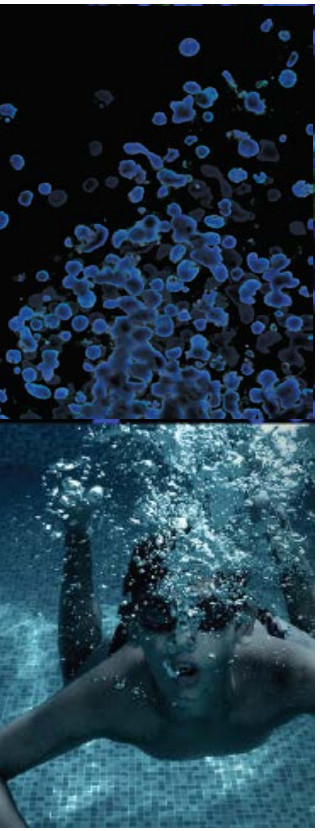


Next-generation cancer models from the Human Cancer Models Initiative

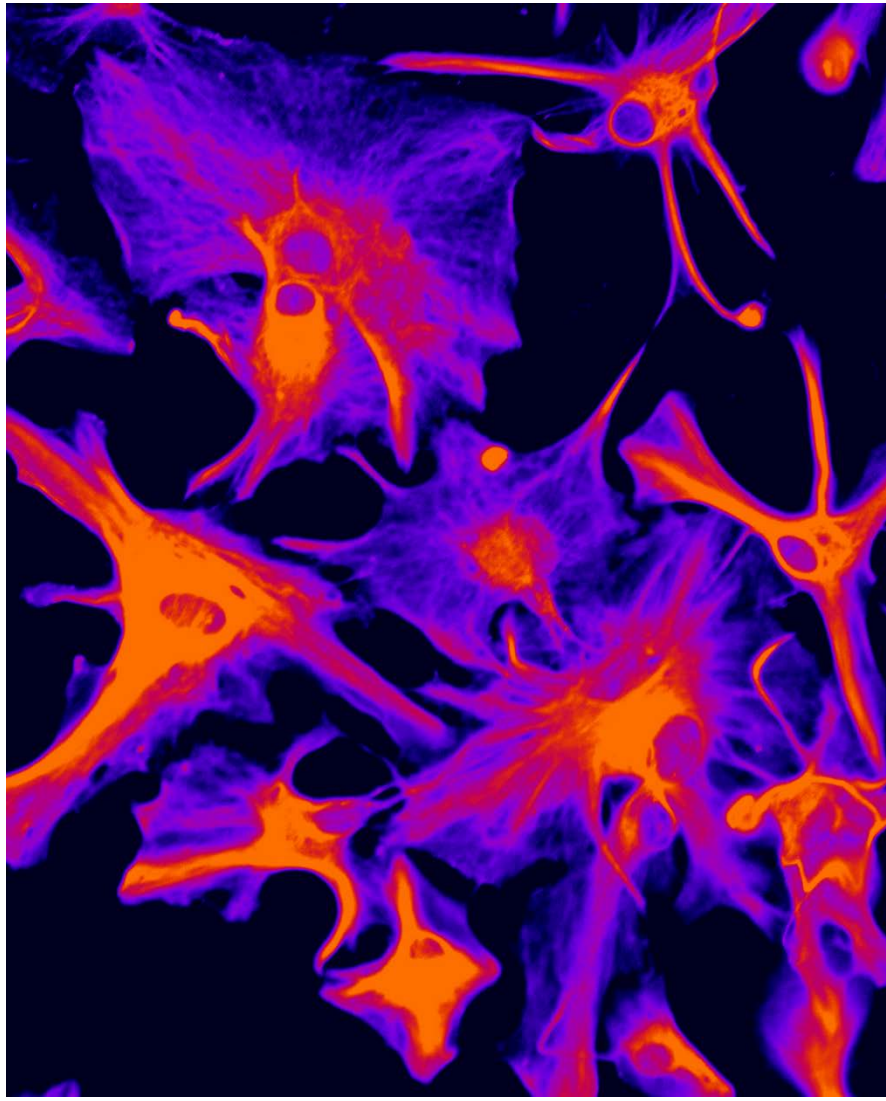
James M. Clinton, Ph.D.

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



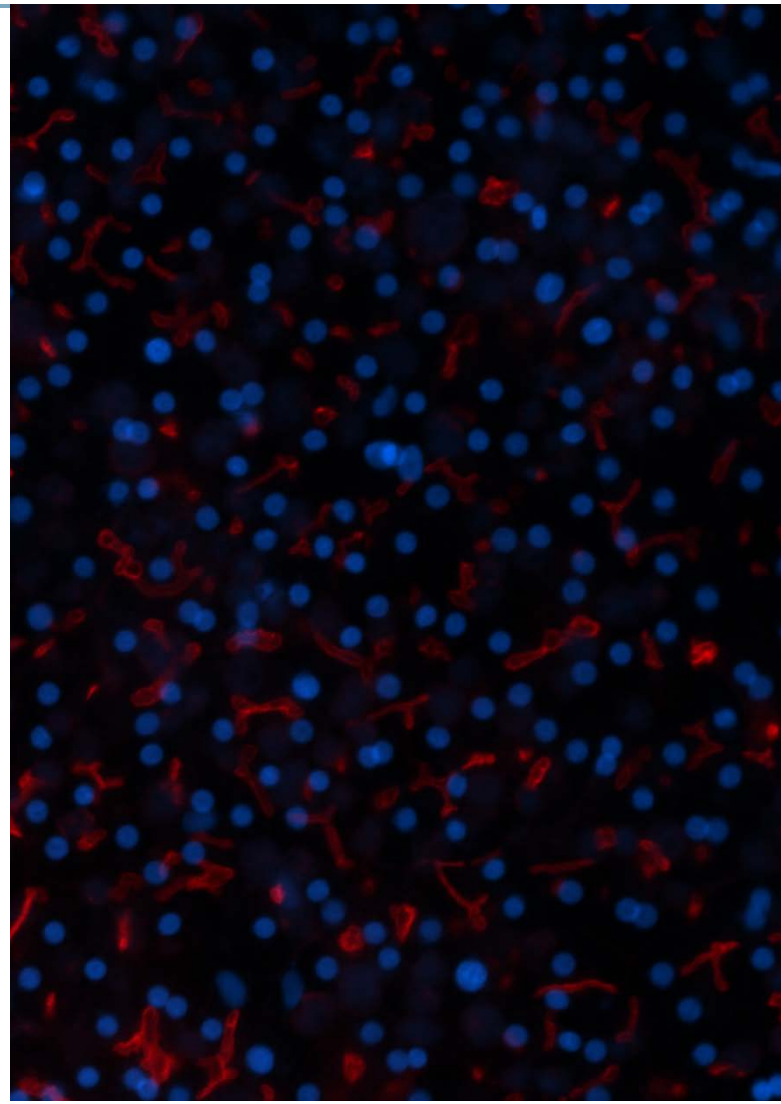
The unmet need

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

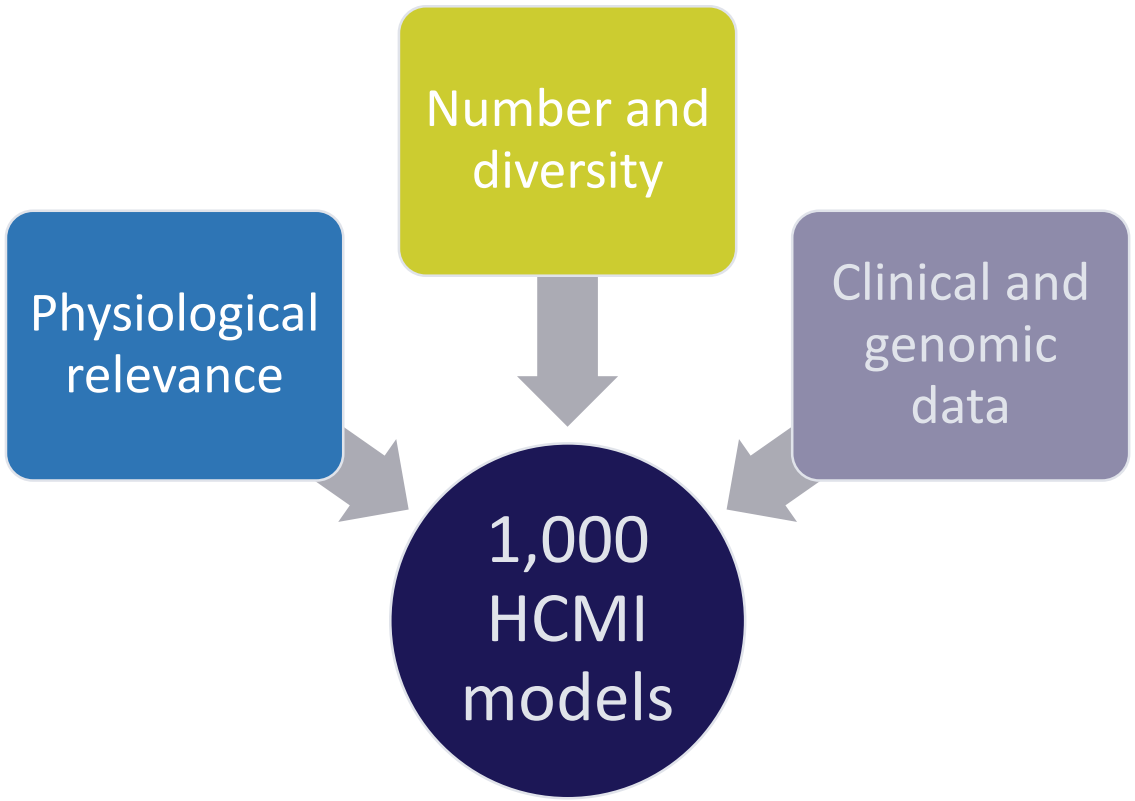
There is a need for better preclinical models to predict therapeutic outcomes.

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.

ATCC

Overview of HCMI and ATCC

Founders

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

Model Development

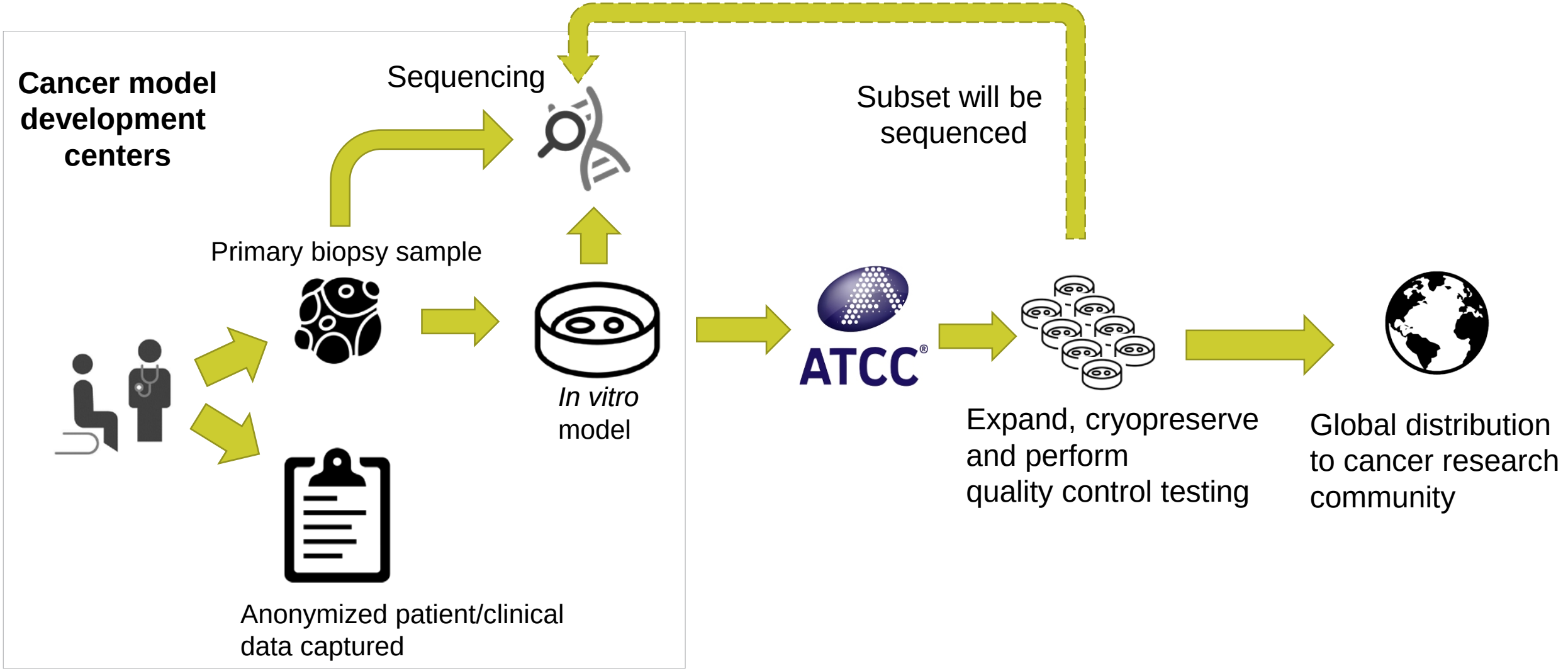
- Broad Institute
- Cold Spring Harbor Laboratory
- Wellcome Sanger Institute
- Hubert Organoid Technology Foundation
- University of Verona
- Hubrecht Institute
- Stanford University
- Weill Cornell Medical College

Distribution

ATCC®

ATCC®

Generation and distribution of HCMI models



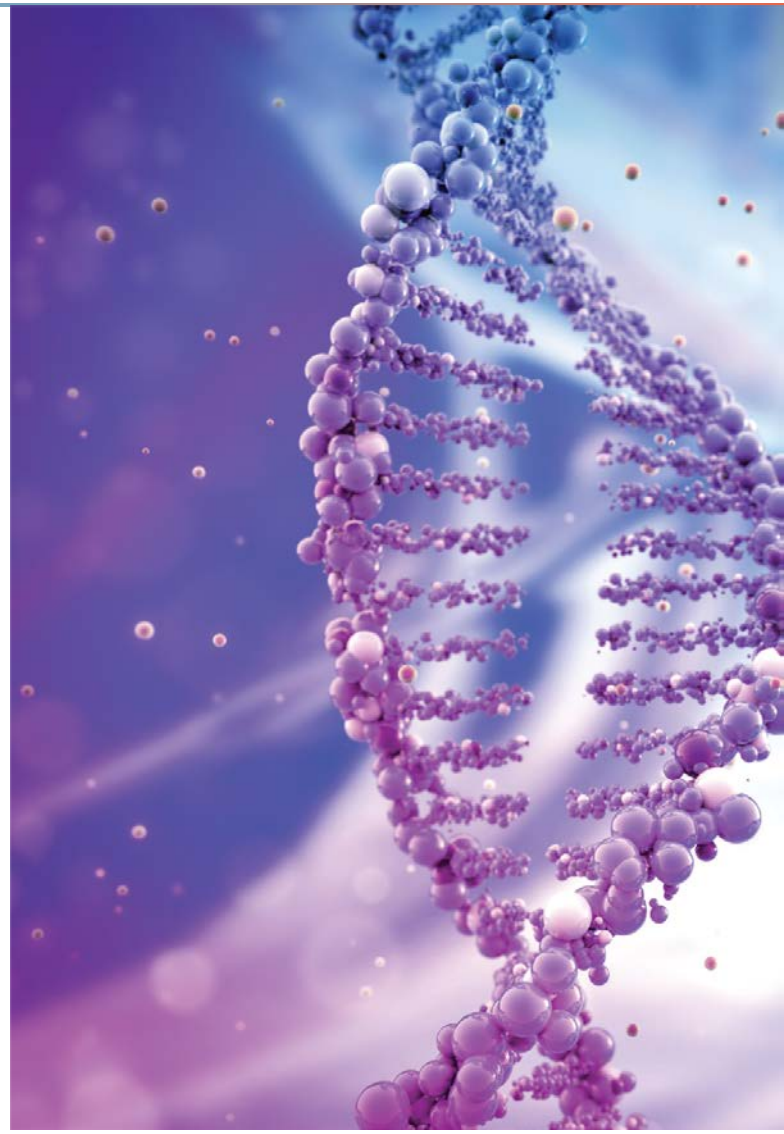
Characterization of models

Molecular

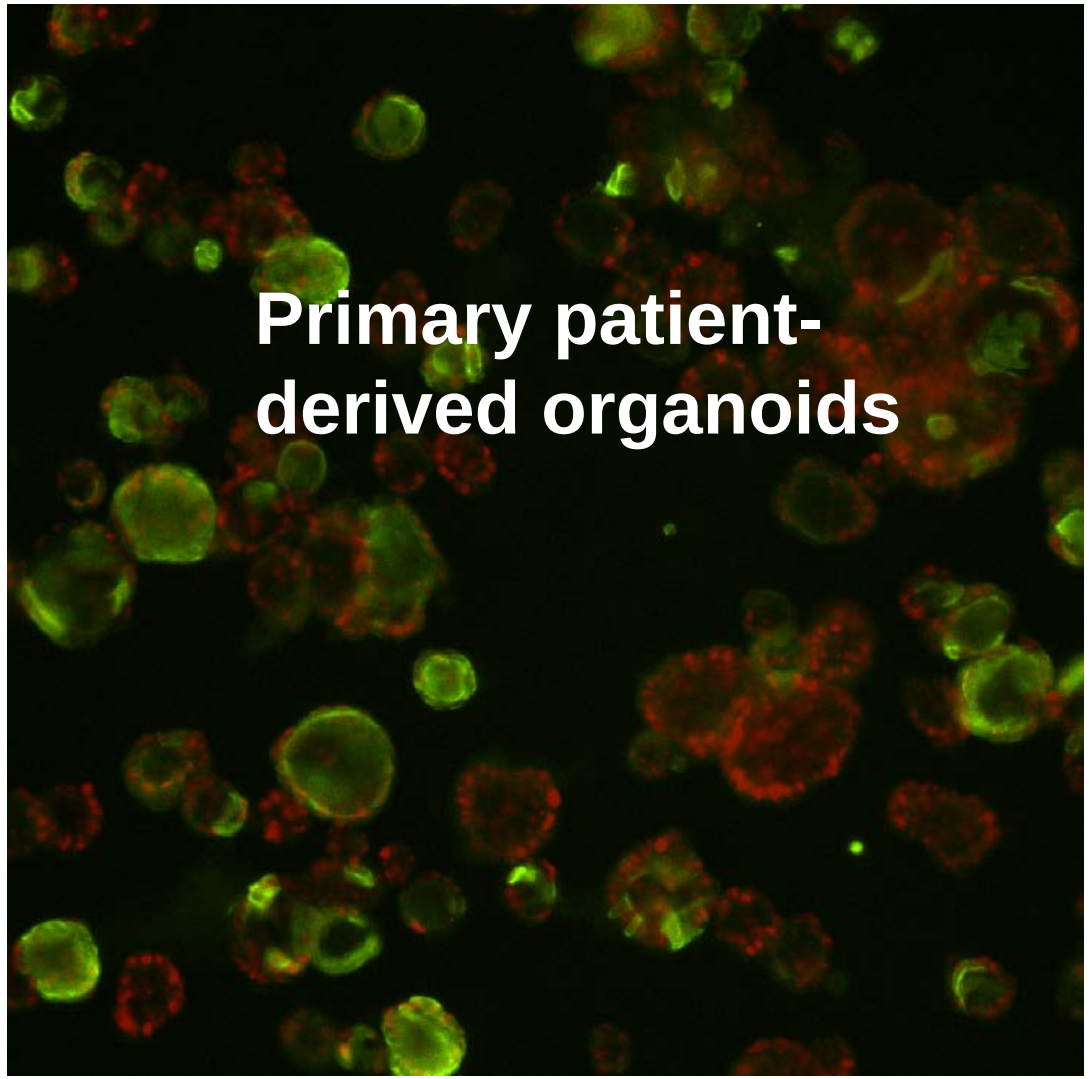
- 15X WGS of model, primary tumor, and normal tissue
- 150X WXS of model, primary tumor, and normal tissue
- RNA-seq of model and primary tumor

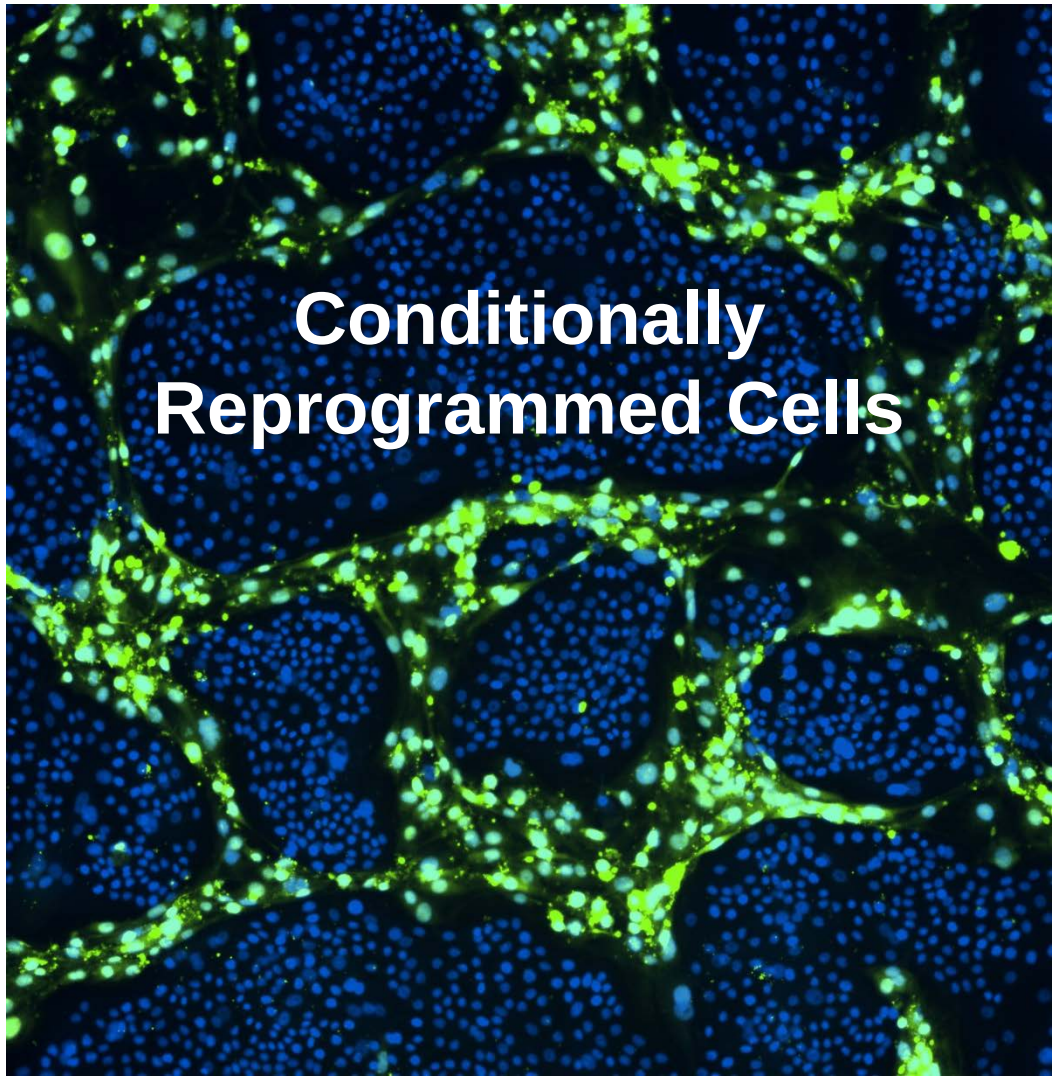
Clinical

- Disease diagnosis
- Patient demographics
- Treatment and outcomes



Advanced culture technologies





Shared features of advanced culture methods

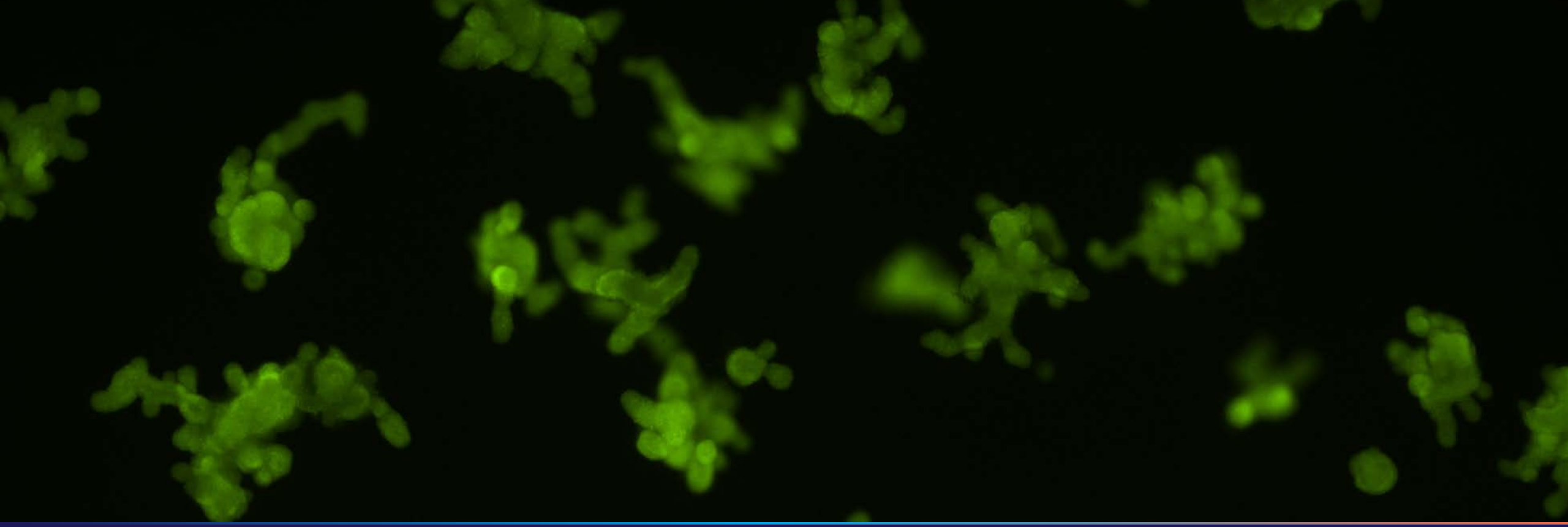
Permits growth and expansion

Limited starting material required

Genetically stable

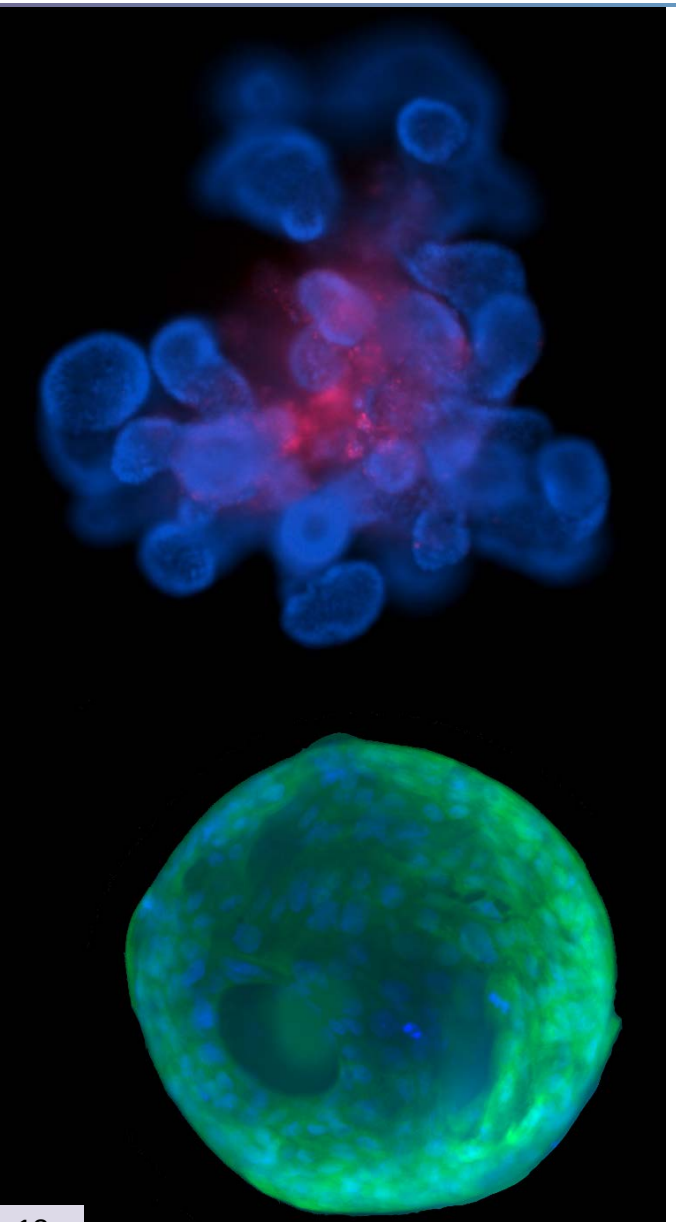
Maintain *in vivo* phenotype

Relatively high success rate

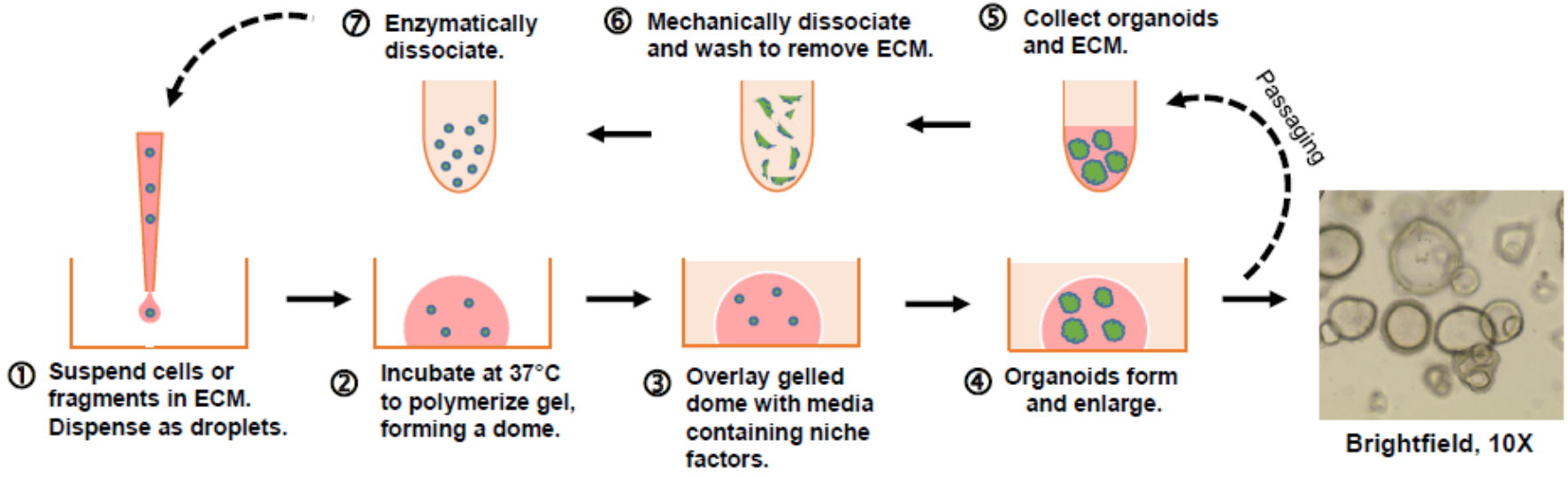


Primary tissue derived organoids

Organoid technology



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

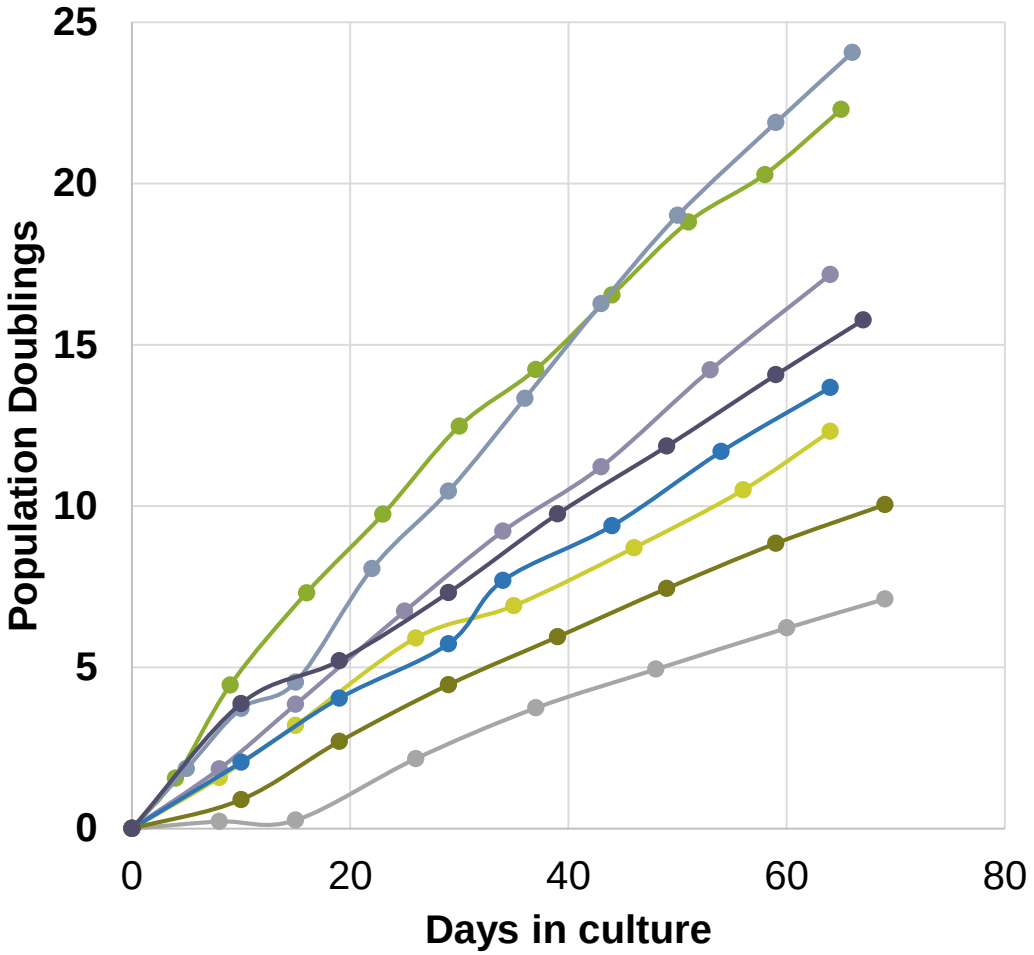


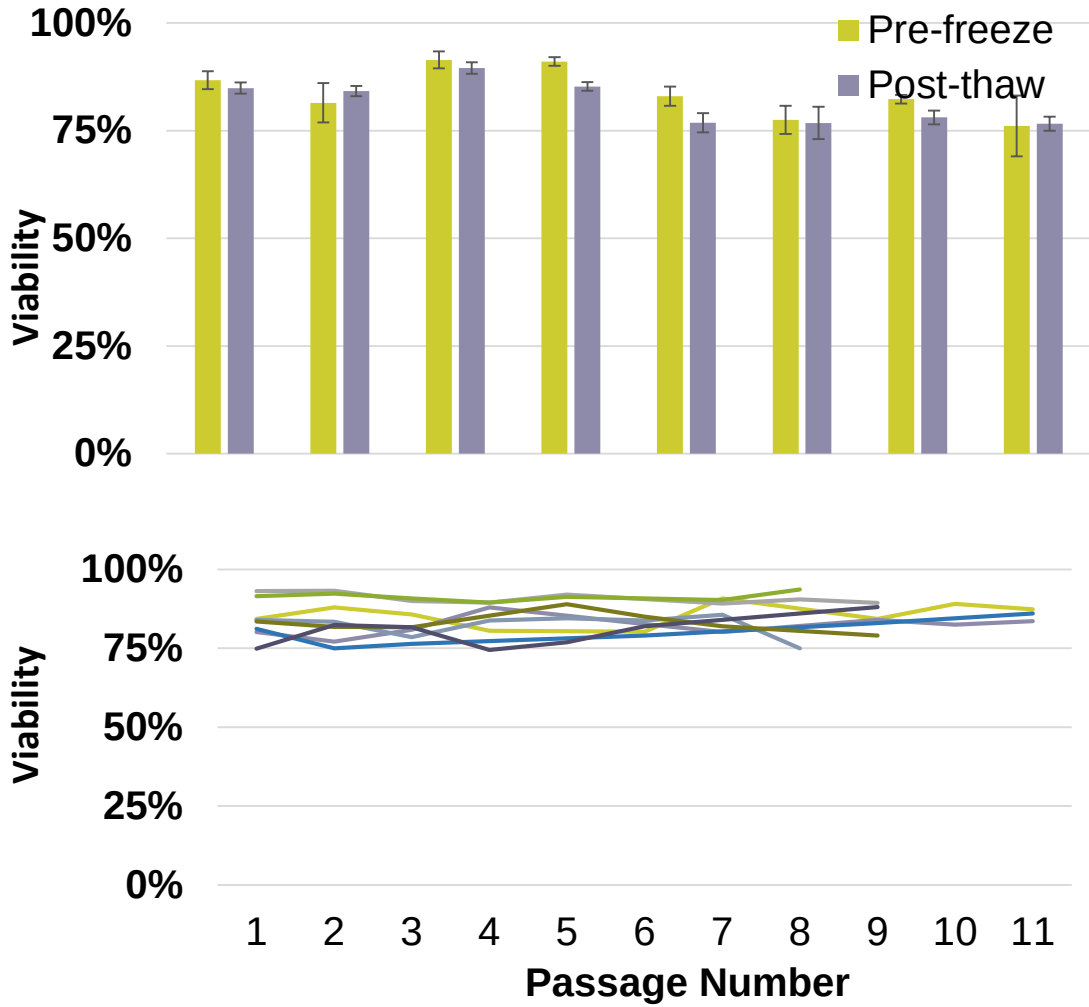
https://currentprotocols.onlinelibrary.wiley.com/doi/epdf/10.1002/cpcb.66

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 *in vitro*	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

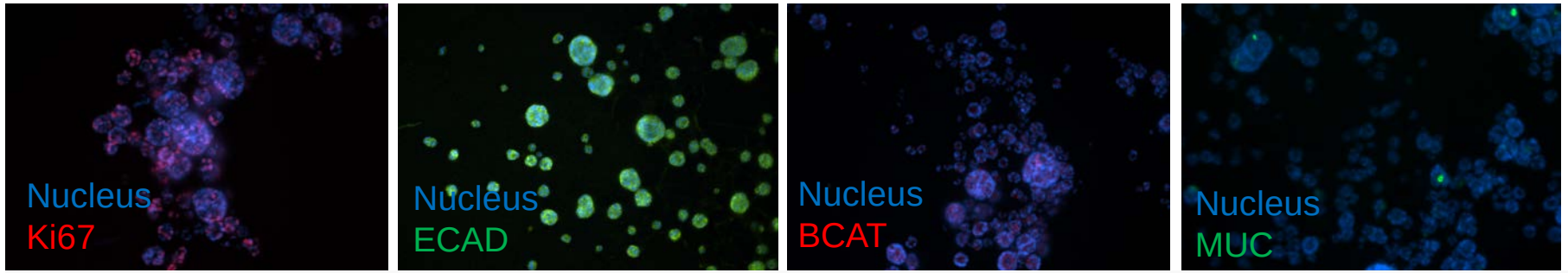
Organoids expansion, cryopreservation, and recovery



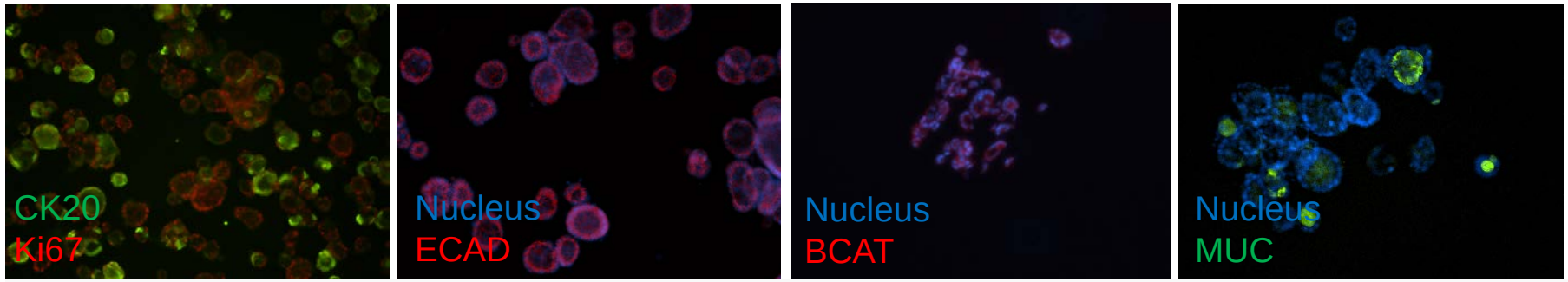


Organoids are amenable to standard lab assays

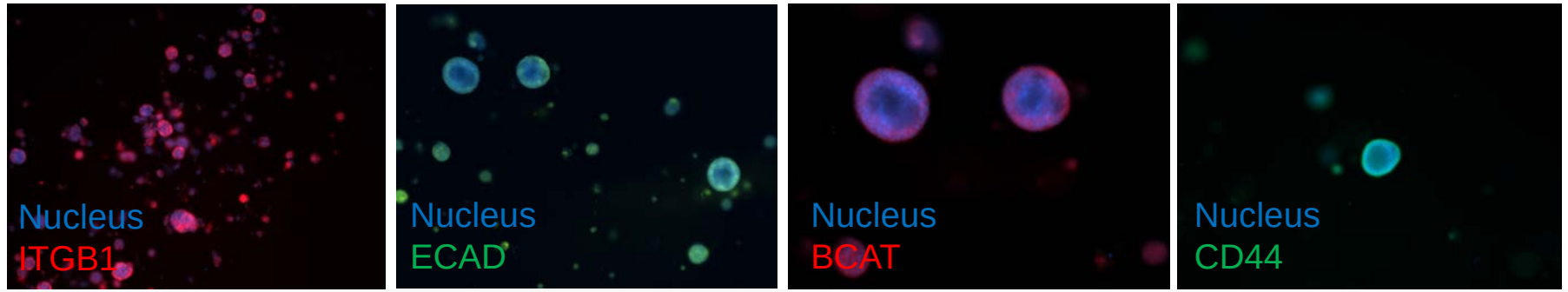
Esophageal adenocarcinoma



Colon adenocarcinoma



Lung adenocarcinoma



HCMI organoid models

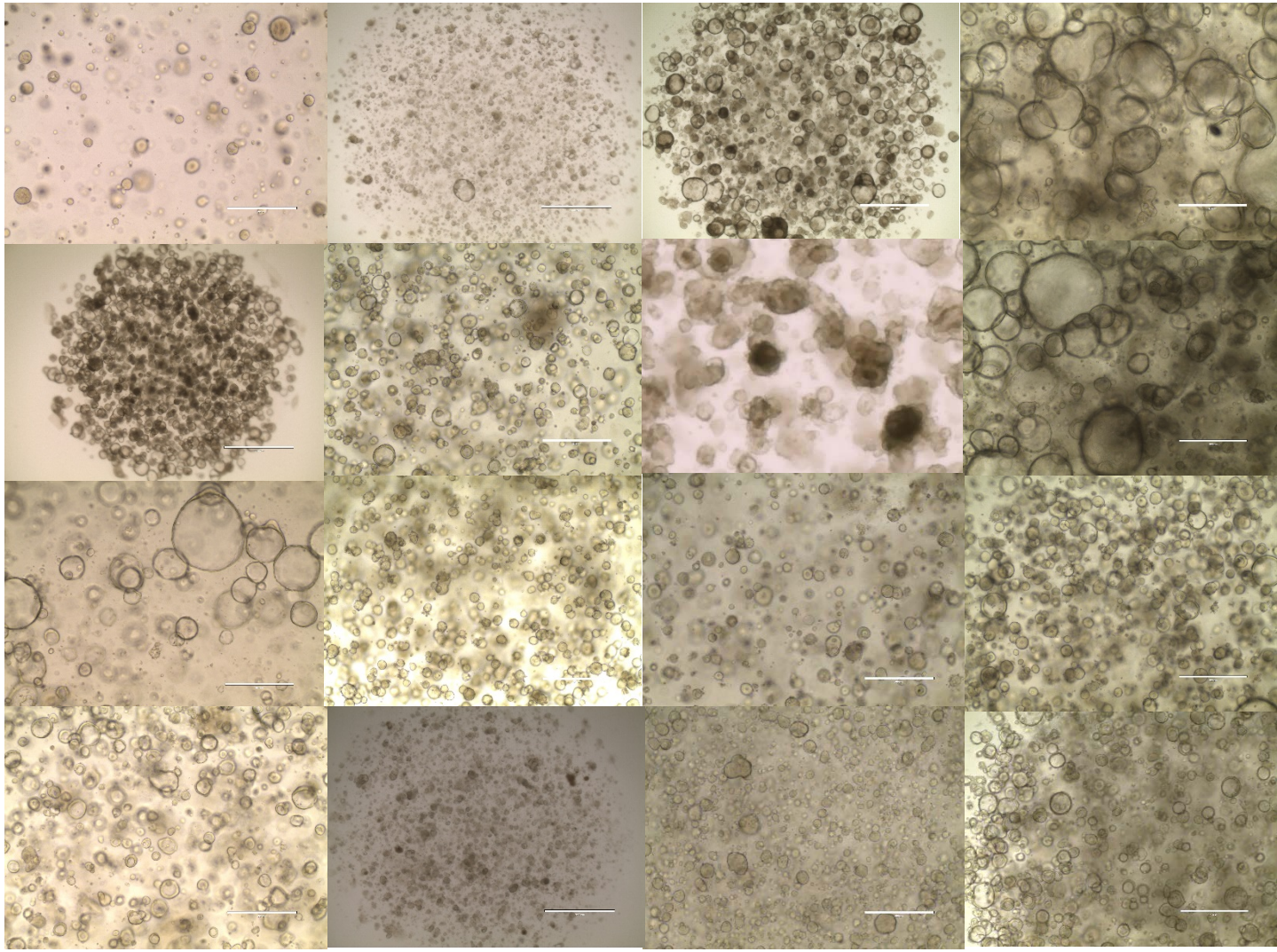
Types

- Adenocarcinoma
- Carcinoma

- Primary
- Recurrent
- Metastatic
- Pre-malignant

Tissues

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



16 unique models from various tissue

Not a comprehensive list

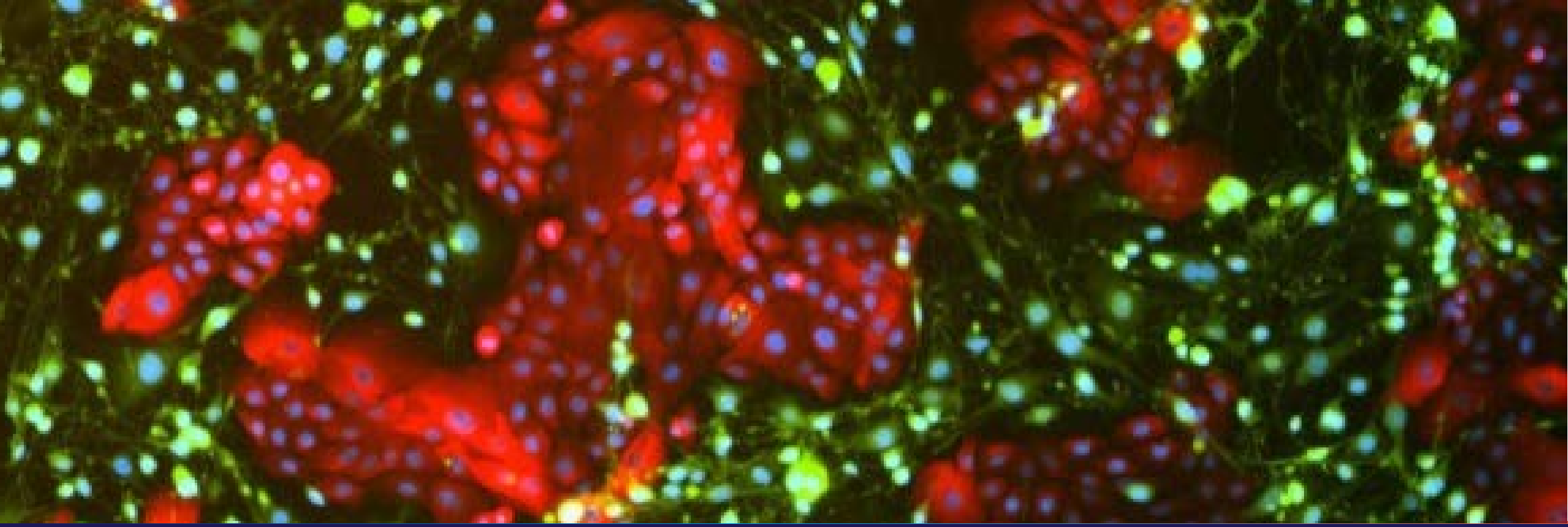
Organoid culture guide

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

ATCC



Conditionally reprogrammed cells

ATCC

Conditionally Reprogrammed Cells (CRC) Technology

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

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

PROTOCOL

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

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

[1]Department of Pathology, Georgetown University Medical Center, Washington, DC, USA. [2]Center for Cell Reprogramming, Georgetown University Medical Center, Washington, DC, USA. [3]Department of Oncology, Georgetown University Medical Center, Washington, DC, USA. [4]Department of Epigenetics and Molecular Carcinogenesis, University of Texas MD Anderson Cancer Center, Smithville, Texas, USA. [5]Department of Dermatology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA. [6]Department of Radiation Medicine, Georgetown University Medical Center, Washington, DC, USA. [7]Department of Cell Biology and Physiology, The University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA. [8]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

RESEARCH ARTICLES

CANCER THERAPY

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

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

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.

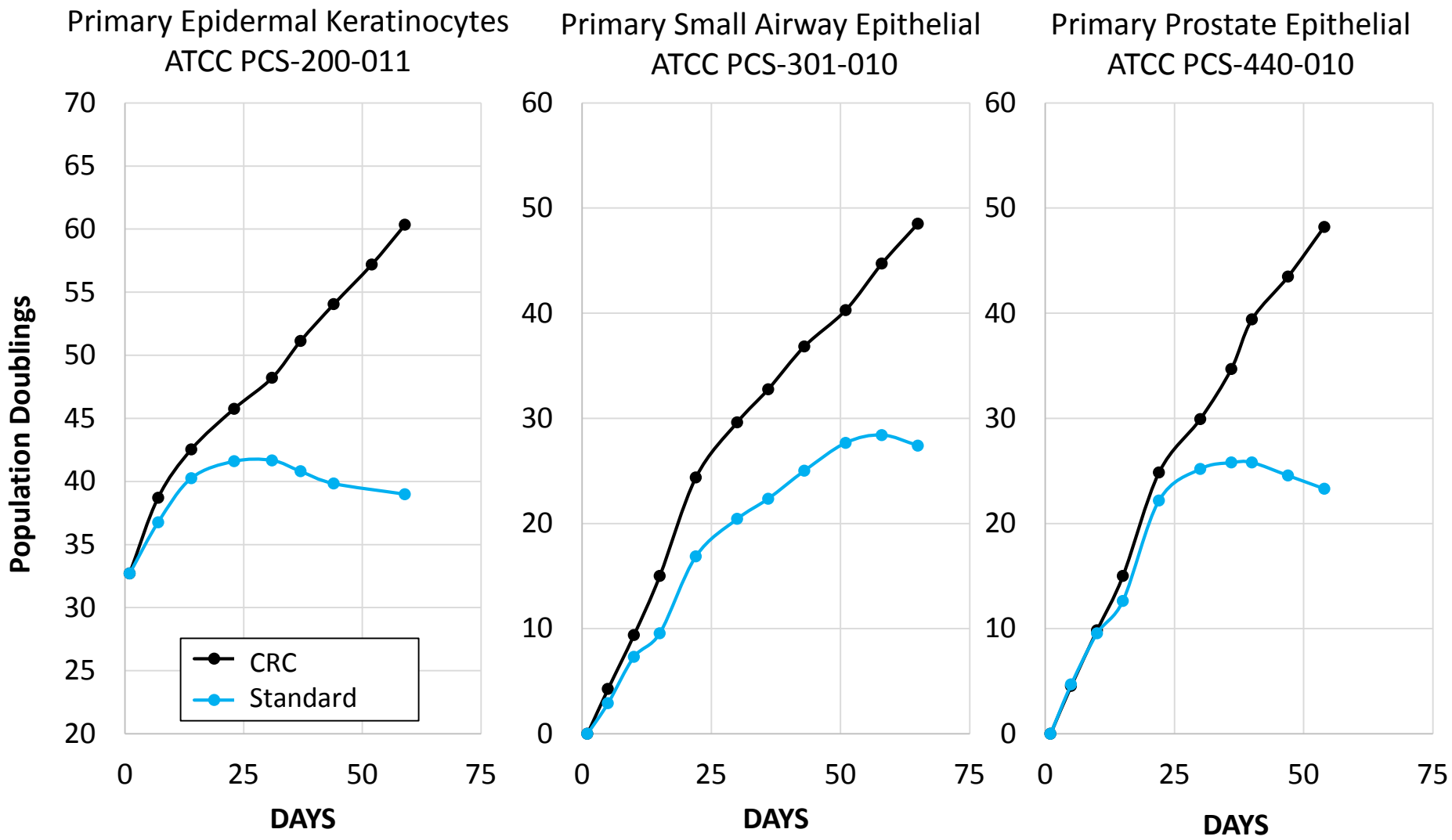
www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2016

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

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

ATCC

CRC culture can prevent senescence of primary cells



HCMI CRC and other non-organoid models

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

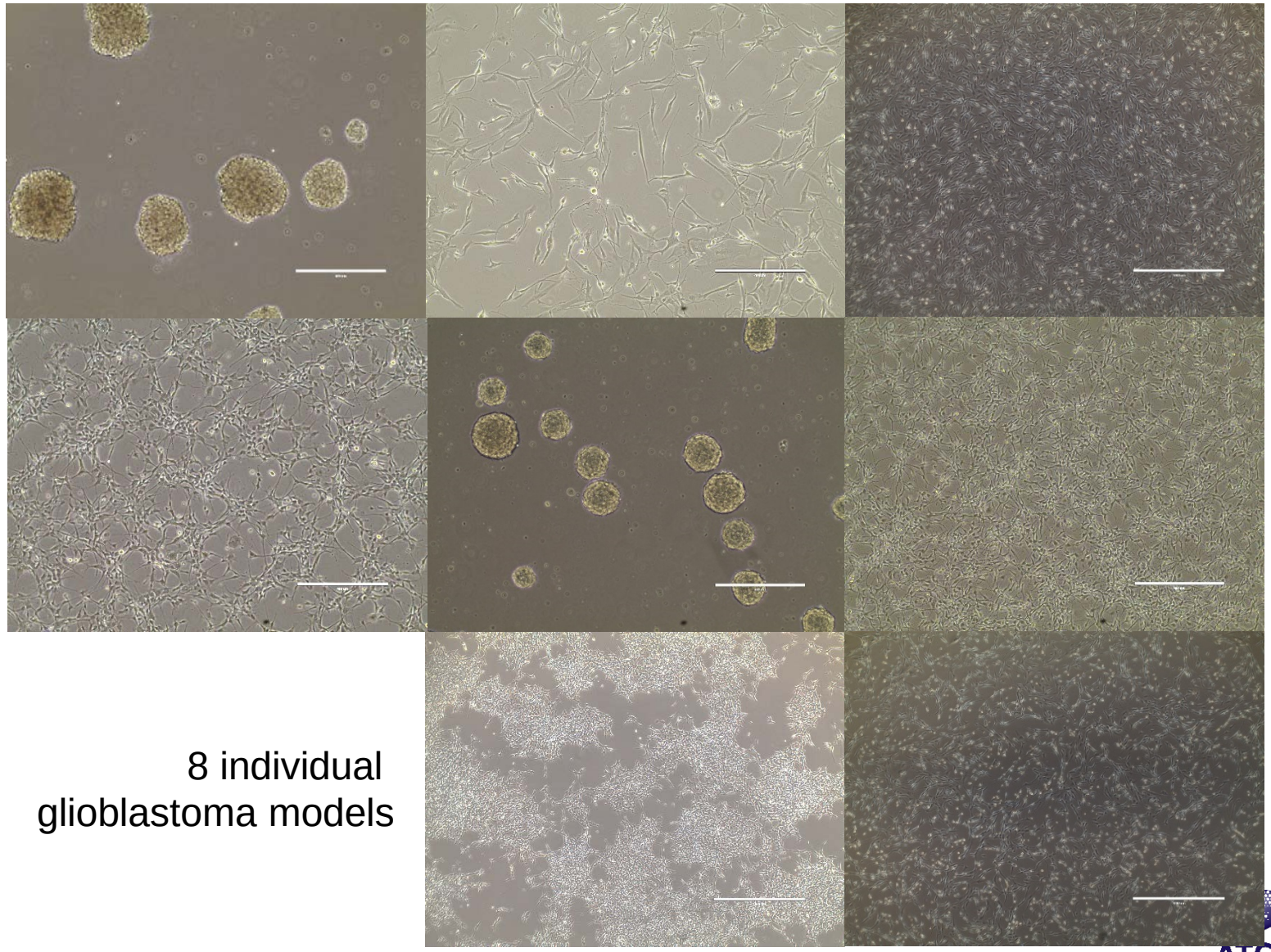
Tissues

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

Types

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

Not a comprehensive list



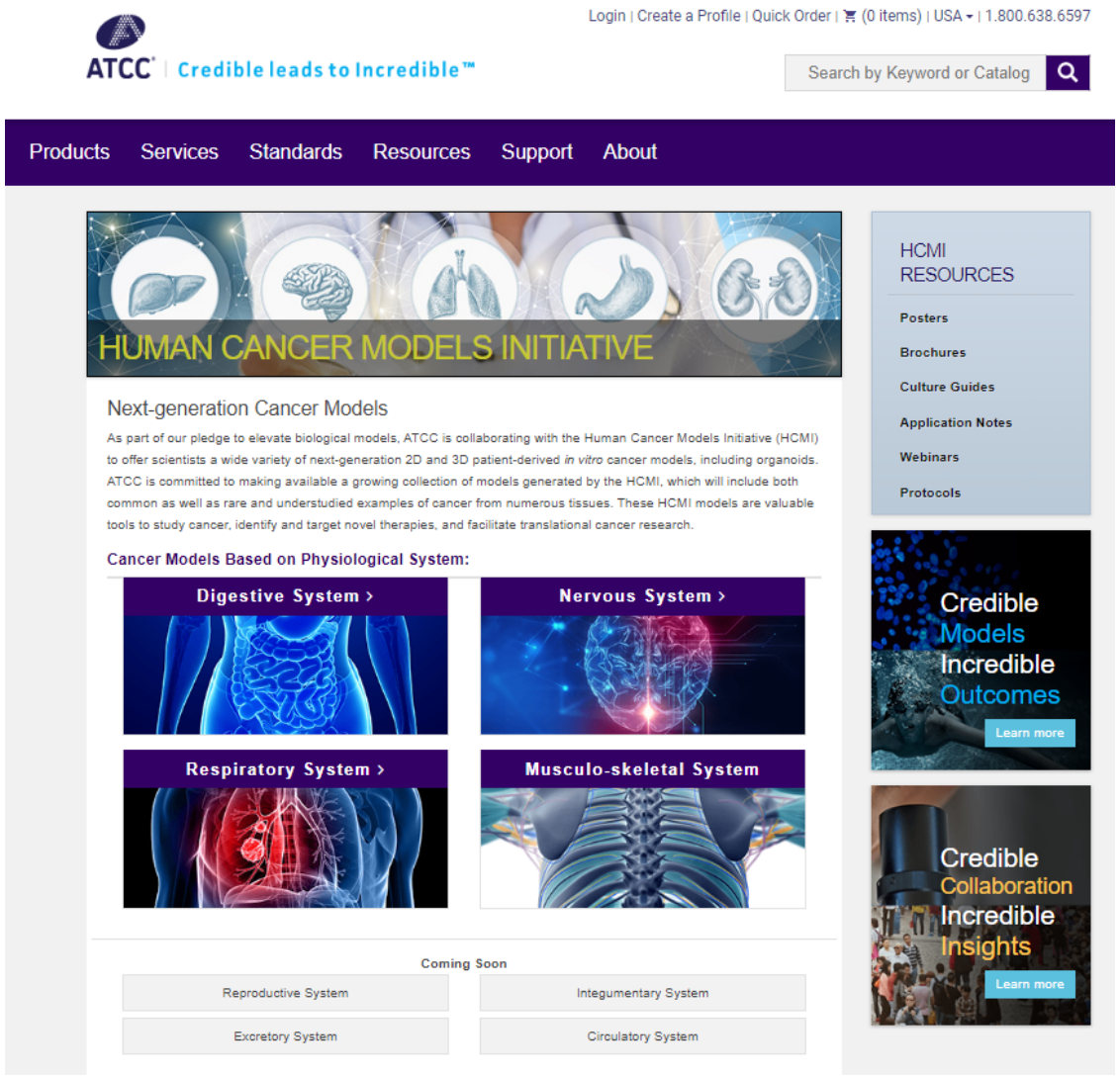
8 individual glioblastoma models

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?
Organoid*	No	3D embedded	Multiple	No	Yes
Conditional Reprogramming	Yes	2D adherent	Multiple	No	No
SmGM-2	Yes	2D adherent and suspension	Bone	No	No
RETM	Yes	2D adherent	Brain	No	No
Neurocult NS-A	Yes	2D adherent and suspension	Brain	Yes	Sometimes

*There are multiple organoid media formulations

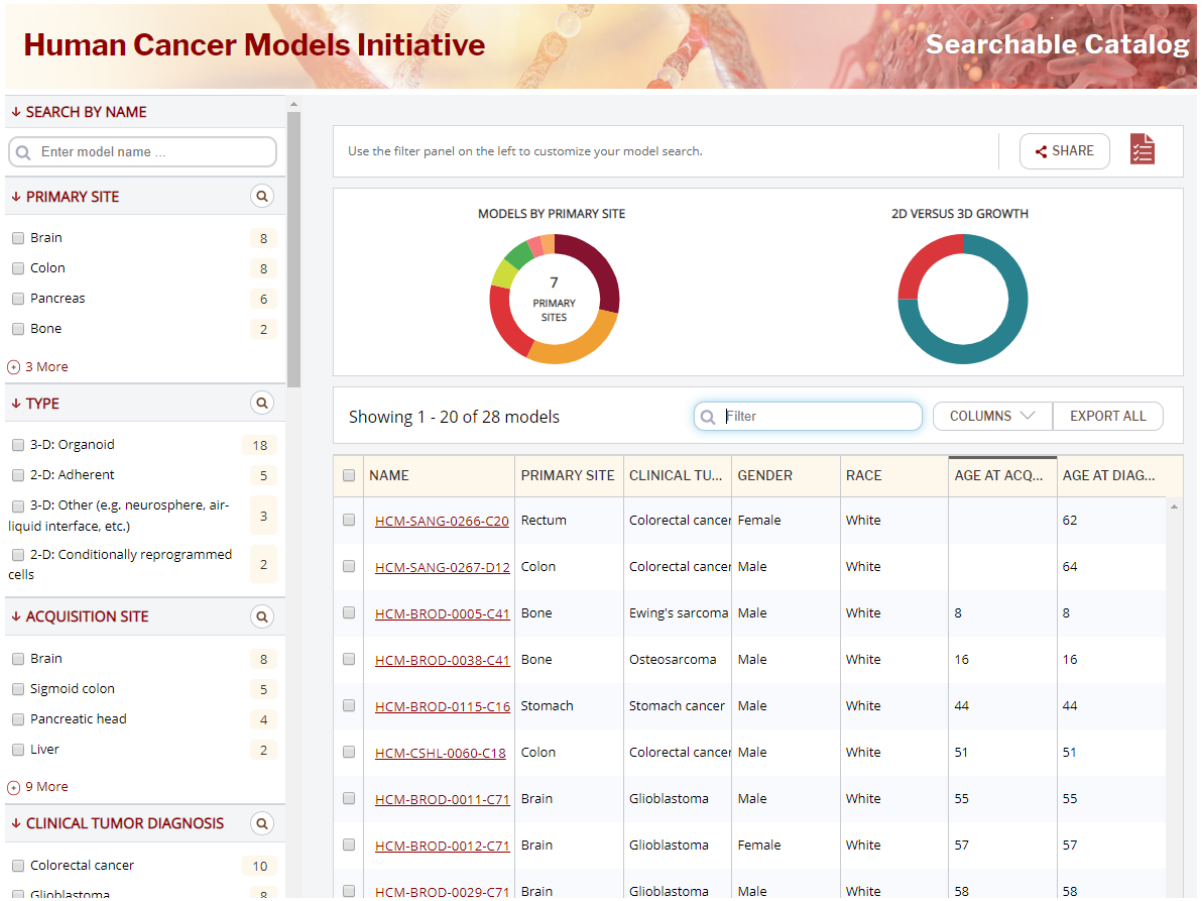
Model resources and data access



www.atcc.org/HCMI

- 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

Model resources and data access

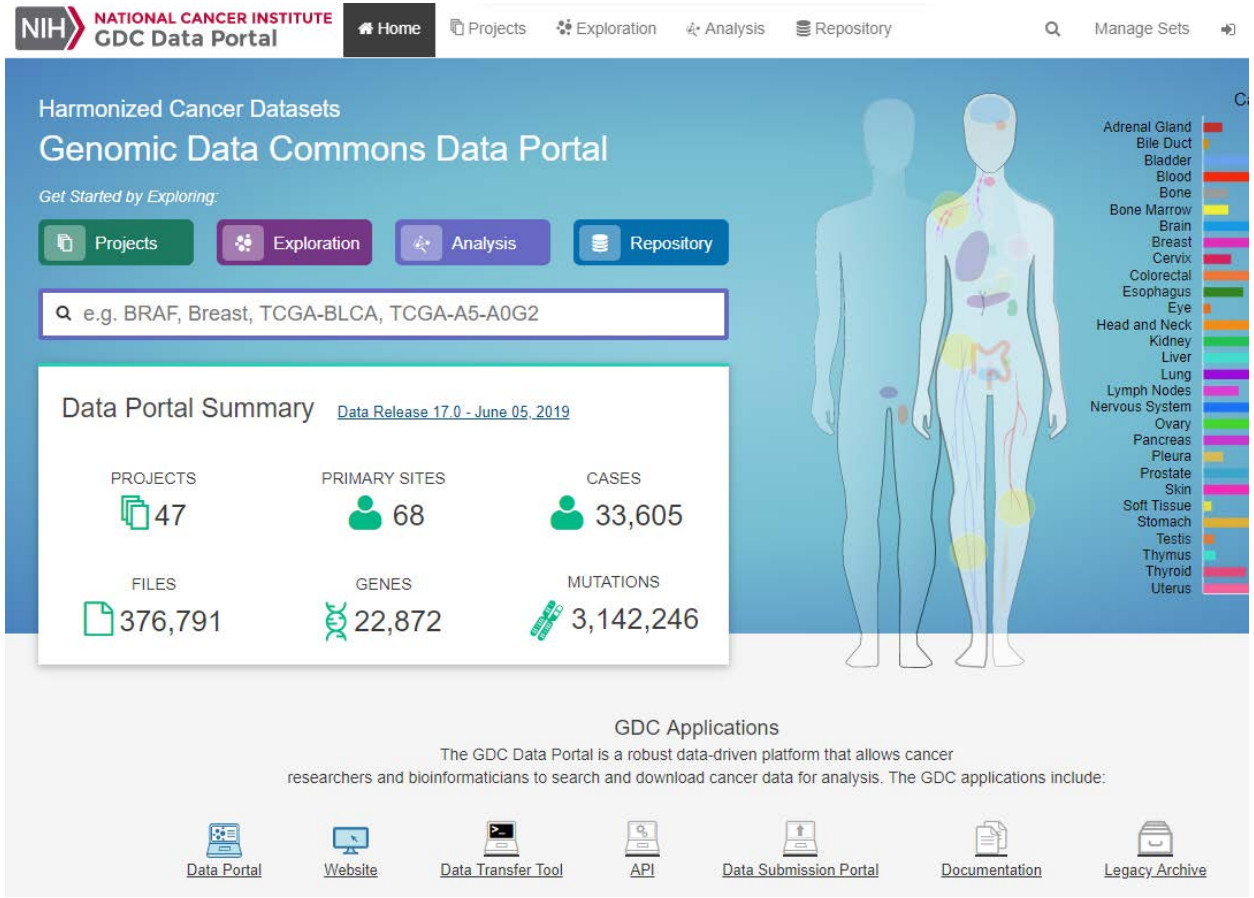


- NCI managed website
- Integrates clinical, model, and genomic information.
- Search for models of interest using various filters
  - Primary tumor site/acquisition site
  - Model type
  - Tumor diagnosis/stage/grade/histological type
  - Gender/age/ethnicity
  - Etc.
- Links out to clinical and genomic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

hcmi-searchable-catalog.nci.nih.gov

ATCC

Model resources and data access

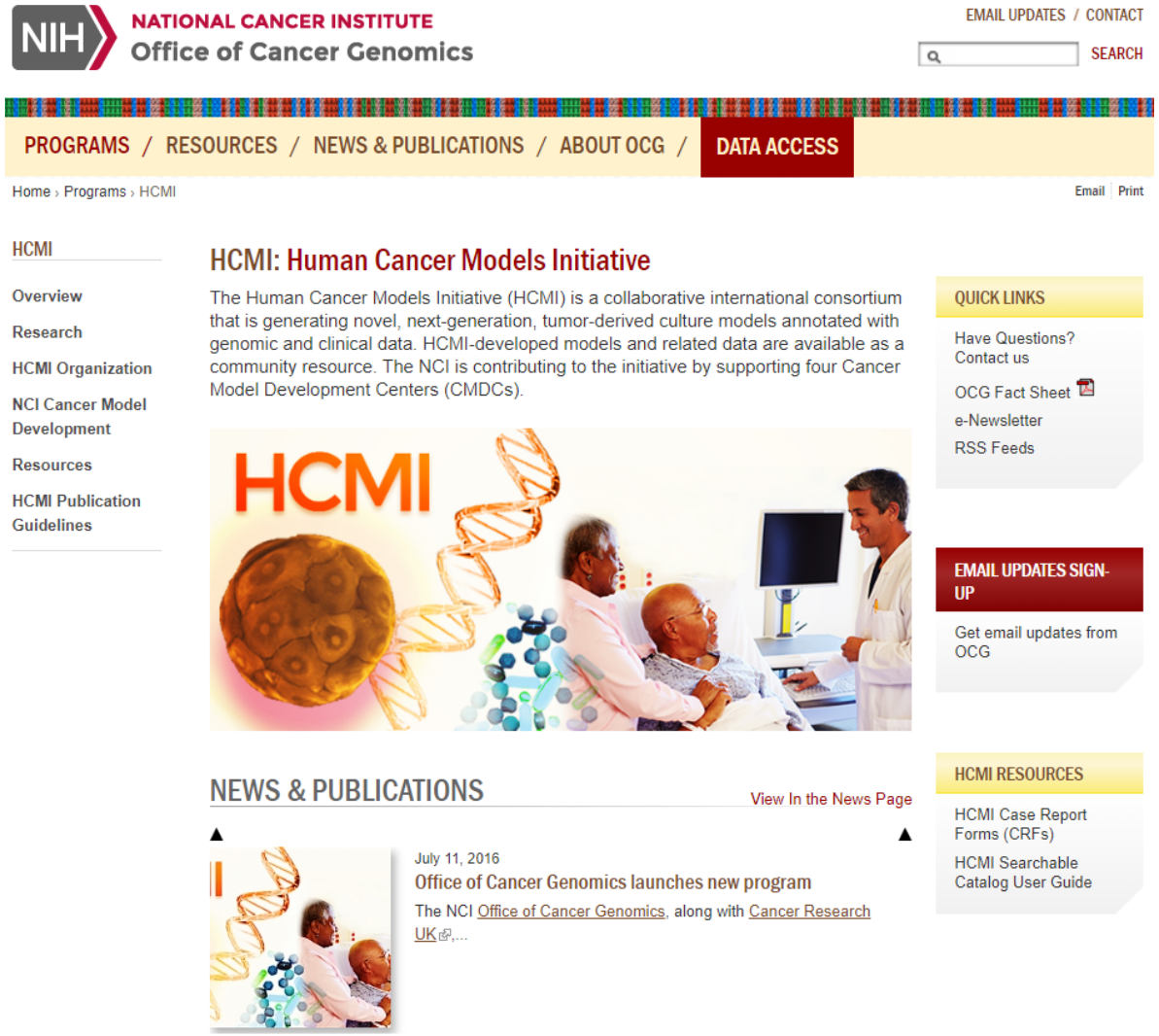


- NCI managed website
- Search and download cancer related datasets for analysis
- Navigate to the “HCMI-CMDC” project for HCMI specific datasets
- Download WGS/WXS/RNAseq data
  - Aligned reads, gene expression, SNVs

portal.gdc.cancer.gov

ATCC

Model resources and data access



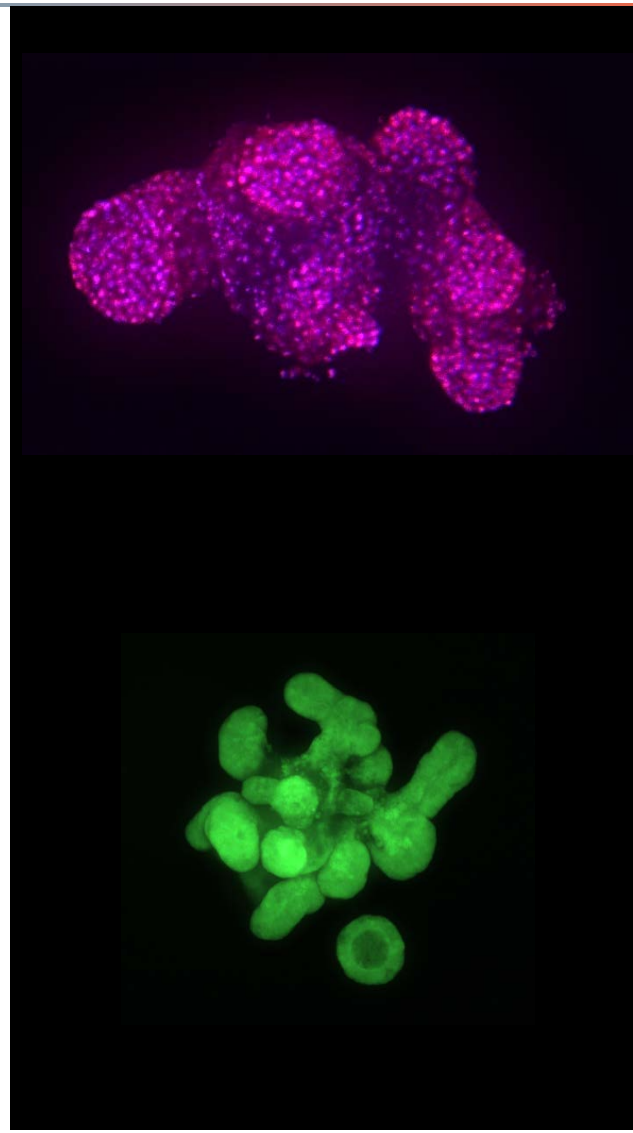
- NCI managed website
- Background information on the HCMI program and organization
- Useful documents
  - Case Report forms for patient enrollment and follow-up
  - HCMI Searchable catalog user guide
  - Informed consent template

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

ATCC

Model availability

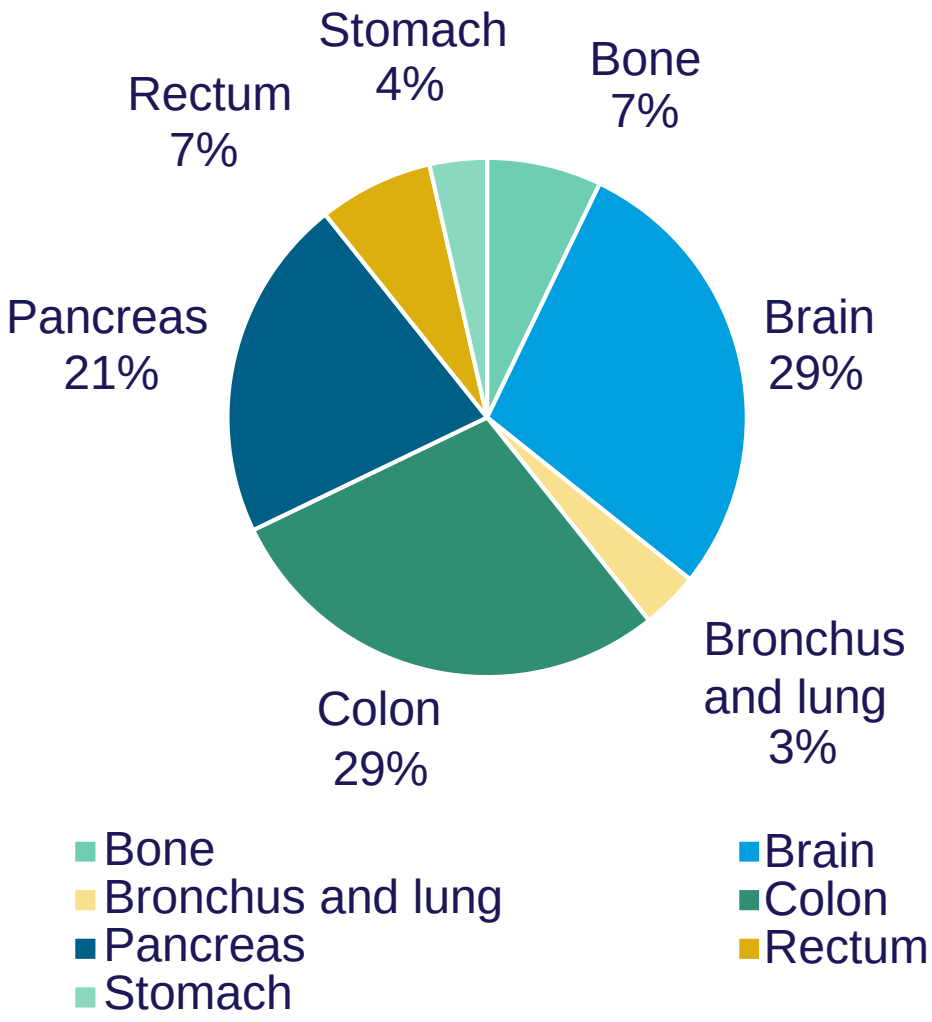
- 28 models currently available from ATCC
- Additional models will be made available on a rolling basis, expect releases every 1-2 months.
- Pipeline includes mammary carcinoma organoids, primary and metastatic esophageal adenocarcinoma organoids, additional colon, pancreas and glioblastoma models.

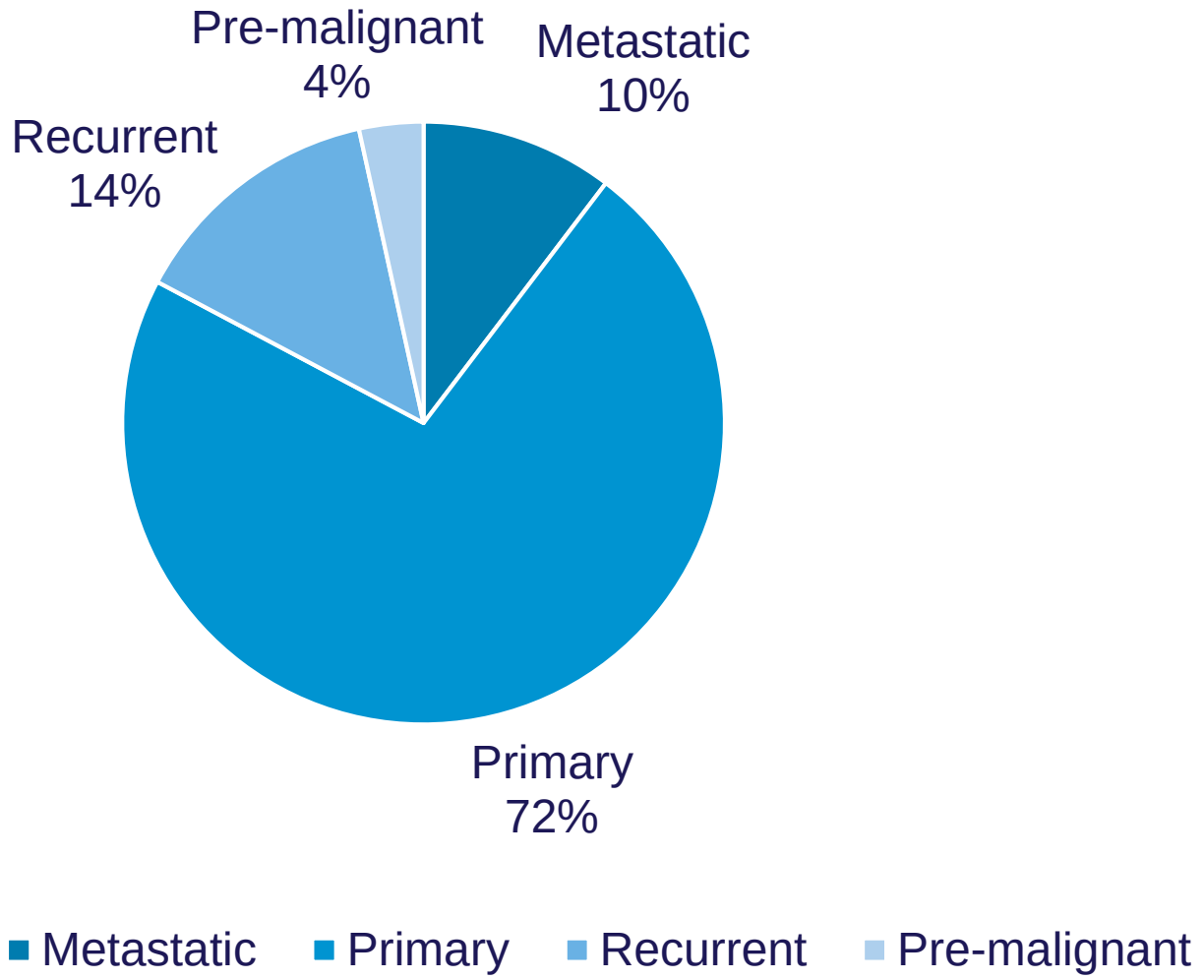


ATCC HCMI model distribution material

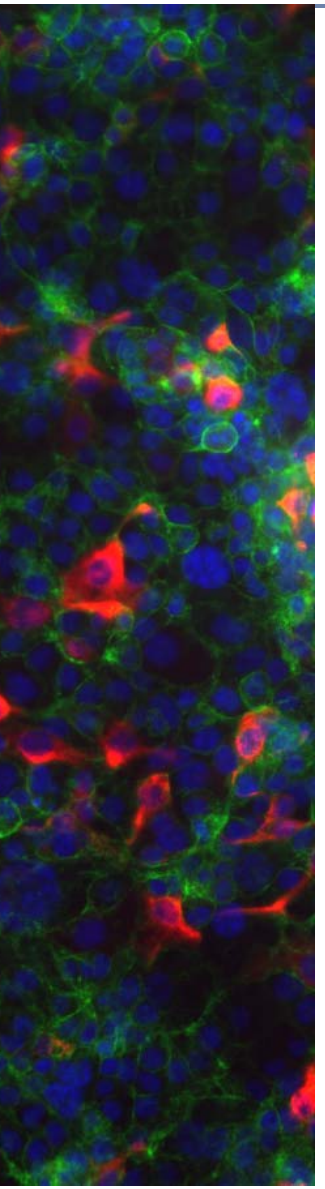
- Target ≥1x10^6 viable cells per vial
- Product documentation includes
  - Recommended growth medium
  - Recommended culture maintenance parameters
- QC
  - Post-thaw cell count and viability
  - Mycoplasma testing
  - Sterility testing (bacteria, fungi and yeast)
  - Species determination
  - STR fingerprinting
  - 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

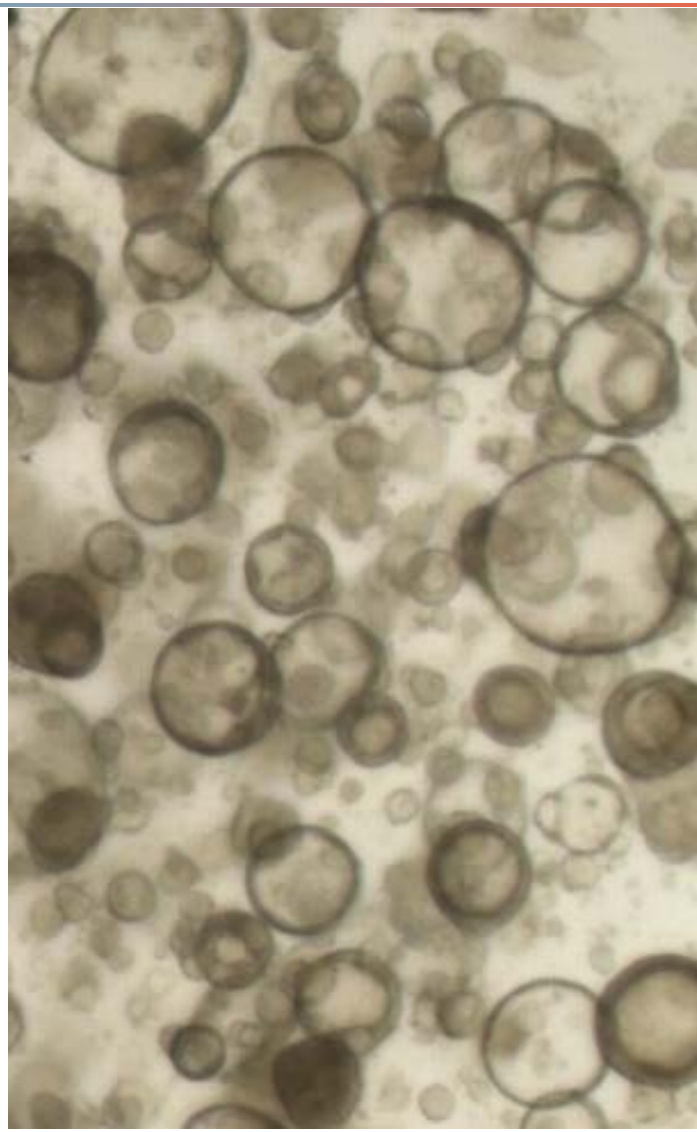
Part No.	Description	Type
PDM-3	Primary Adenocarcinoma of lung	Organoid
PDM-127	Metastatic Ewing sarcoma	2D adherent
PDM-114	Primary Osteosarcoma	2D adherent
PDM-16	Primary Glioblastoma	2D adherent
PDM-17	Primary Glioblastoma	2D adherent
PDM-18	Primary Glioblastoma	Suspension
PDM-20	Primary Glioblastoma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

www.atcc.org/HCMI

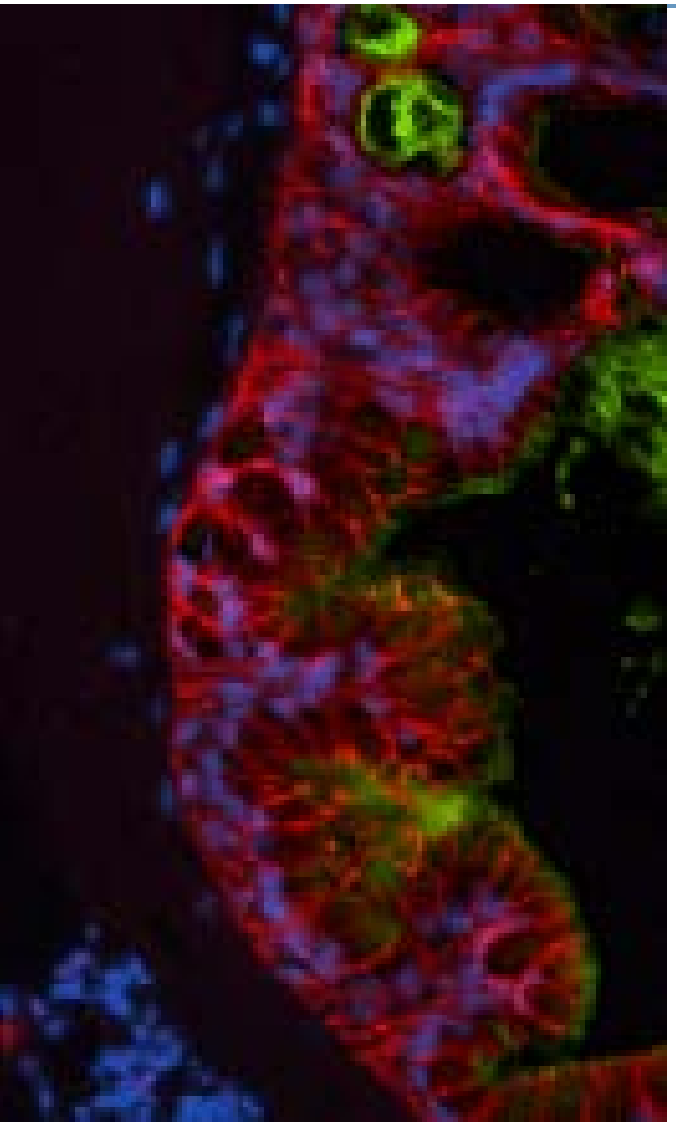
Model availability

- 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

- 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

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