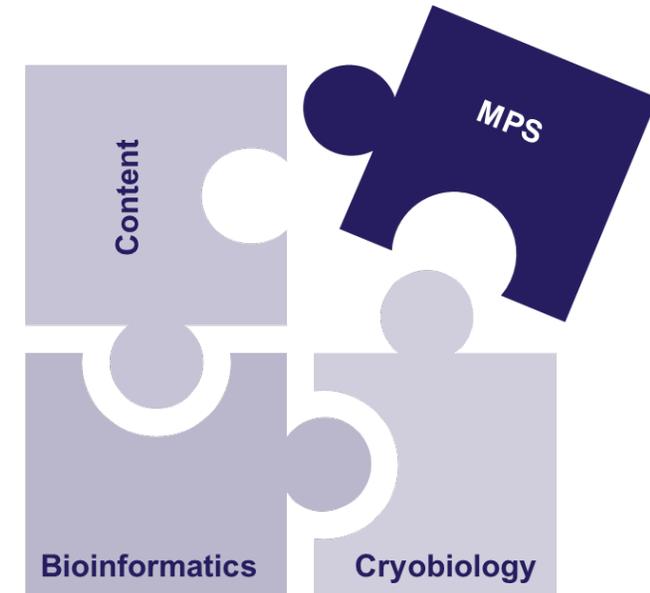
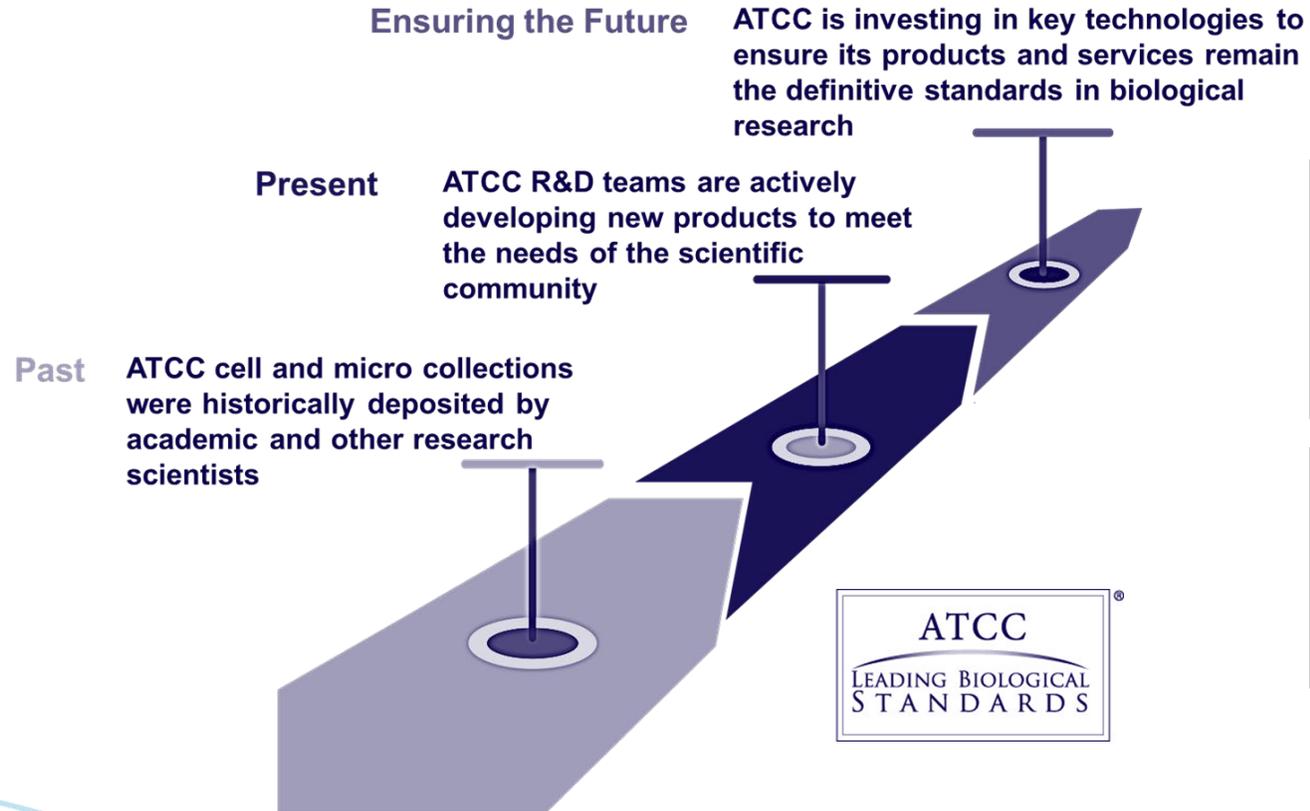


# Mini Organs, Major Insights: Toxicology Goes 3-D

Carolina Lucchesi, PhD  
Principal Scientist  
Head of MPS Department  
ATCC

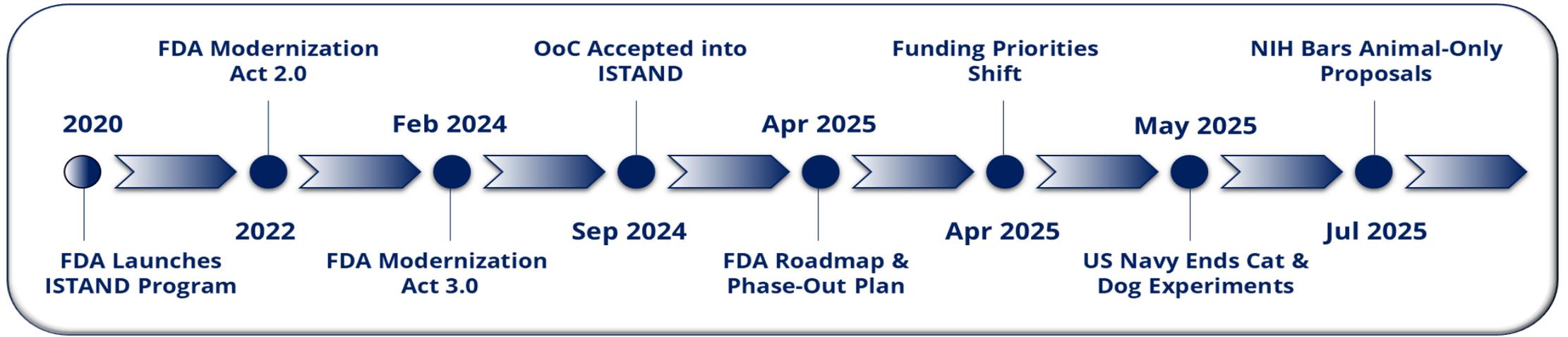


# Modernization of the ATCC In Vitro Cell Model Portfolio

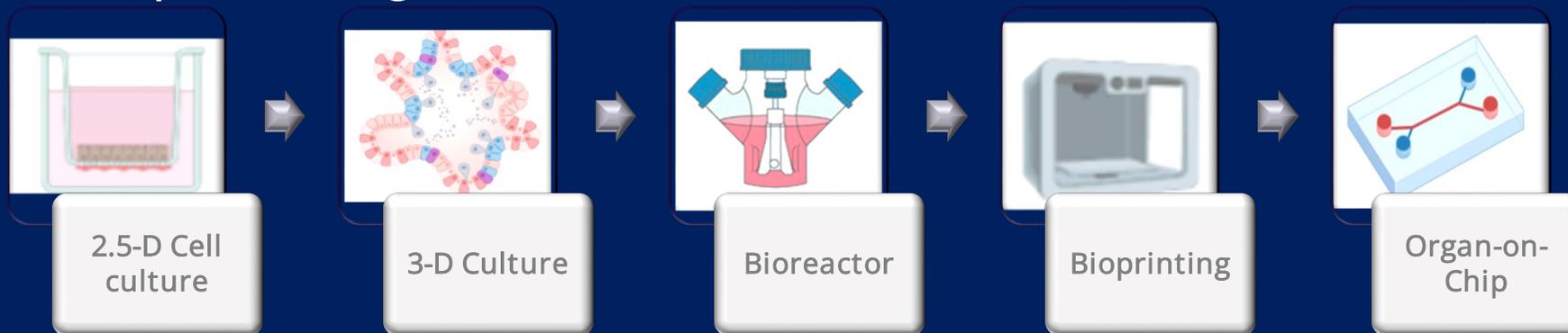


Research & Development

# Overview



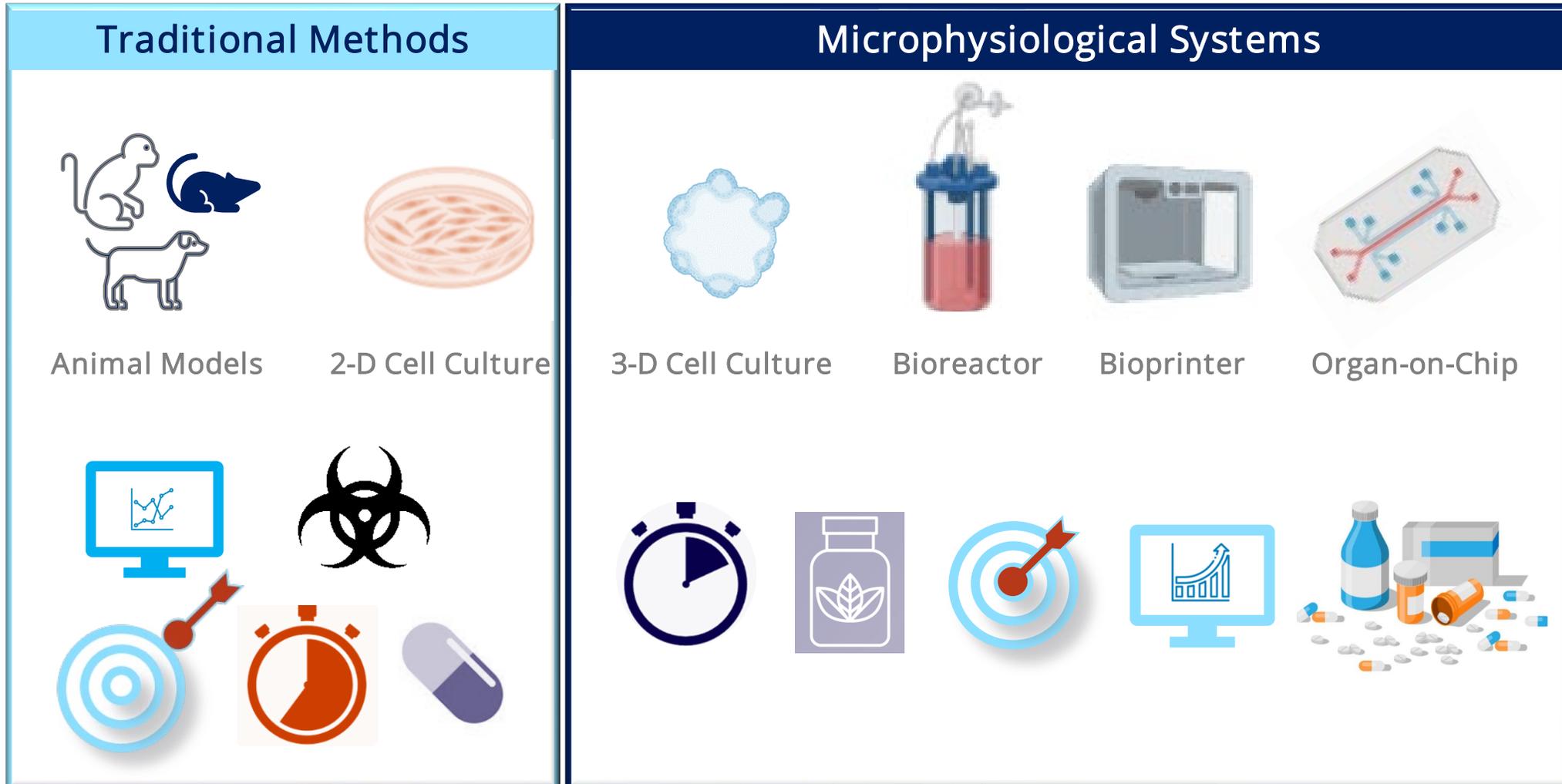
Microphysiological systems (MPS) comprise a number of bioengineering breakthroughs that reproduce organ architecture and function in vitro. (International MPS Society)



Created with BioRender.com

# Investigative Methods

## Past, present, and future of research



Adapted from Organ-on-a-Chip Technologies Report 2018 - NC3Rs and Kim, S. (2021) using BioRender.

# The Evolution of Cell Culture

## Cell culture shaping the future of science

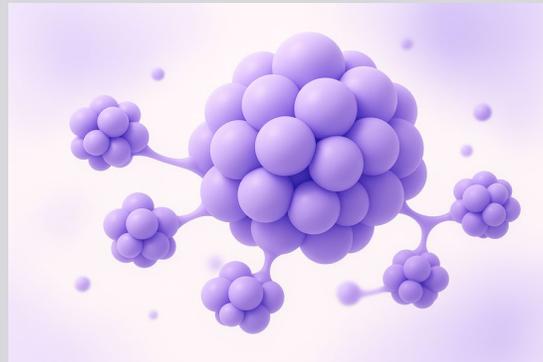


### 2-D Cell culture



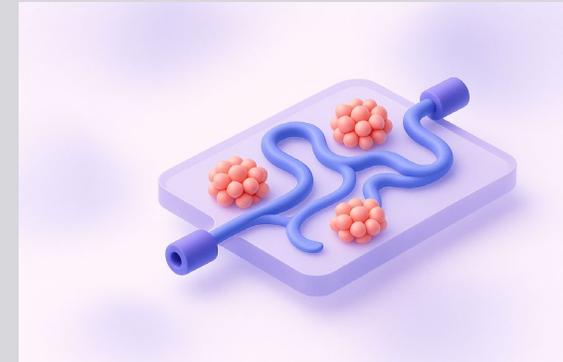
Foundation and Limitation

### 3-D Cell Culture



A new dimension

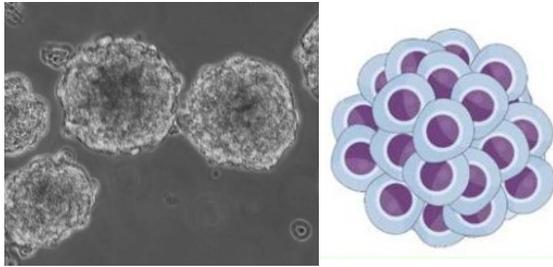
### Organ-on-Chip



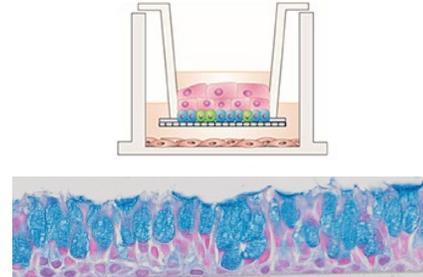
The future of cell culture

# Advanced In Vitro Models

### Spheroids



### Co-Culture Inserts



ATCC

### Bioprinted Tissue

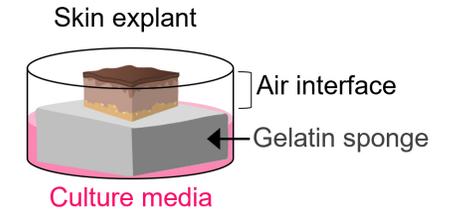


3D Bioprinted Tissues

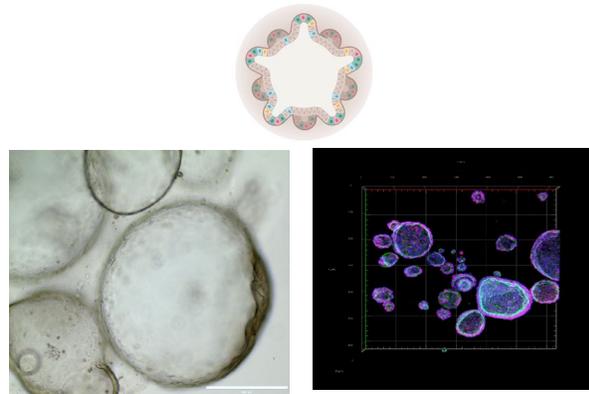
Biofabricated Constructs

[Theconversation.com/3d-printing-of-body-parts](https://theconversation.com/3d-printing-of-body-parts)

### Ex-vivo

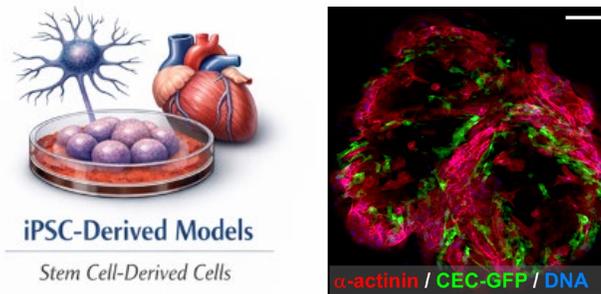


### Organoids



ATCC

### Cardioid

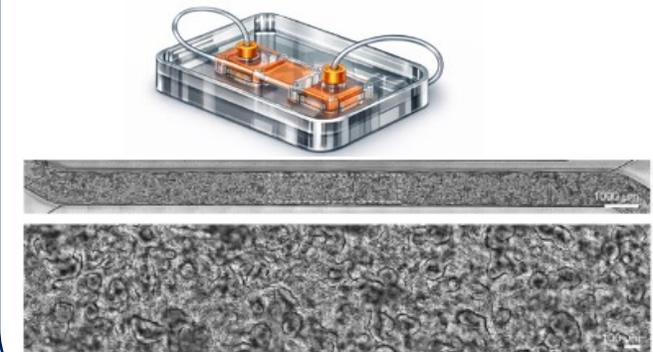


iPSC-Derived Models

Stem Cell-Derived Cells

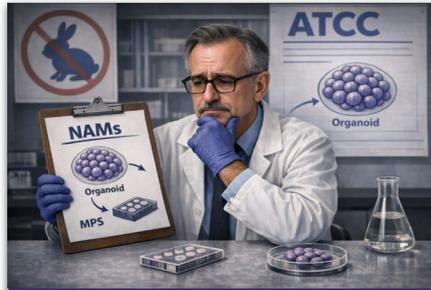
Ghosheh M et al 2023  
[doi.org/10.1038/s41551-023-01071-9](https://doi.org/10.1038/s41551-023-01071-9)

### Organ-on-Chip

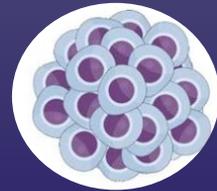


Kasendra et al 2018 [doi.org/10.1038/s41598-018-21201-7](https://doi.org/10.1038/s41598-018-21201-7)

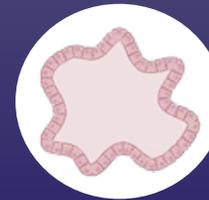
# Advanced In Vitro Models



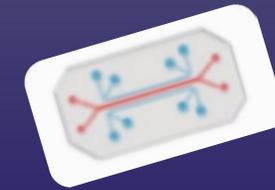
## Spheroids



## Organoids

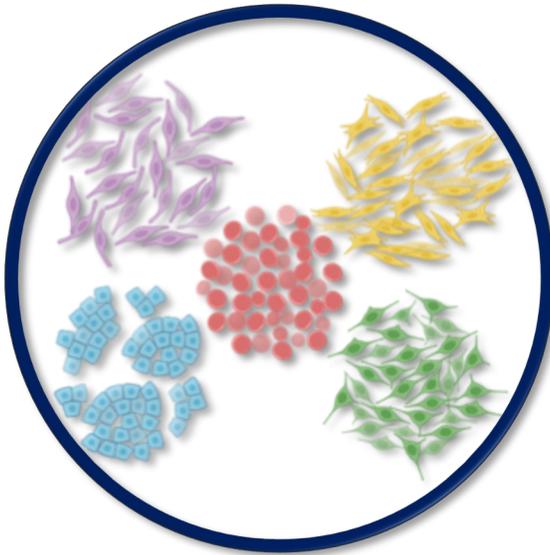


## Organ-Chips



<b>Description</b>	<ul style="list-style-type: none"> <li>3-D cell aggregates (typically mono-culture)</li> </ul>	<ul style="list-style-type: none"> <li>Self-organized 3-D tissues derived from stem cells (heterogenous)</li> </ul>	<ul style="list-style-type: none"> <li>Microfluidic device recapitulating the tissue vascular interface</li> </ul>
<b>Cell types</b>	<ul style="list-style-type: none"> <li>Cancer cell lines</li> <li>Primary cell</li> </ul>	<ul style="list-style-type: none"> <li>Stem cells (ASC, iPSC)</li> </ul>	<ul style="list-style-type: none"> <li>Primary</li> <li>iPSC</li> <li>Organoids</li> <li>Cell lines</li> </ul>
<b>Use Case</b>	<ul style="list-style-type: none"> <li>Screening (cancer, efficacy, toxicity)</li> </ul>	<ul style="list-style-type: none"> <li>Disease modeling</li> <li>Personalized medicine</li> <li>Efficacy testing</li> </ul>	<ul style="list-style-type: none"> <li>Complex disease modeling</li> <li>High-fidelity toxicity</li> <li>Efficacy testing</li> </ul>
<b>Throughput</b>	Medium-High	Medium	Low
<b>Mechanical Forces</b>	✗	✗	✓
<b>Complexity</b>	Low	Medium	High

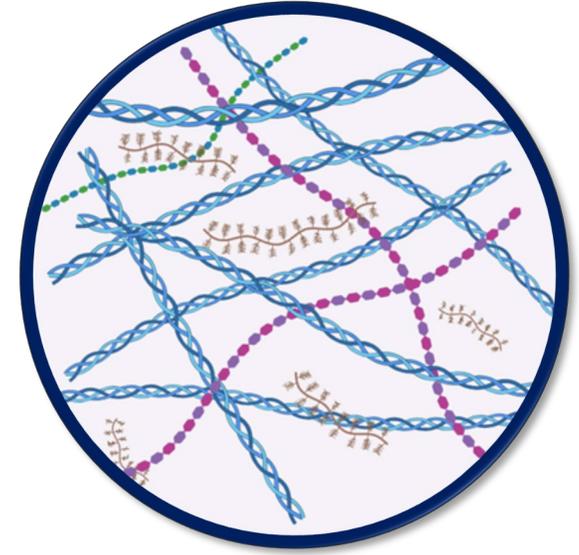
# Required Biological Resources



**Cells**



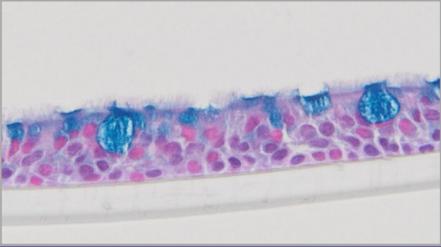
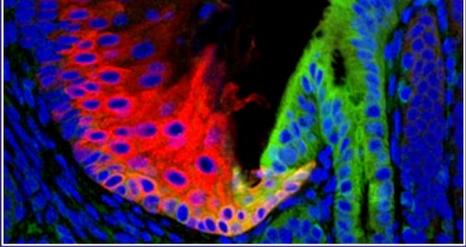
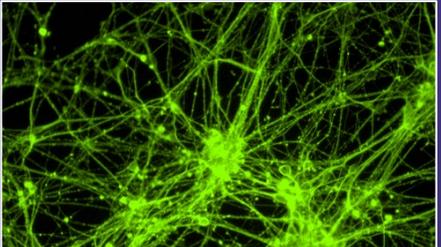
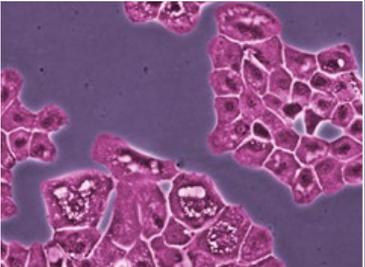
**Media**



**ECM**

Biological components required to build an advanced model

# Cell Type of Choice

Primary Cells	Organoids	iPS Cells	Cell Lines
<ul style="list-style-type: none"><li>• Most accepted cell types due to the physiological relevance</li><li>• Maintain many of the important markers and functions</li><li>• Higher predictability</li><li>• Donor-donor variability</li><li>• Finite lifespan and limited expansion capacity</li><li>• Difficult to preserve some tissue types (alveolus, cardiomyocytes, neurons)</li></ul>	<ul style="list-style-type: none"><li>• Similar composition and architecture to primary tissue</li><li>• Stable system for extended cultivation</li><li>• Well accepted for functional assays</li><li>• Need experienced users to culture and maintain</li></ul>	<ul style="list-style-type: none"><li>• Advantages of precision medicine</li><li>• It might maintain many of the important markers and functions</li><li>• Multiple cell types from the same donor</li><li>• Need experienced users to culture and maintain</li><li>• Long-term culture</li><li>• Preservation is an issue</li><li>• Poor differentiation/maturation</li></ul>	<ul style="list-style-type: none"><li>• Highly proliferative</li><li>• Easier to culture, and transfect</li><li>• Differ genetically and phenotypically from their tissue origin</li><li>• Accepted for specific functions, i.e., Caco-2 is well accepted for drug transporters studies, however, it lacks physiological CYP activities.</li></ul>
 <p data-bbox="206 1186 545 1215">Bronchial Epithelial Cells</p>	 <p data-bbox="779 1186 1169 1215">Esophagus Cancer Organoid</p>	 <p data-bbox="1411 1186 1735 1215">Neural Progenitor Cells</p>	 <p data-bbox="2040 1186 2303 1215">Chordoma Cell Line</p>

The most critical resources for MPS

# Biological Resources Consideration



Cells	Media	Extracellular Matrix (ECM)
<ul style="list-style-type: none"><li>• Proper differentiation with major tissue cell types</li><li>• Target of interest</li><li>• Response to a stimulus</li><li>• Readiness to the experimental phase</li><li>• System viability/longevity</li><li>• Minimum number of donors for acceptance (healthy vs diseased)</li><li>• Donor demographics of interest</li><li>• Presence of specific mutation</li></ul>	<ul style="list-style-type: none"><li>• Recover</li><li>• Growth/proliferation</li><li>• Maintenance</li><li>• Differentiation</li><li>• Experimental phase</li><li>• Suitable across donors</li><li>• <b>Co-culture suitable</b></li></ul>	<ul style="list-style-type: none"><li>• Physiological state</li><li>• Concentration</li><li>• Ratio</li><li>• Healthy or diseased state</li><li>• Co-culture</li></ul>

Harmonization of biological resources can support and speed up the adoption

# Colon Rectal Cancer (CRC)

Patient-Derived Relevance

# KRAS-Focused Drug Sensitivity Testing on Pancreatic Cancer Organoid Models

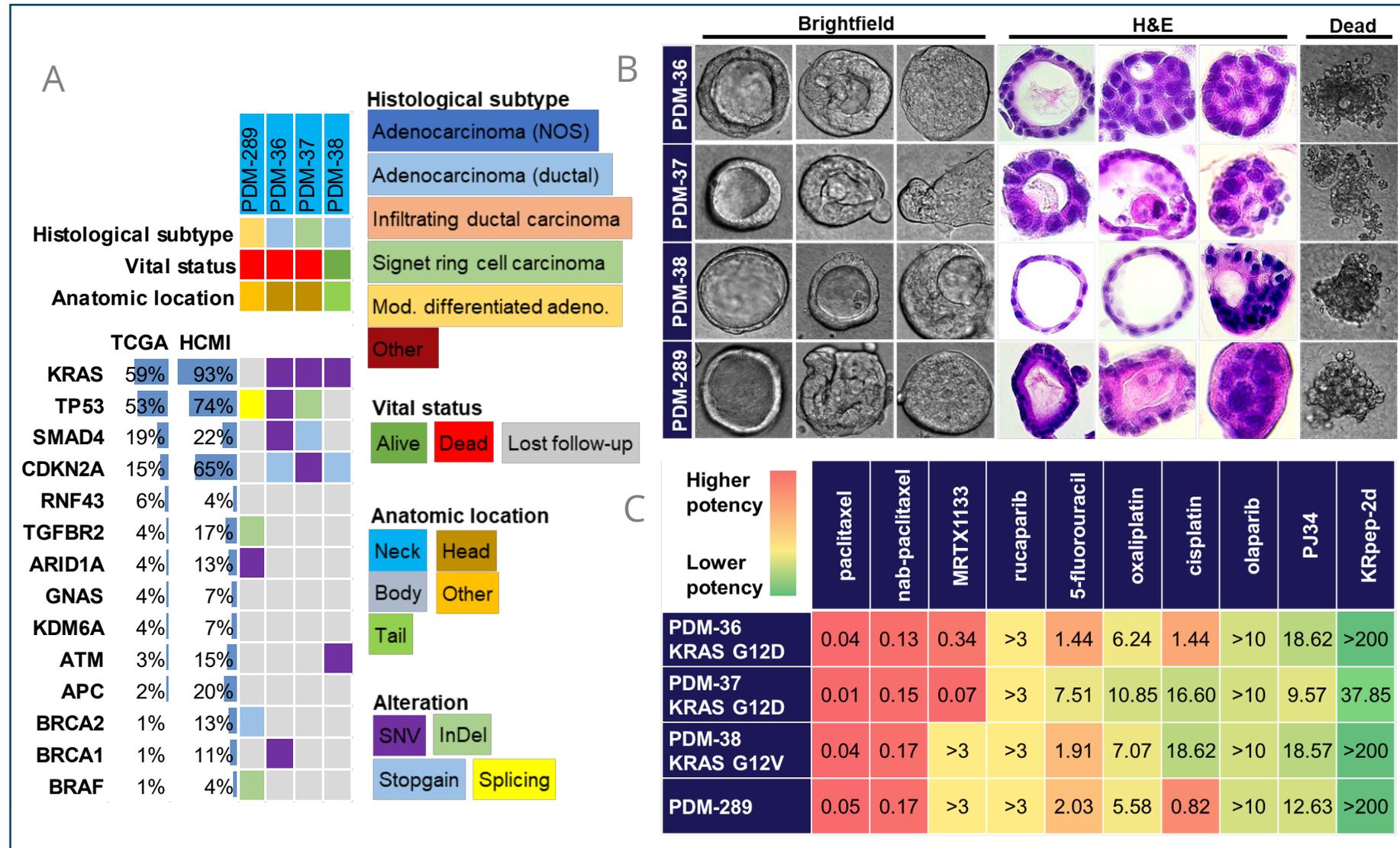
## A. Genomic signature of PDAC models tested

- PDM-36™ – KRAS G12D
- PDM-37™ – KRAS G12D
- PDM-38™ – KRAS G12V
- PDM-289™ – no KRAS expression

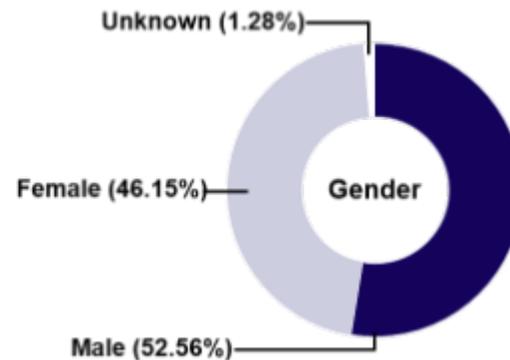
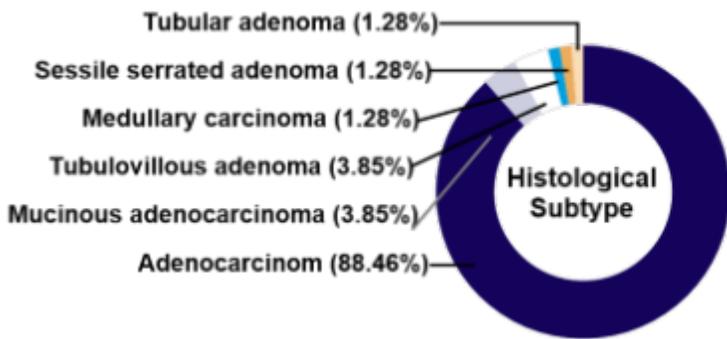
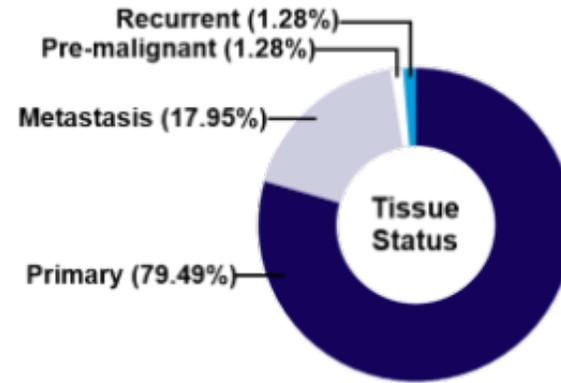
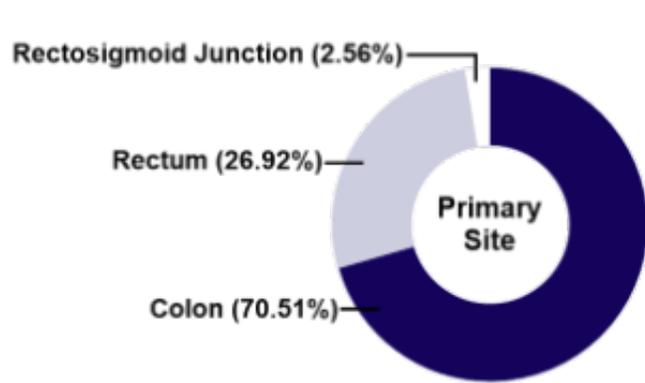
## B. Morphology and H&E staining

## C. Drug sensitivity assessment across KRAS

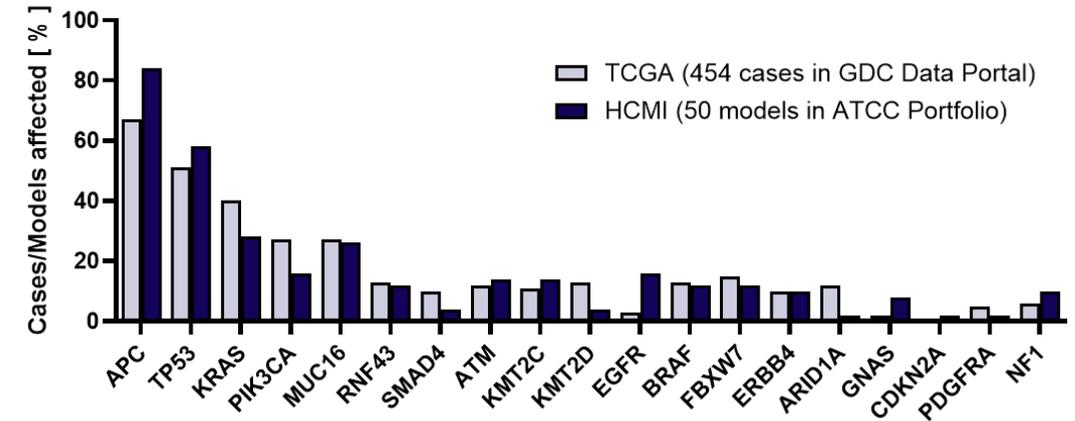
- PDM-36™ and PDM-37™ showed high sensitivity to KRAS inhibitor MRTX1133



# HCFI Colorectal Cancer Model Cohort



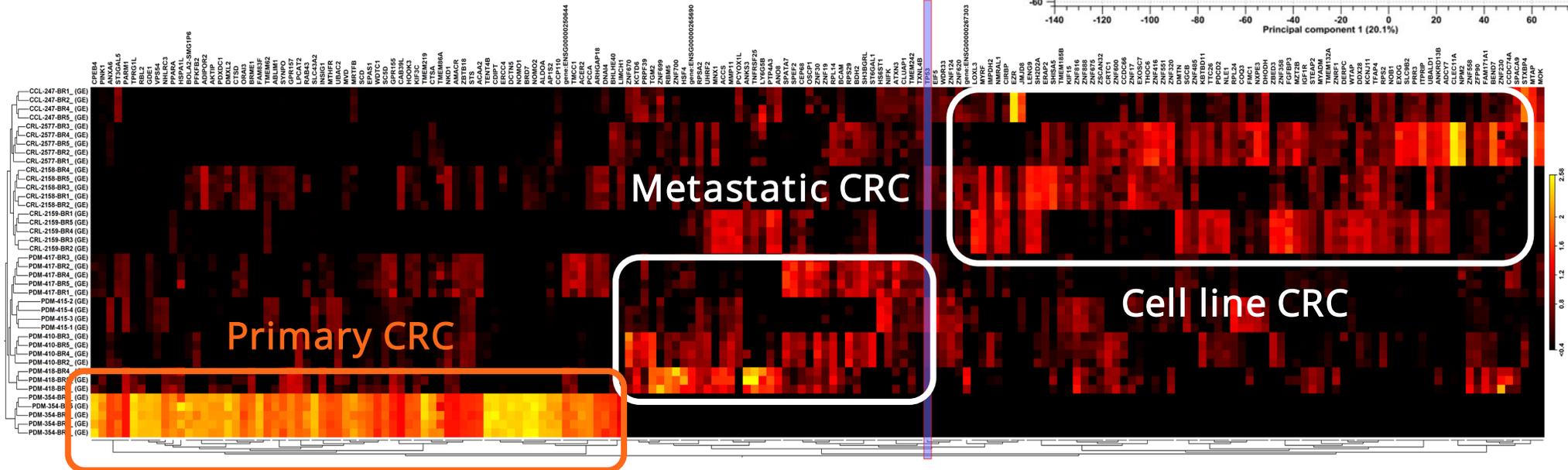
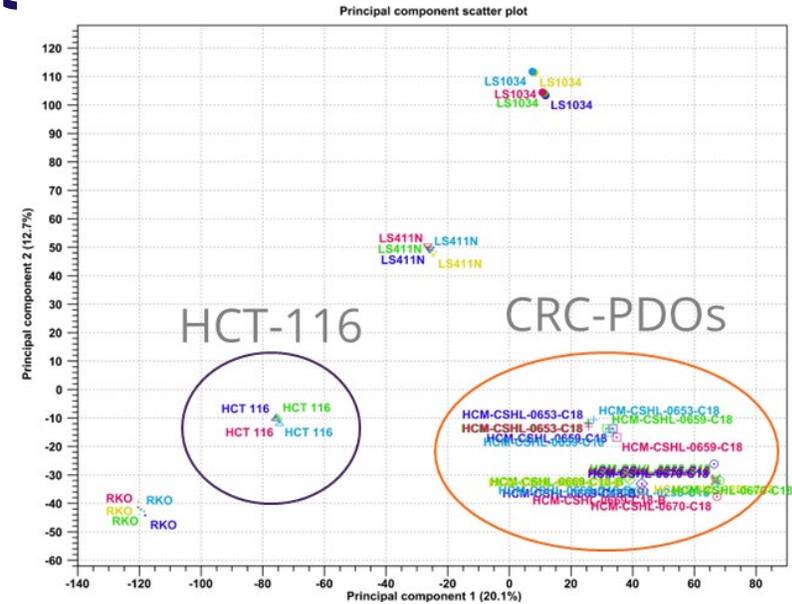
Most Frequently Mutated Genes in Colorectal Cancer



Diverse population dynamics and gene mutations in our colorectal cancer model

# Genomic Comparisons CRC Organoids Versus Cell Lines

- Clustering of patient-derived organoids
  - Metastatic and primary sub-cluster
  - Cell lines – HCT116 for example
- Gene expressions across primary-PDOs, metastatic PDOs seem vastly different from cell lines



# Key Takeaways

- Demand for 3-D formats is undeniable and growing rapidly
- Multiple platform technologies are commercially available
- Reproducible and reliable biological resources needed
- Lack of harmonized and robust protocols across platforms
- Acceptance criteria specification



FDA and NIH initiatives highlight a significant shift towards ethical research practices and the adoption of innovative, human-relevant methodologies in biomedical research.



**ATCC<sup>®</sup>**

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# Thank You