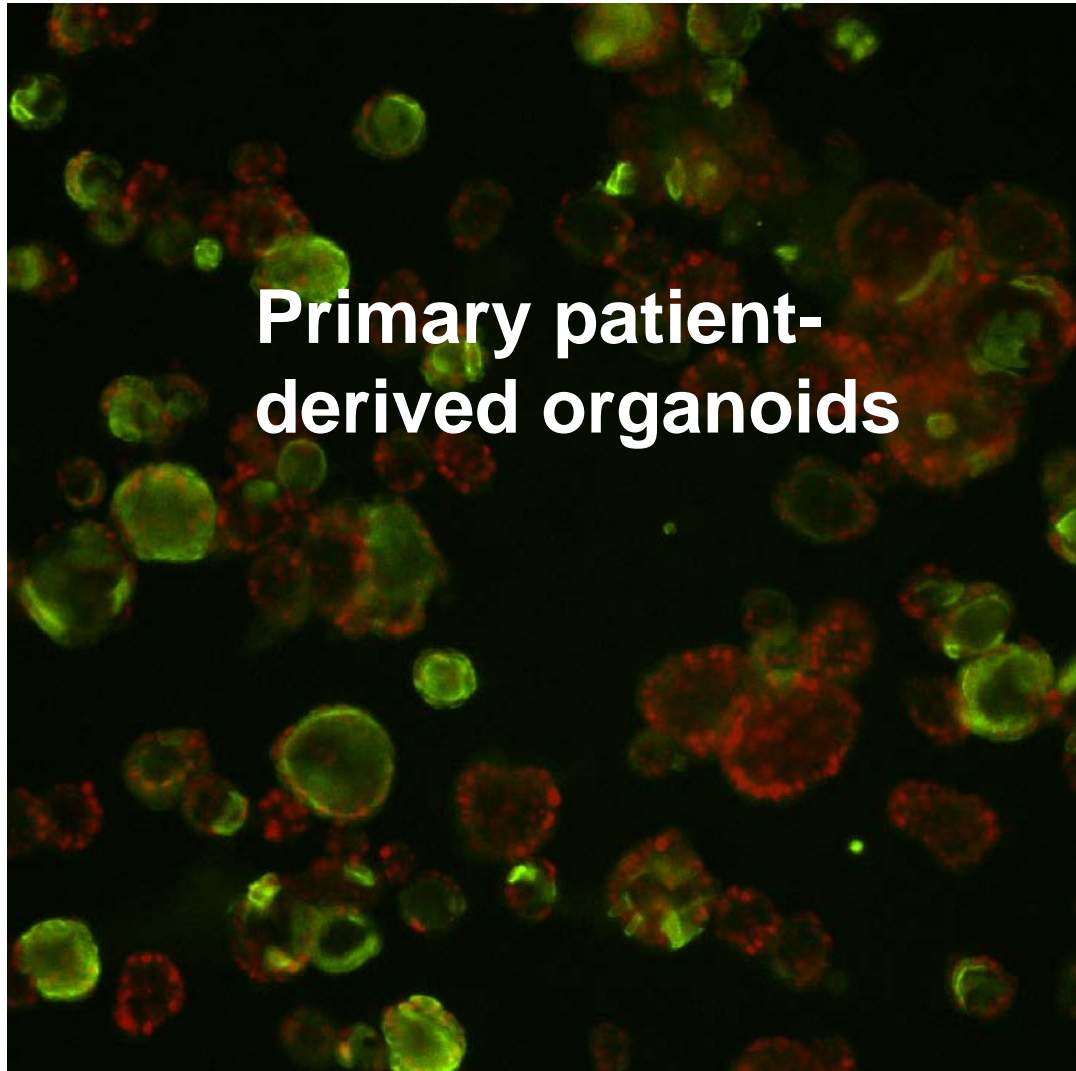
- 15X WGS of model, primary tumor, and normal tissue
- 150X WXS of model, primary tumor, and normal tissue
- RNA-seq of model and primary tumor

## Clinical

- Disease diagnosis
- Patient demographics
- Treatment and outcomes



# Advanced culture technologies



# Shared features of advanced culture methods

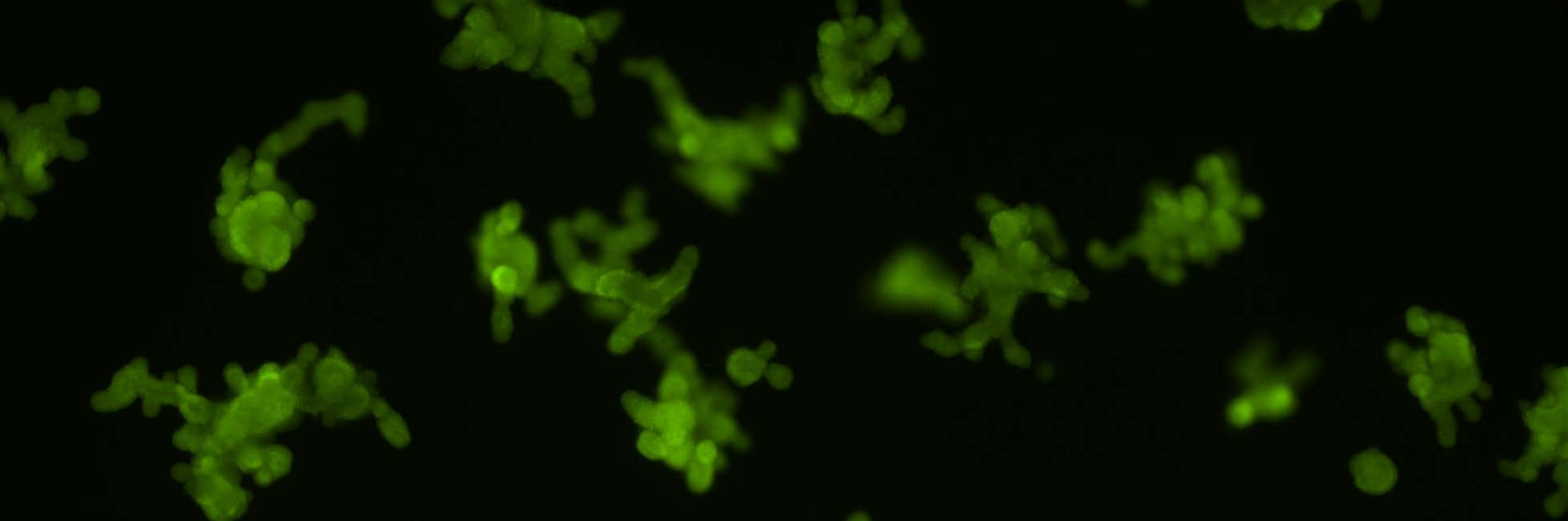
Permits growth  
and expansion

Limited starting  
material  
required

Genetically  
stable

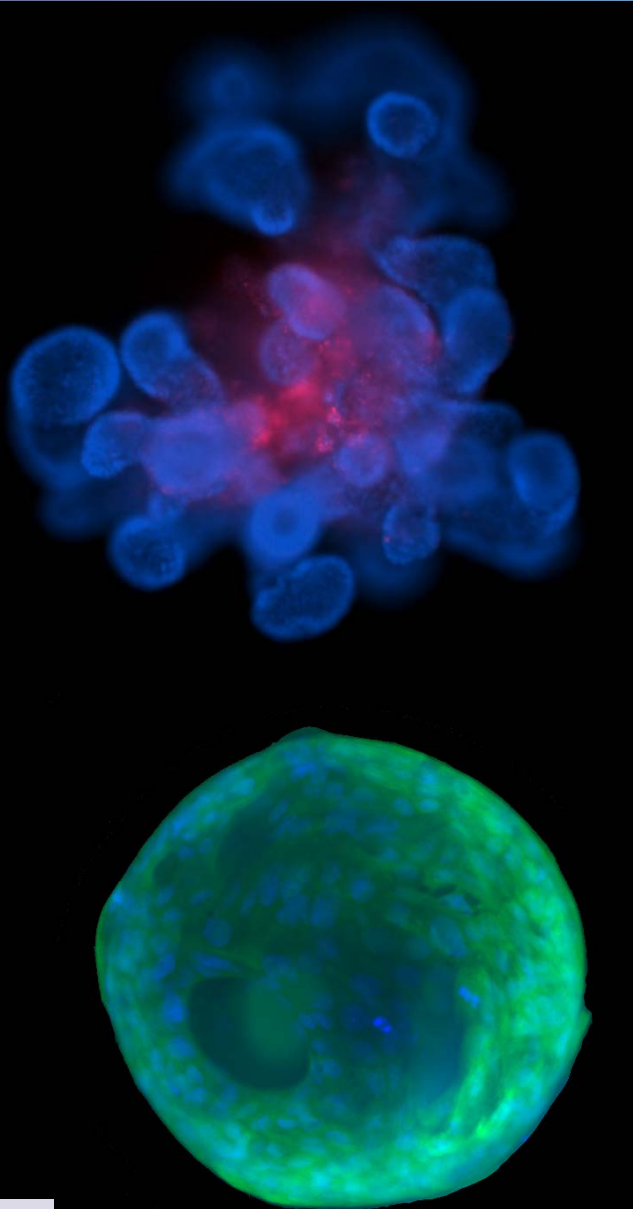
Maintain *in  
vivo* phenotype

Relatively high  
success rate

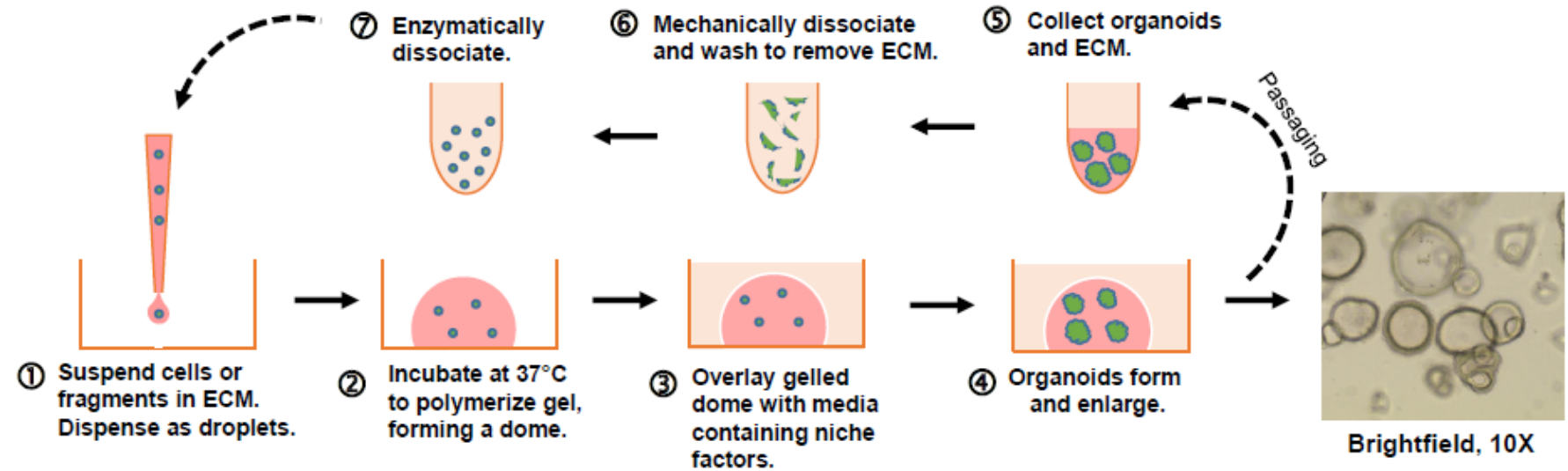


## Primary tissue derived organoids

# Organoid technology



Embedded three-dimensional culture technique that utilizes model-specific growth media formulations in combination with undefined extracellular matrix

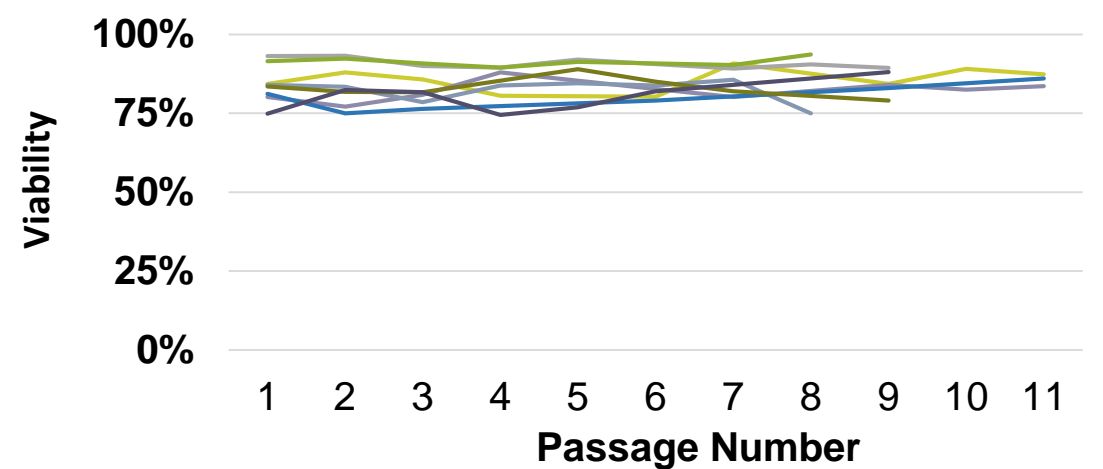
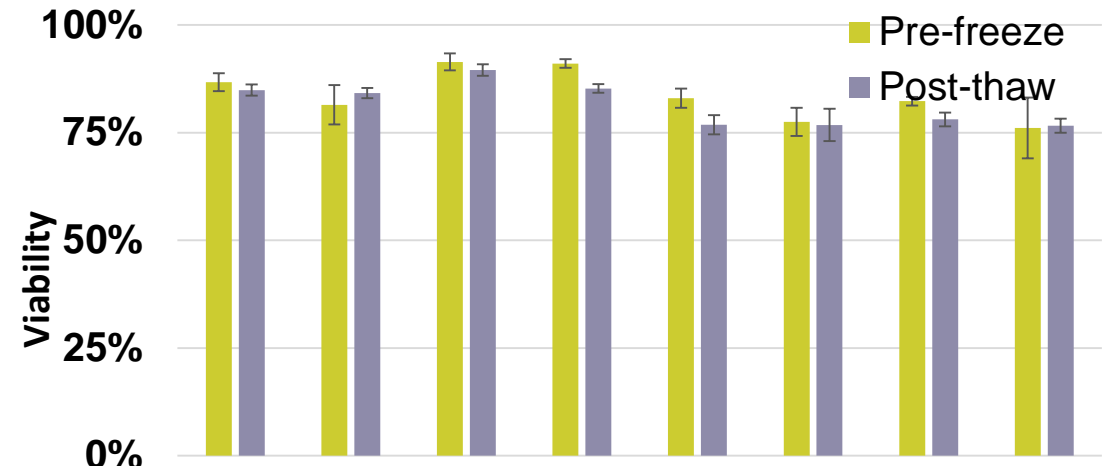
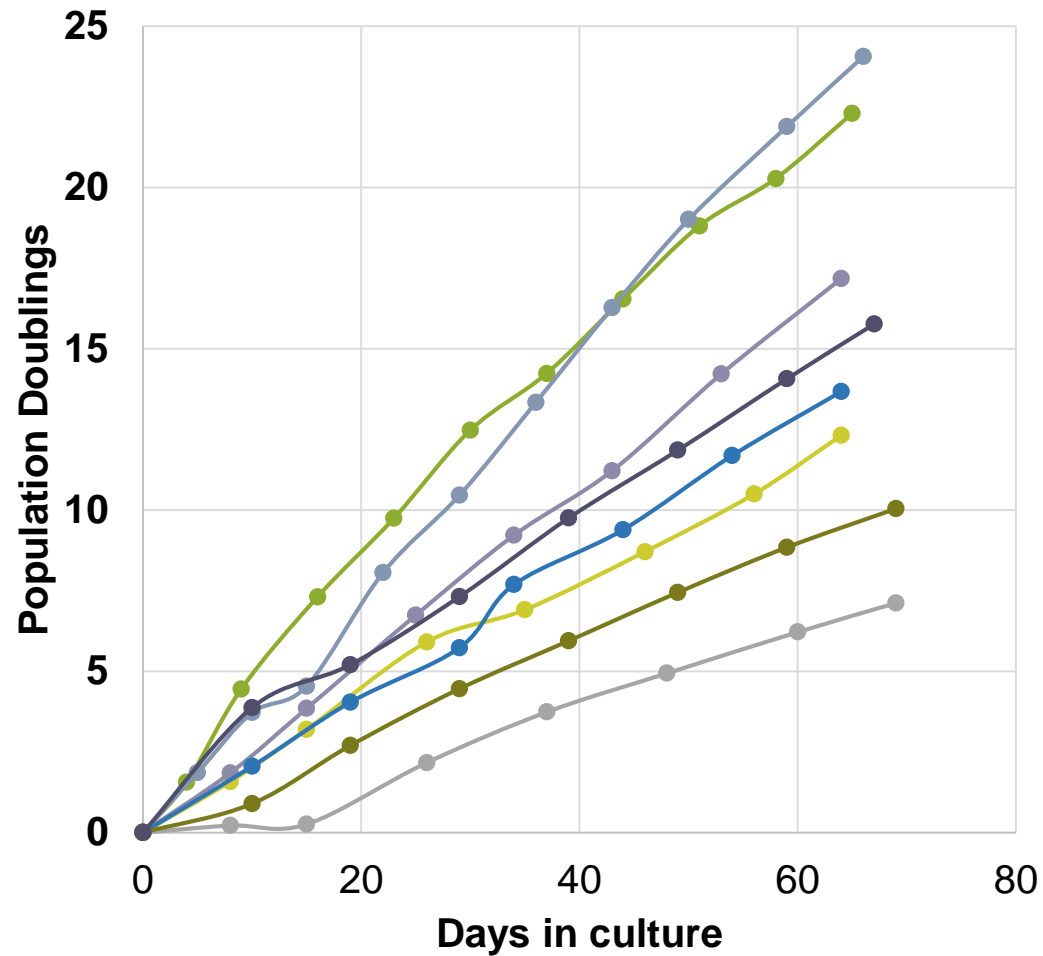


<https://currentprotocols.onlinelibrary.wiley.com/doi/epdf/10.1002/cpcb.66>

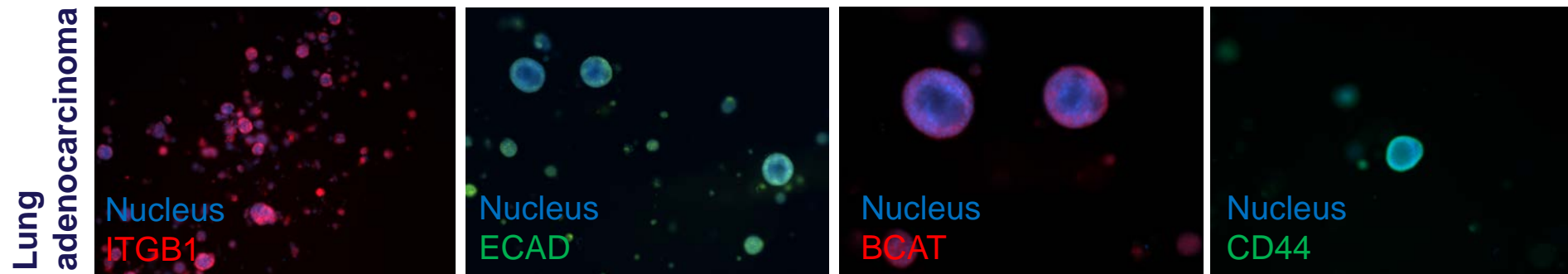
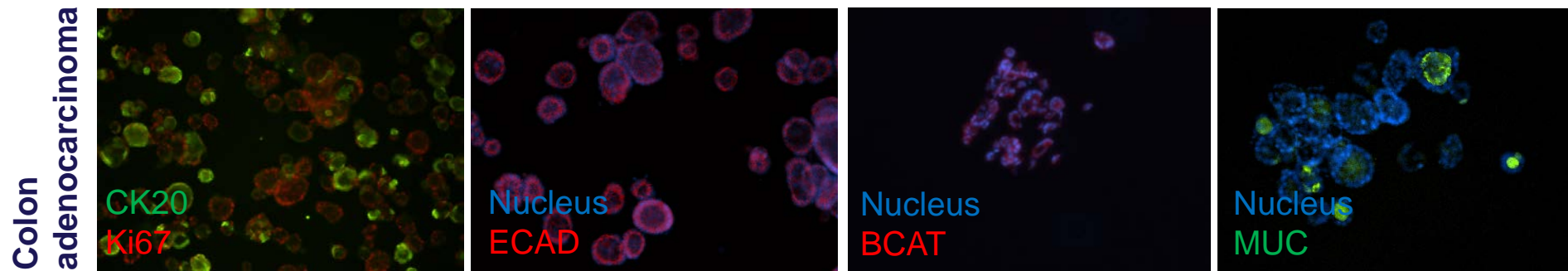
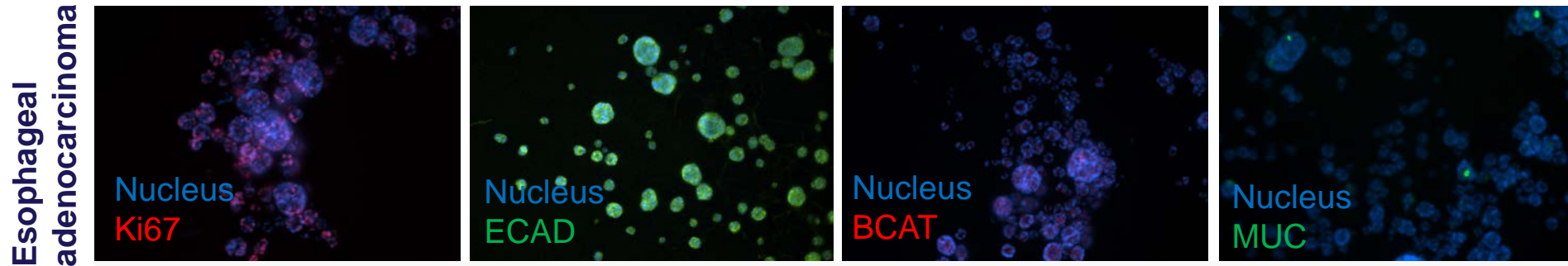
# Primary tissue organoids compared with other models

Characteristic	Primary tissue-derived organoids	iPSC-derived organoids	Cancer cell line-derived spheroids
Derived from primary patient tissue	Yes	No	No
Can be continuously propagated <i>in vitro</i>	Yes	No	No
Can be mechanically or enzymatically dissociated to expand culture (i.e., serial passage)	Yes	No	No
Self-organize into complex 3D structures	Yes	Yes	No
Exhibit multiple tissue specific cell types	Yes	Yes	No
Exhibit tissue or cell type specific functionality	Yes	Yes	No
Requires multi step differentiation and formation process	No	Yes	No

# Organoids expansion, cryopreservation, and recovery



# Organoids are amenable to standard lab assays





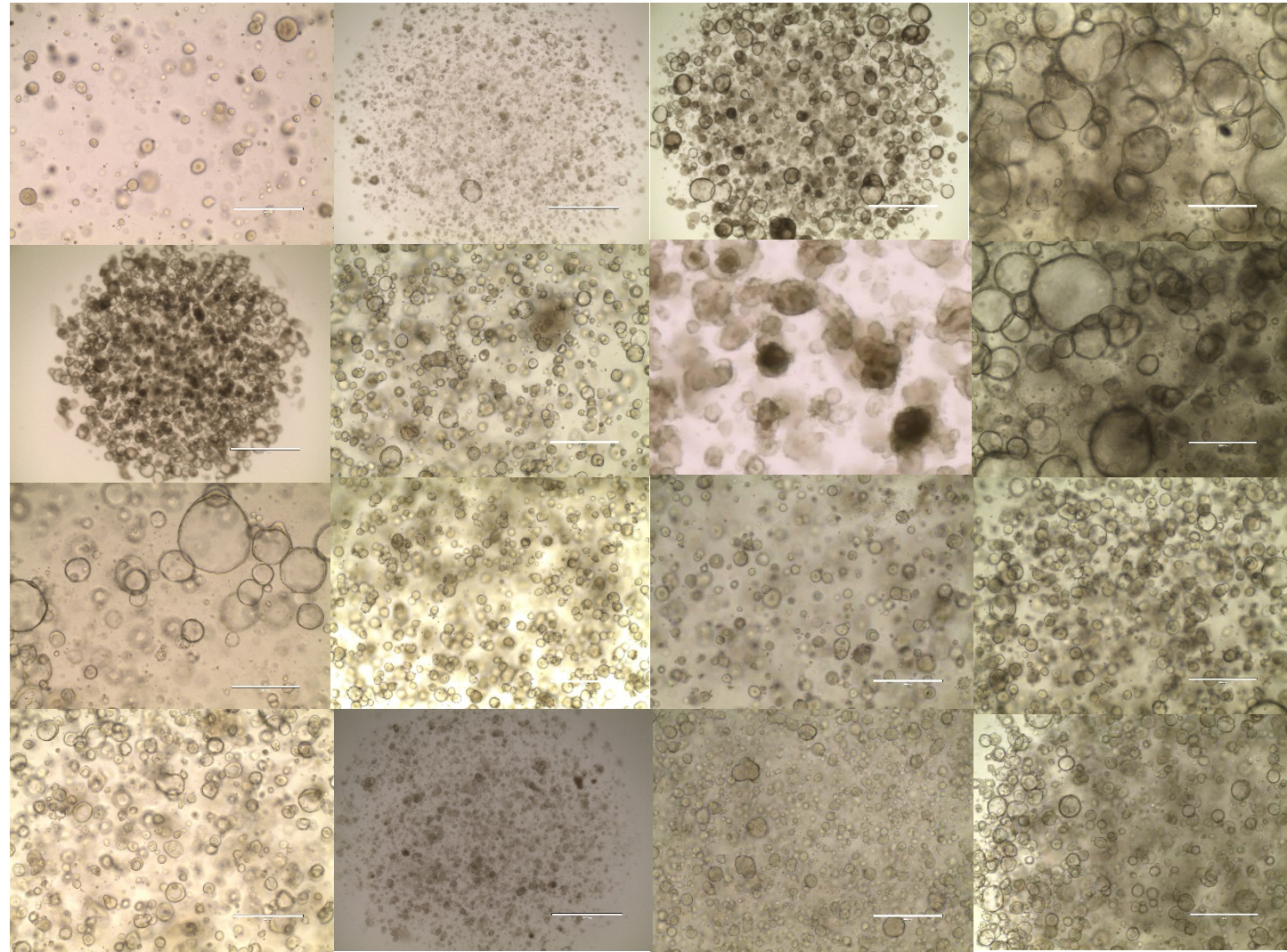
# HCMI organoid models

## Types

- Adenocarcinoma
- Carcinoma
- Primary
- Recurrent
- Metastatic
- Pre-malignant

## Tissues

- Lung
- Colon
- Rectum
- Mammary
- Esophagus
- Pancreas
- Prostate
- Liver
- Ovary
- Stomach



*Not a comprehensive list*

**16 unique models from various tissue**

# Organoid culture guide

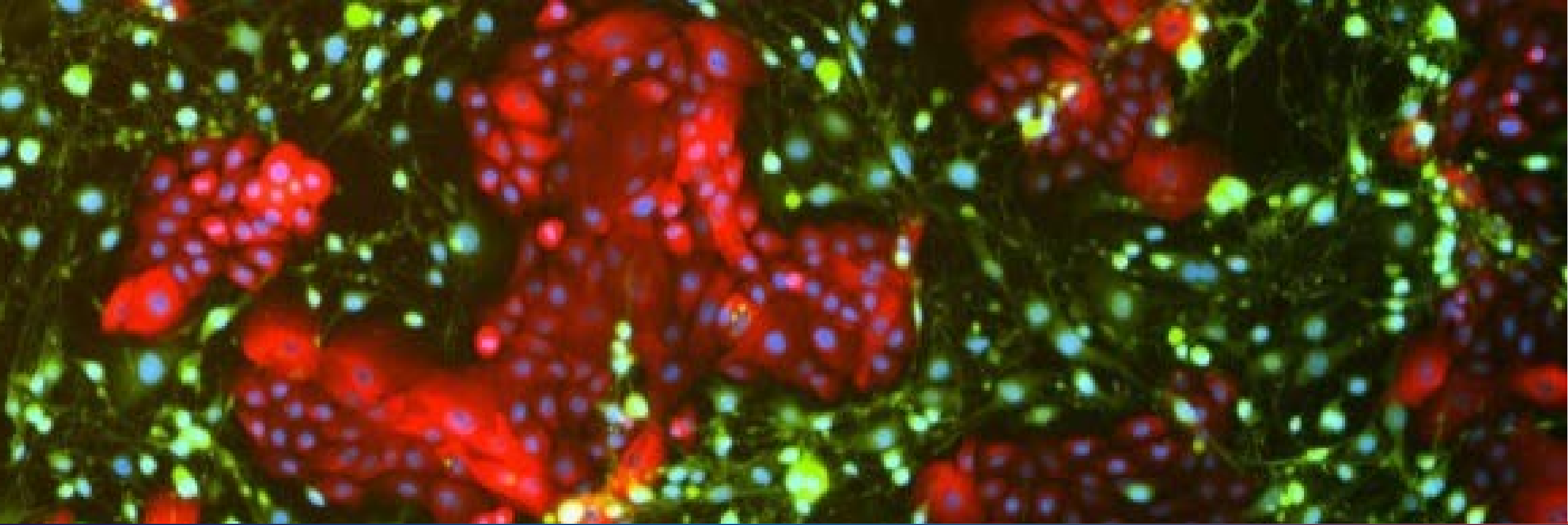


in Cell Biology

UNIT |  Free Access

## Initiation, Expansion, and Cryopreservation of Human Primary Tissue-Derived Normal and Diseased Organoids in Embedded Three-Dimensional Culture

<https://currentprotocols.onlinelibrary.wiley.com/doi/epdf/10.1002/cpcb.66>



## Conditionally reprogrammed cells

# Conditionally Reprogrammed Cells (CRC) Technology

PROTOCOL

## ROCK Inhibitor and Feeder Cells Induce the Conditional Reprogramming of Epithelial Cells

Xuefeng Liu,\* Virginie Ory,<sup>†</sup> Sandra Chapman,<sup>‡</sup> Hang Yuan,\* Chris Albanese,\*<sup>†</sup> Bhaskar Kallakury,\* Olga A. Timofeeva,<sup>†</sup> Caitlin Nealon,\* Aleksandra Dakic,\* Vera Simic,\* Bassem R. Haddad,<sup>†</sup> Johng S. Rhim,<sup>§</sup> Anatoly Dritschilo,<sup>†</sup> Anna Riegel,<sup>†</sup> Alison McBride,<sup>‡</sup> and Richard Schlegel\*

**CRC method allows for the genetic manipulation of epithelial cells *ex vivo* and their subsequent evaluation *in vivo* in the same host.** (*Am J Pathol* 2012, 180: 599–607; DOI: 10.1016/j.ajpath.2011.10.036)

The unlimited propagation of adult mammalian, nonkeratinocyte epithelial cells offers exciting opportunities for

## Conditional reprogramming and long-term expansion of normal and tumor cells from human biospecimens

Xuefeng Liu<sup>1,2,8</sup>, Ewa Krawczyk<sup>1,2,8</sup>, Frank A Supryniewicz<sup>1,2</sup>, Nancy Palechor-Ceron<sup>1,2</sup>, Hang Yuan<sup>1,2</sup>, Aleksandra Dakic<sup>1,2</sup>, Vera Simic<sup>1,2</sup>, Yun-Ling Zheng<sup>3</sup>, Praathibha Sripadhan<sup>1,2</sup>, Chen Chen<sup>1,2</sup>, Jie Lu<sup>1,2</sup>, Tung-Wei Hou<sup>1,2</sup>, Sujata Choudhury<sup>1,2</sup>, Bhaskar Kallakury<sup>1,2</sup>, Dean Tang<sup>4</sup>, Thomas Darling<sup>5</sup>, Rajesh Thangapazham<sup>5</sup>, Olga Timofeeva<sup>3,6</sup>, Anatoly Dritschilo<sup>6</sup>, Scott H Randell<sup>7</sup>, Christopher Albanese<sup>1-3</sup>, Seema Agarwal<sup>1,2</sup> & Richard Schlegel<sup>1,2</sup>

<sup>1</sup>Department of Pathology, Georgetown University Medical Center, Washington, DC, USA. <sup>2</sup>Center for Cell Reprogramming, Georgetown University Medical Center, Washington, DC, USA. <sup>3</sup>Department of Oncology, Georgetown University Medical Center, Washington, DC, USA. <sup>4</sup>Department of Epigenetics and Molecular Carcinogenesis, University of Texas MD Anderson Cancer Center, Smithville, Texas, USA. <sup>5</sup>Department of Dermatology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA. <sup>6</sup>Department of Radiation Medicine, Georgetown University Medical Center, Washington, DC, USA. <sup>7</sup>Department of Cell Biology and Physiology, The University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA. <sup>8</sup>These authors contributed equally to this work. Correspondence should be addressed to X.L. (xuefeng.liu@georgetown.edu) or R.S. (richard.schlegel@georgetown.edu).

Published online 26 January 2017; doi:10.1038/nprot.2016.174

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

## Use of Reprogrammed Cells to Identify Therapy for Respiratory Papillomatosis

Hang Yuan, Ph.D., Scott Myers, M.D., Jingang Wang, Ph.D., Dan Zhou, M.S., Jennifer A. Woo, M.S., Bhaskar Kallakury, M.D., Andrew Ju, M.D., Michael Bazylewicz, M.D., Yvonne M. Carter, M.D., Christopher Albanese, Ph.D., Nazaneen Grant, M.D., Aziza Shad, M.D., Anatoly Dritschilo, M.D., Xuefeng Liu, M.D., and Richard Schlegel, M.D., Ph.D.

[www.impactjournals.com/oncotarget/](http://www.impactjournals.com/oncotarget/)

Oncotarget, Advance Publications 2016

## Conditionally reprogrammed normal and primary tumor prostate epithelial cells: a novel patient-derived cell model for studies of human prostate cancer

Olga A. Timofeeva<sup>1,2</sup>, Nancy Palechor-Ceron<sup>3</sup>, Guanglei Li<sup>4</sup>, Hang Yuan<sup>3</sup>, Ewa Krawczyk<sup>3</sup>, Xiaogang Zhong<sup>5</sup>, Geng Liu<sup>4</sup>, Geeta Upadhyay<sup>1</sup>, Aleksandra Dakic<sup>3</sup>, Songtao Yu<sup>3</sup>, Shuang Fang<sup>3</sup>, Sujata Choudhury<sup>3</sup>, Xueping Zhang<sup>1</sup>, Andrew Ju<sup>6</sup>, Myeong-Seon Lee<sup>7</sup>, Han C. Dan<sup>8</sup>, Youngmi Ji<sup>9</sup>, Yong Hou<sup>4</sup>, Yun-Ling Zheng<sup>1</sup>, Chris Albanese<sup>1,3</sup>, Johng Rhim<sup>9</sup>, Richard Schlegel<sup>3</sup>, Anatoly Dritschilo<sup>1,6</sup>, Xuefeng Liu<sup>3</sup>

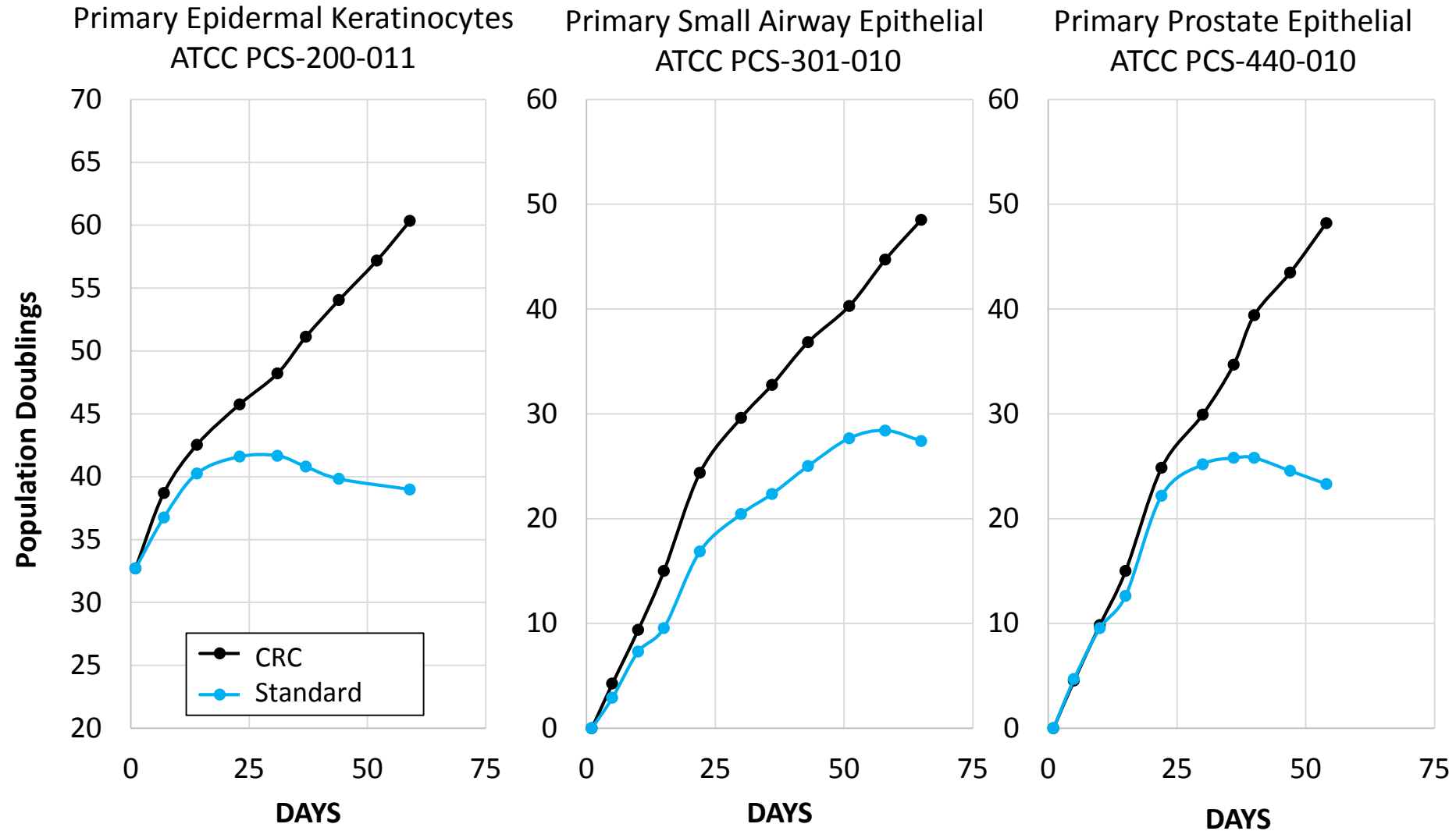
RESEARCH ARTICLES

CANCER THERAPY

## Patient-derived models of acquired resistance can identify effective drug combinations for cancer

Adam S. Crystal,<sup>1</sup> Alice T. Shaw,<sup>1</sup> Lecia V. Sequist,<sup>1</sup> Luc Friboulet,<sup>1</sup> Matthew J. Niederst,<sup>1</sup> Elizabeth L. Lockerman,<sup>1</sup> Rosa L. Frias,<sup>1</sup> Justin F. Gainor,<sup>1</sup> Arnaud Amzallag,<sup>1</sup> Patricia Greninger,<sup>1</sup> Dana Lee,<sup>1</sup> Anuj Kalsy,<sup>1</sup> Maria Gomez-Caraballo,<sup>1</sup> Lella Elamine,<sup>1</sup> Emily Howe,<sup>1</sup> Wooyoung Hur,<sup>3,4</sup> Eugene Lifshits,<sup>1</sup> Hayley E. Robinson,<sup>2</sup> Ryohei Katayama,<sup>1</sup> Anthony C. Faber,<sup>1</sup> Mark M. Awad,<sup>1</sup> Sridhar Ramaswamy,<sup>1</sup> Mari Mino-Kenudson,<sup>2</sup> A. John Iafrate,<sup>2</sup> Cyril H. Benes,<sup>1\*</sup> Jeffrey A. Engelman<sup>1\*</sup>

# CRC culture can prevent senescence of primary cells



# HCMI CRC and other non-organoid models

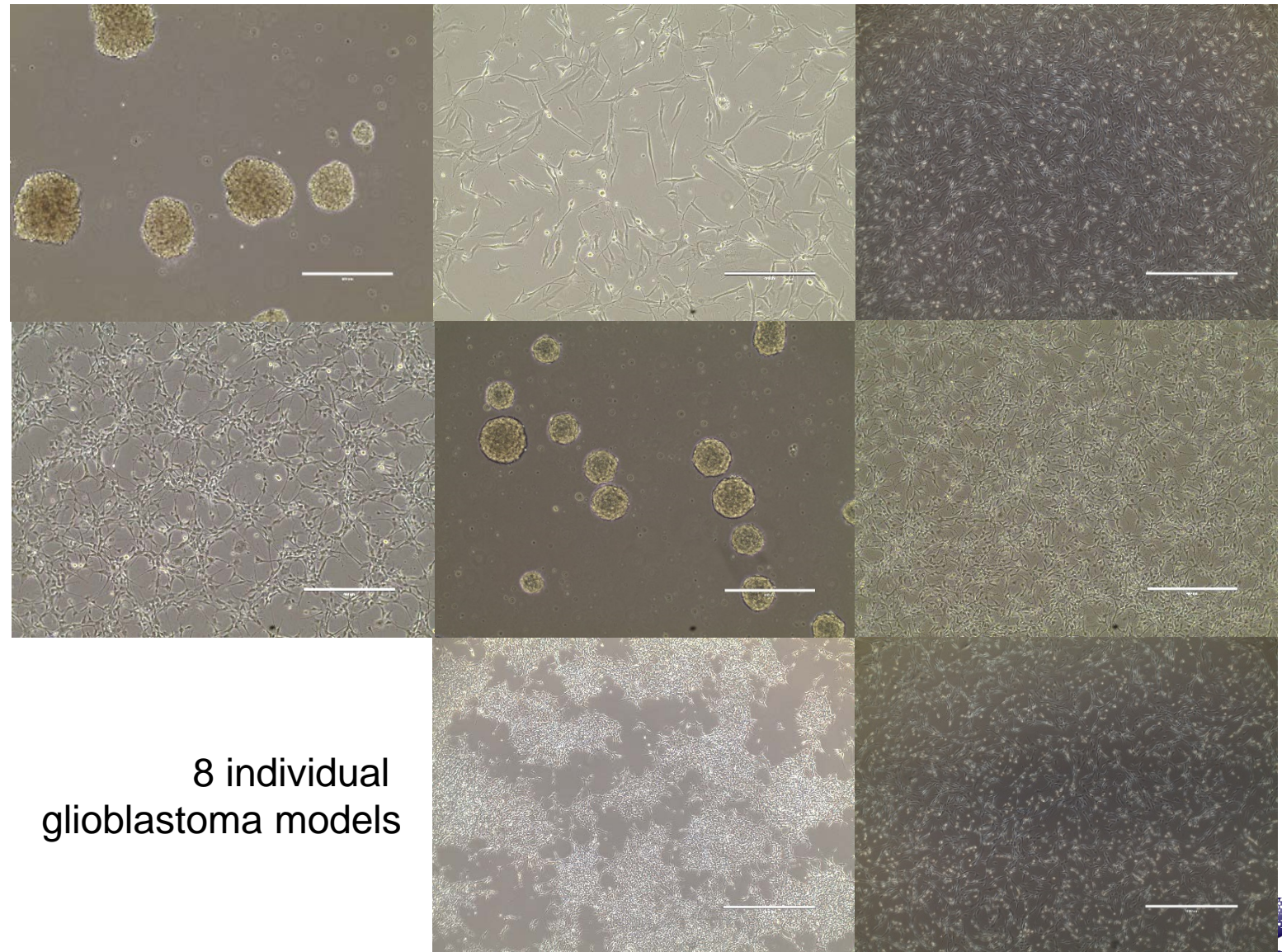
Includes CRC, various other 2D and 3D models types

## Tissues

- Adrenal gland
- Soft tissue/bone
- Head and neck
- Brain
- Kidney

## Types

- Neuroblastoma
- Glioblastoma
- Ewing Sarcoma
- Rhabdomyosarcoma
- Wilms Tumor



*Not a comprehensive list*

# Culture conditions for currently released HCMI models

Media/ Technology	Off-the-shelf growth media	Growth properties	Tissue type(s)	Serum- free/defined	ECM or special surface required?
<b>Organoid*</b>	No	3D embedded	Multiple	No	Yes
<b>Conditional Reprogramming</b>	Yes	2D adherent	Multiple	No	No
<b>SmGM-2</b>	Yes	2D adherent and suspension	Bone	No	No
<b>RETM</b>	Yes	2D adherent	Brain	No	No
<b>Neurocult NS-A</b>	Yes	2D adherent and suspension	Brain	Yes	Sometimes

\*There are multiple organoid media formulations

# Model resources and data access

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Search by Keyword or Catalog 🔍

Products Services Standards Resources Support About

## HUMAN CANCER MODELS INITIATIVE

### Next-generation Cancer Models

As part of our pledge to elevate biological models, ATCC is collaborating with the Human Cancer Models Initiative (HCMI) to offer scientists a wide variety of next-generation 2D and 3D patient-derived *in vitro* cancer models, including organoids. ATCC is committed to making available a growing collection of models generated by the HCMI, which will include both common as well as rare and understudied examples of cancer from numerous tissues. These HCMI models are valuable tools to study cancer, identify and target novel therapies, and facilitate translational cancer research.

#### Cancer Models Based on Physiological System:

- Digestive System >
- Nervous System >
- Respiratory System >
- Musculo-skeletal System

Coming Soon

- Reproductive System
- Integumentary System
- Excretory System
- Circulatory System

HCMI RESOURCES

- Posters
- Brochures
- Culture Guides
- Application Notes
- Webinars
- Protocols

Credible Models Incredible Outcomes [Learn more](#)

Credible Collaboration Incredible Insights [Learn more](#)

- View all models available or grouped by tissue
- Model specific information such as culture images, seeding densities, media change frequencies, etc.
- Individual model product pages include detailed culture protocols
  - Complete media formulation
  - Thawing/subculturing/freezing guides
- Model pages link to other resource pages that host clinical and sequencing data
- Frequently asked questions

[www.atcc.org/HCMI](http://www.atcc.org/HCMI)



# Model resources and data access

**Human Cancer Models Initiative** Searchable Catalog

SEARCH BY NAME  
Enter model name ...

PRIMARY SITE  
Brain 8  
Colon 8  
Pancreas 6  
Bone 2  
3 More

TYPE  
3-D: Organoid 18  
2-D: Adherent 5  
3-D: Other (e.g. neurosphere, air-liquid interface, etc.) 3  
2-D: Conditionally reprogrammed cells 2

ACQUISITION SITE  
Brain 8  
Sigmoid colon 5  
Pancreatic head 4  
Liver 2  
9 More

CLINICAL TUMOR DIAGNOSIS  
Colorectal cancer 10  
Glioblastoma 8

Use the filter panel on the left to customize your model search. [SHARE]

MODELS BY PRIMARY SITE: 7 PRIMARY SITES  
2D VERSUS 3D GROWTH

Showing 1 - 20 of 28 models [Filter] [COLUMNS] [EXPORT ALL]

NAME	PRIMARY SITE	CLINICAL TU...	GENDER	RACE	AGE AT ACQ...	AGE AT DIAG...
<a href="#">HCM-SANG-0266-C20</a>	Rectum	Colorectal cancer	Female	White		62
<a href="#">HCM-SANG-0267-D12</a>	Colon	Colorectal cancer	Male	White		64
<a href="#">HCM-BROD-0005-C41</a>	Bone	Ewing's sarcoma	Male	White	8	8
<a href="#">HCM-BROD-0038-C41</a>	Bone	Osteosarcoma	Male	White	16	16
<a href="#">HCM-BROD-0115-C16</a>	Stomach	Stomach cancer	Male	White	44	44
<a href="#">HCM-CSHL-0060-C18</a>	Colon	Colorectal cancer	Male	White	51	51
<a href="#">HCM-BROD-0011-C71</a>	Brain	Glioblastoma	Male	White	55	55
<a href="#">HCM-BROD-0012-C71</a>	Brain	Glioblastoma	Female	White	57	57
<a href="#">HCM-BROD-0029-C71</a>	Brain	Glioblastoma	Male	White	58	58

- NCI managed website
- Integrates clinical, model, and genomic information.
- Search for models of interest using various filters
  - Primary tumor site/acquisition site
  - Model type
  - Tumor diagnosis/stage/grade/histological type
  - Gender/age/ethnicity
  - Etc.
- Links out to clinical and genomic data, ATCC model product page.

[hcmi-searchable-catalog.nci.nih.gov](https://hcmi-searchable-catalog.nci.nih.gov)

# Model resources and data access

NIH NATIONAL CANCER INSTITUTE GDC Data Portal

Home Projects Exploration Analysis Repository Manage Sets

Harmonized Cancer Datasets  
Genomic Data Commons Data Portal

Get Started by Exploring:

Projects Exploration Analysis Repository

Q e.g. BRAF, Breast, TCGA-BLCA, TCGA-A5-A0G2

Data Portal Summary Data Release 17.0 - June 05, 2019

PROJECTS 47	PRIMARY SITES 68	CASES 33,605
FILES 376,791	GENES 22,872	MUTATIONS 3,142,246

GDC Applications

The GDC Data Portal is a robust data-driven platform that allows cancer researchers and bioinformaticians to search and download cancer data for analysis. The GDC applications include:

Data Portal Website Data Transfer Tool API Data Submission Portal Documentation Legacy Archive

- NCI managed website
- Search and download cancer related datasets for analysis
- Navigate to the “HCMI-CMDC” project for HCMI specific datasets
- Download WGS/WXS/RNAseq data
  - Aligned reads, gene expression, SNVs

[portal.gdc.cancer.gov](http://portal.gdc.cancer.gov)

# Model resources and data access

The screenshot shows the NCI Office of Cancer Genomics website. At the top left is the NIH logo and the text "NATIONAL CANCER INSTITUTE Office of Cancer Genomics". To the right are links for "EMAIL UPDATES / CONTACT" and a search bar. A navigation bar below contains "PROGRAMS / RESOURCES / NEWS & PUBLICATIONS / ABOUT OCG / DATA ACCESS", with "DATA ACCESS" highlighted. Below the navigation bar is a breadcrumb trail: "Home > Programs > HCMI".

The main content area is titled "HCMI: Human Cancer Models Initiative". It includes a description: "The Human Cancer Models Initiative (HCMI) is a collaborative international consortium that is generating novel, next-generation, tumor-derived culture models annotated with genomic and clinical data. HCMI-developed models and related data are available as a community resource. The NCI is contributing to the initiative by supporting four Cancer Model Development Centers (CMDs)." Below the text is a large image showing a doctor talking to a patient, with a DNA double helix and a cell model overlaid.

On the left side, there is a sidebar menu with links: "HCMI", "Overview", "Research", "HCMI Organization", "NCI Cancer Model Development", "Resources", "HCMI Publication Guidelines".

On the right side, there are several boxes: "QUICK LINKS" with links for "Have Questions? Contact us", "OCG Fact Sheet", "e-Newsletter", and "RSS Feeds"; "EMAIL UPDATES SIGN-UP" with the text "Get email updates from OCG"; and "HCMI RESOURCES" with links for "HCMI Case Report Forms (CRFs)" and "HCMI Searchable Catalog User Guide".

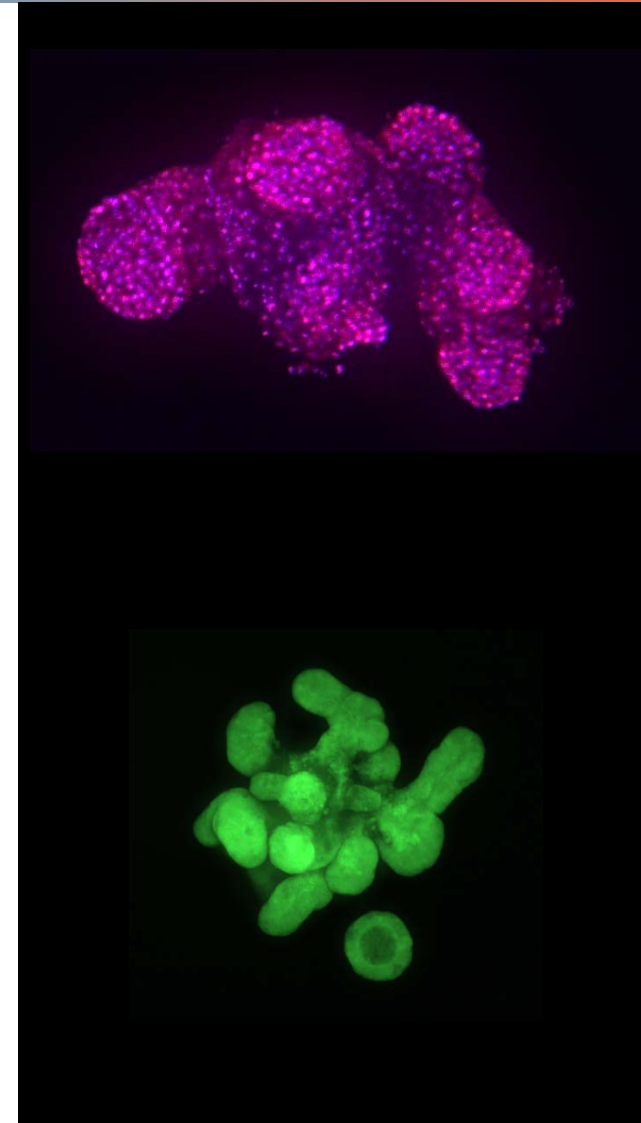
Below the main image is a "NEWS & PUBLICATIONS" section. It features a news item dated "July 11, 2016" titled "Office of Cancer Genomics launches new program". The text reads: "The NCI Office of Cancer Genomics, along with Cancer Research UK, ...". There is a small image of a DNA helix and a person next to the text.

- NCI managed website
- Background information on the HCMI program and organization
- Useful documents
  - Case Report forms for patient enrollment and follow-up
  - HCMI Searchable catalog user guide
  - Informed consent template

<https://ocg.cancer.gov/programs/HCMI>

# Model availability

- 28 models currently available from ATCC
- Additional models will be made available on a rolling basis, expect releases every 1-2 months.
- Pipeline includes mammary carcinoma organoids, primary and metastatic esophageal adenocarcinoma organoids, additional colon, pancreas and glioblastoma models.

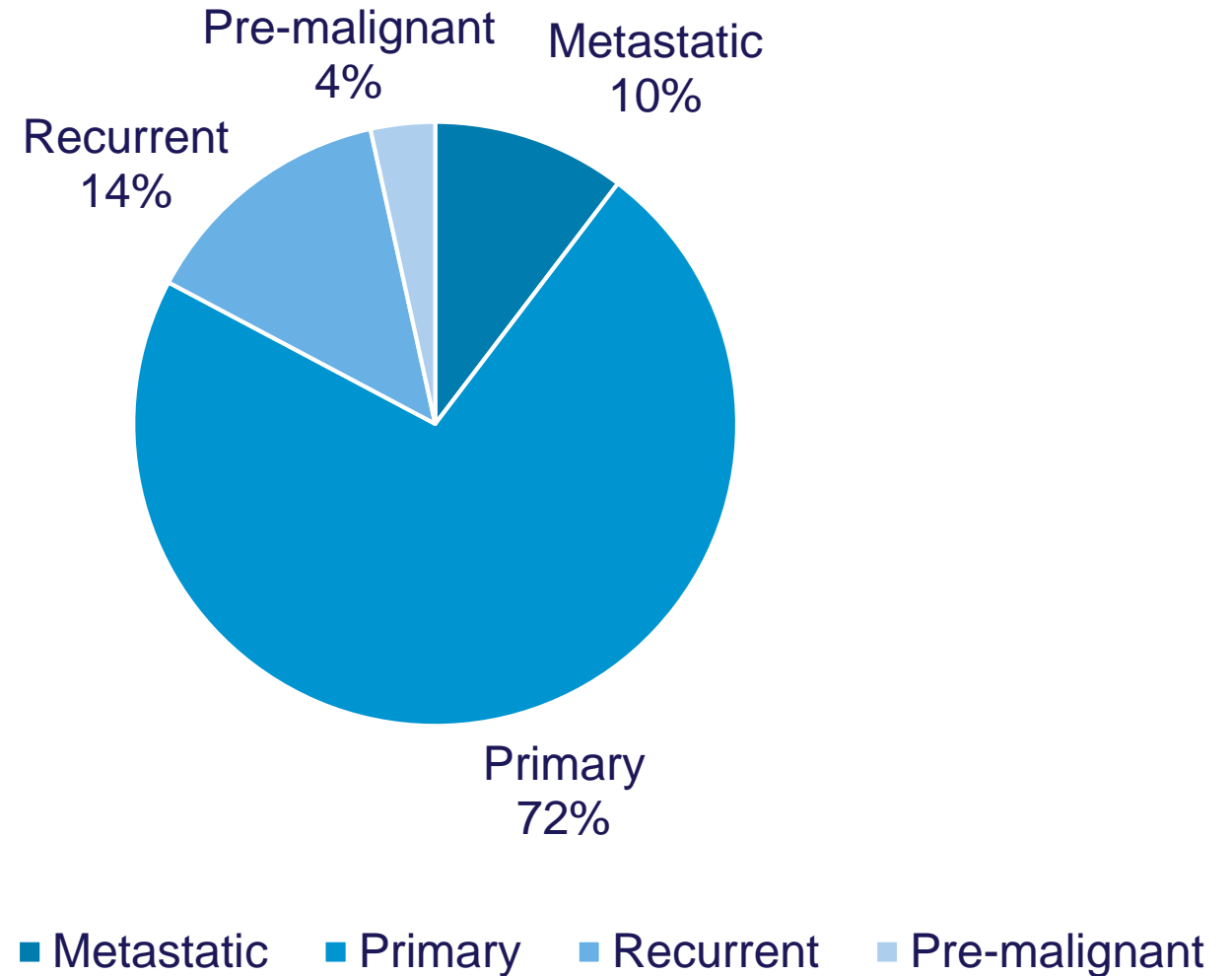
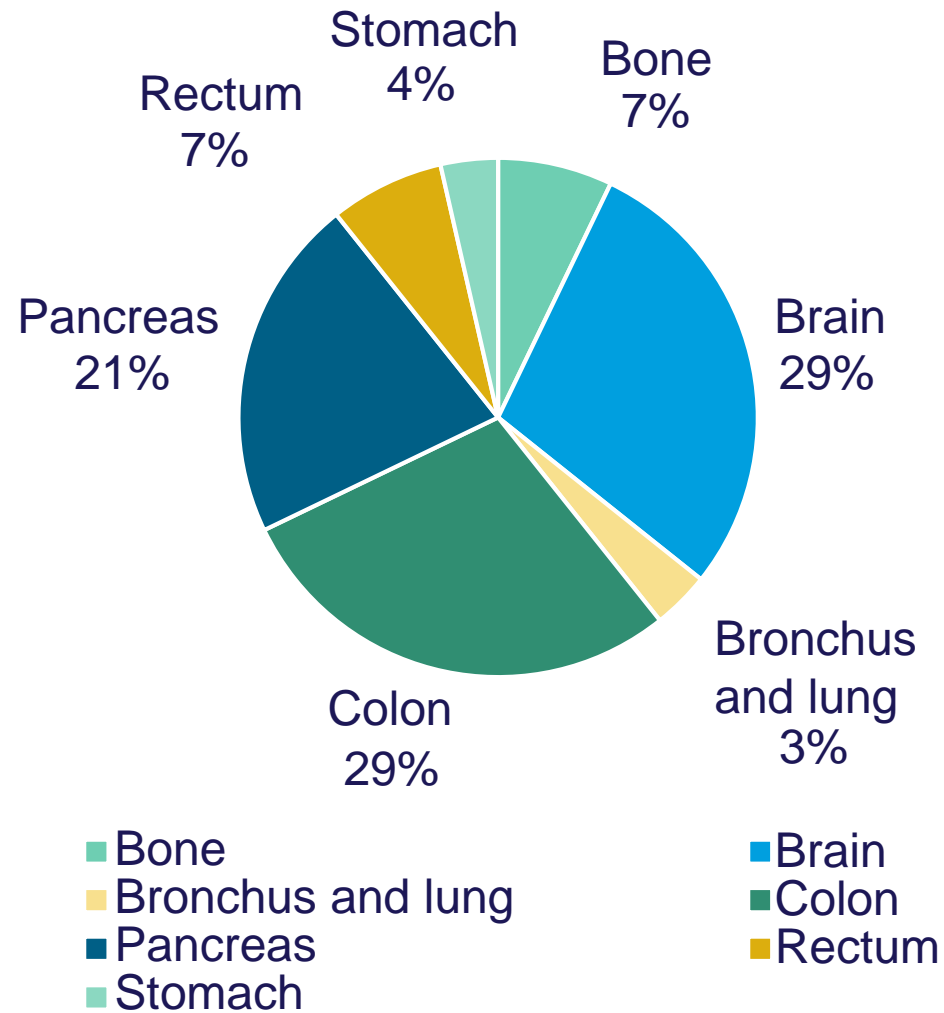


# ATCC HCMI model distribution material

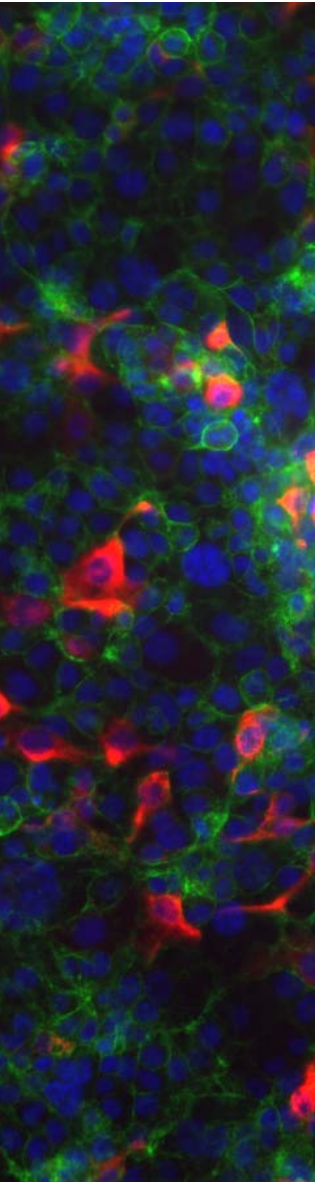
- Target  $\geq 1 \times 10^6$  viable cells per vial
- Product documentation includes
  - Recommended growth medium
  - Recommended culture maintenance parameters
- QC
  - Post-thaw cell count and viability
  - Mycoplasma testing
  - Sterility testing (bacteria, fungi and yeast)
  - Species determination
  - STR fingerprinting
  - Human pathogenic virus testing (HIV, HBV, EBV, CMV, WNV)



# Models currently available



# Models currently available

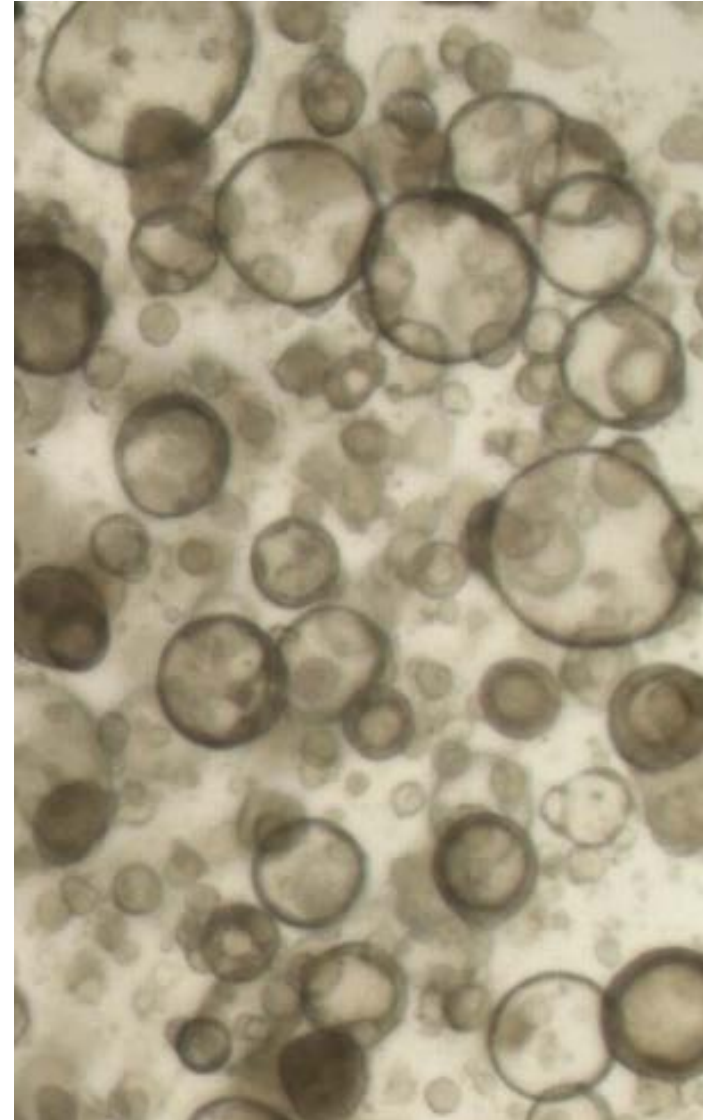


Part No.	Description	Type
PDM-135	Metastatic Adenocarcinoma of stomach	Organoid
PDM-1	Primary Adenocarcinoma of colon	Organoid
PDM-2	Primary Adenocarcinoma of colon	Organoid
PDM-4	Primary Adenocarcinoma of colon	Organoid
PDM-5	Primary Adenocarcinoma of colon	Organoid
PDM-6	Primary Adenocarcinoma of colon	Organoid
PDM-7	Primary Adenocarcinoma of colon	Organoid
PDM-8	Primary Adenocarcinoma of colon	Organoid
PDM-44	Pre-malignant Adenoma of colon	Organoid
PDM-9	Metastatic Adenocarcinoma of rectum	Organoid
PDM-43	Primary Adenocarcinoma of rectum	Organoid
PDM-106	Metastatic Adenocarcinoma of pancreas	Organoid
PDM-36	Primary Adenocarcinoma of pancreas	Organoid
PDM-38	Primary Adenocarcinoma of pancreas	Organoid
PDM-39	Primary Adenocarcinoma of pancreas	Organoid
PDM-40	Primary Adenocarcinoma of pancreas	Organoid
PDM-41	Primary Adenocarcinoma of pancreas	Organoid

Part No.	Description	Type
PDM-3	Primary Adenocarcinoma of lung	Organoid
PDM-127	Metastatic Ewing sarcoma	2D adherent
PDM-114	Primary Osteosarcoma	2D adherent
PDM-16	Primary Glioblastoma	2D adherent
PDM-17	Primary Glioblastoma	2D adherent
PDM-18	Primary Glioblastoma	Suspension
PDM-20	Primary Glioblastoma	2D adherent
PDM-19	Recurrent Glioblastoma	2D adherent
PDM-21	Recurrent Glioblastoma	2D adherent
PDM-22	Recurrent Glioblastoma	Suspension
PDM-23	Recurrent Glioblastoma	2D adherent

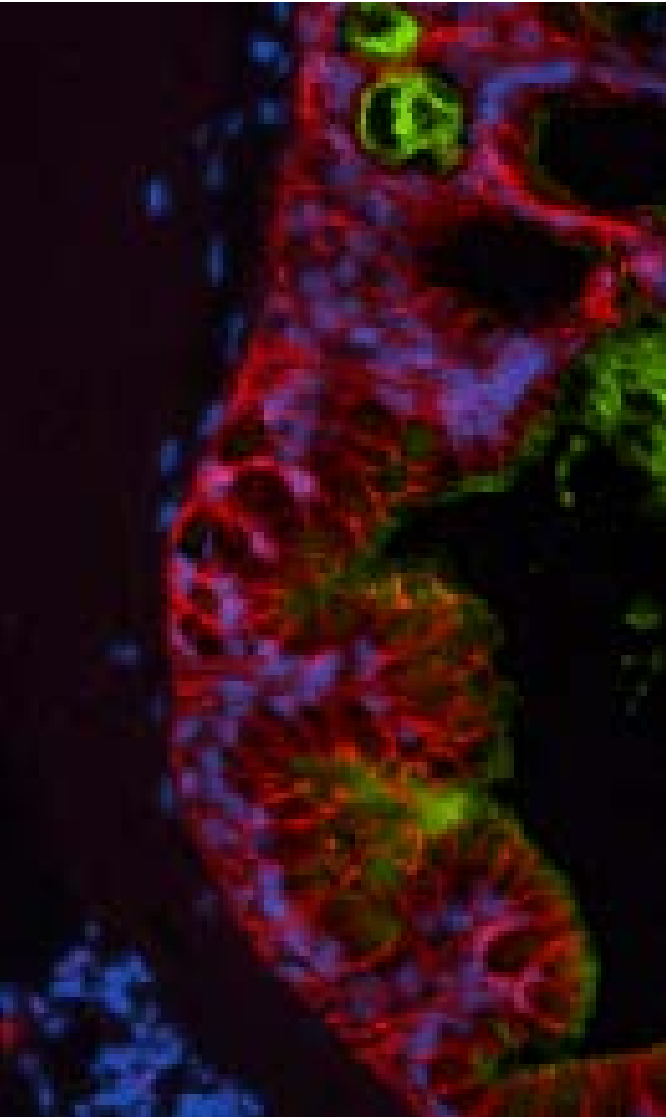
# Model availability

- Sign up on the ATCC HCMI website to join the early adopter program and gain access to models prior to release.
- Sign up for the ATCC mailing list to be notified of new HCMI model releases.





# Summary



- HCMI models are primary patient-derived models from a variety of tissues and cancer types that are paired with patient clinical and molecular characterization via WGS/WXS/RNA-Seq.
- 28 models from a variety of tissues/cancer types are currently available and new models will be continually released in the coming months.
- ATCC is excited to support the HCMI and their goal of developing and distributing next-generation cancer models.

# Thank you for joining today!

- Register for more ATCC webinars at [www.atcc.org/webinars](http://www.atcc.org/webinars)
- June 27 | 12:00 PM ET  
**iPSC-derived Primary Cells: Expand Your Cell-based Assays With an Unlimited, Biologically Relevant Resource**  
Yalin Firinci, M.B.A.  
*Product Line Business Specialist, ATCC*

