



VANDERBILT
SCHOOL OF MEDICINE

Research Initiatives in Patient-Derived Organoids

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RESEARCH CONVOCATION
Section of Surgical Sciences
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Outline

- **Introduction to Human Organoids**

 - Types of organoids

 - As models of human physiology and pathophysiology

- **Organoids as Tools for Precision Medicine**

 - Organoids recapitulate human disease (metabolic disease, IBD, celiac)

 - Carcinogenesis

 - Gene editing

- **Applying State-of-the-Art Technologies for Organoid Studies**

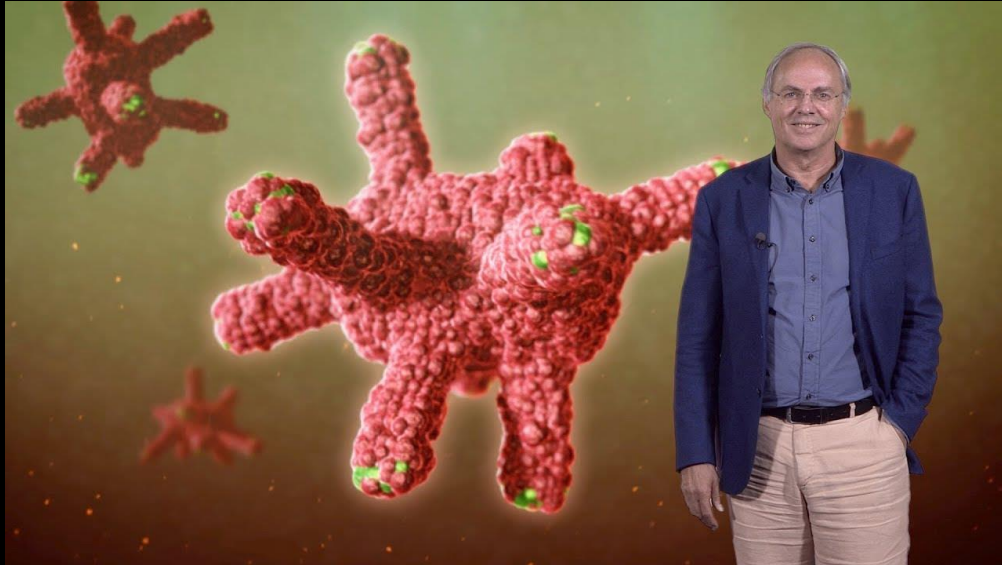
 - Enhancing biological, immune, environmental, microbial complexity

 - Recreating the network of human organs

 - Cellular therapies

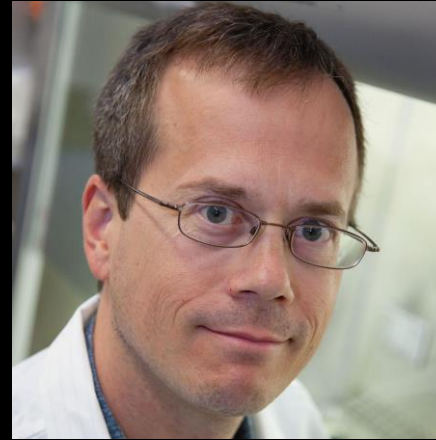
- **Organoids and VUMC**

Adult Stem Cell Organoids



Hans Clevers

Inducible Pluripotent Stem Cell Organoids



Jim Wells



Jason Spence



Michael Helmraath

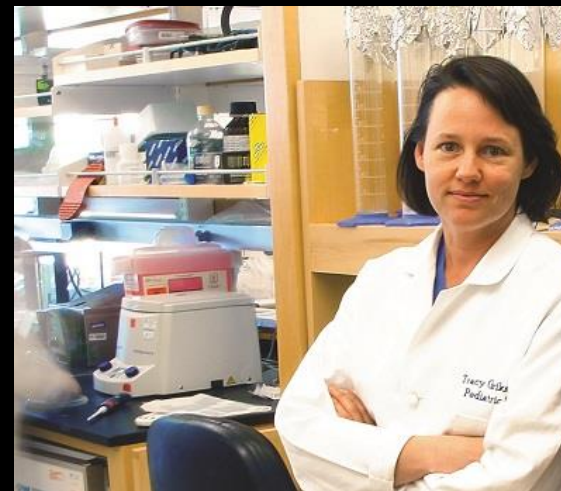


Toshiro Sato



Nick Barker

Tissue Engineered Intestine



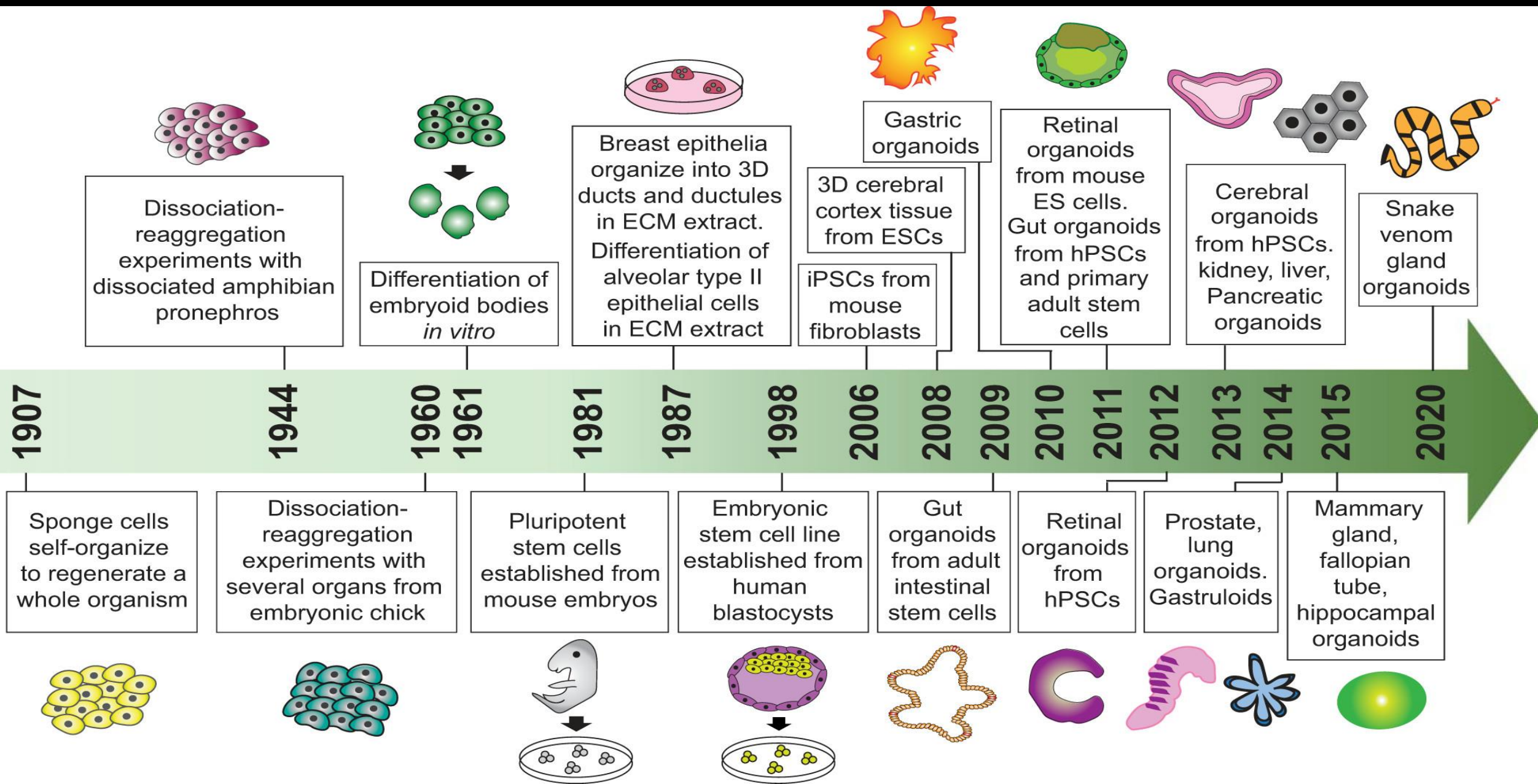
Tracy Grikscheit

Air-Liquid Interface Organoids



Calvin Kuo

How did we get to human organoids?



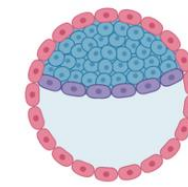
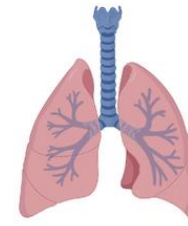
Introduction

An **organoid** is a "mini-organ" that is generated *in vitro* with the ability to self-renew and self-organize and performs organ functions similar to those of the tissue of origin.

Organoids mimic organ of origin:

- Cells exhibit spatially restricted lineage commitment.
- Contain more than one cell type.
- Can recapitulate organ-specific functions.

Tissue sources for organoids



Embryonic stem cells

Induced pluripotent stem cells



Organoid cultured *in vitro*

Lung organoids



Brain organoids



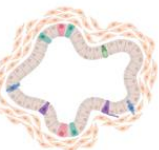
Kidney organoids



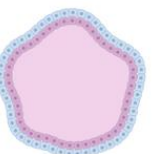
Intestinal organoids



Stomach organoids



Liver organoids



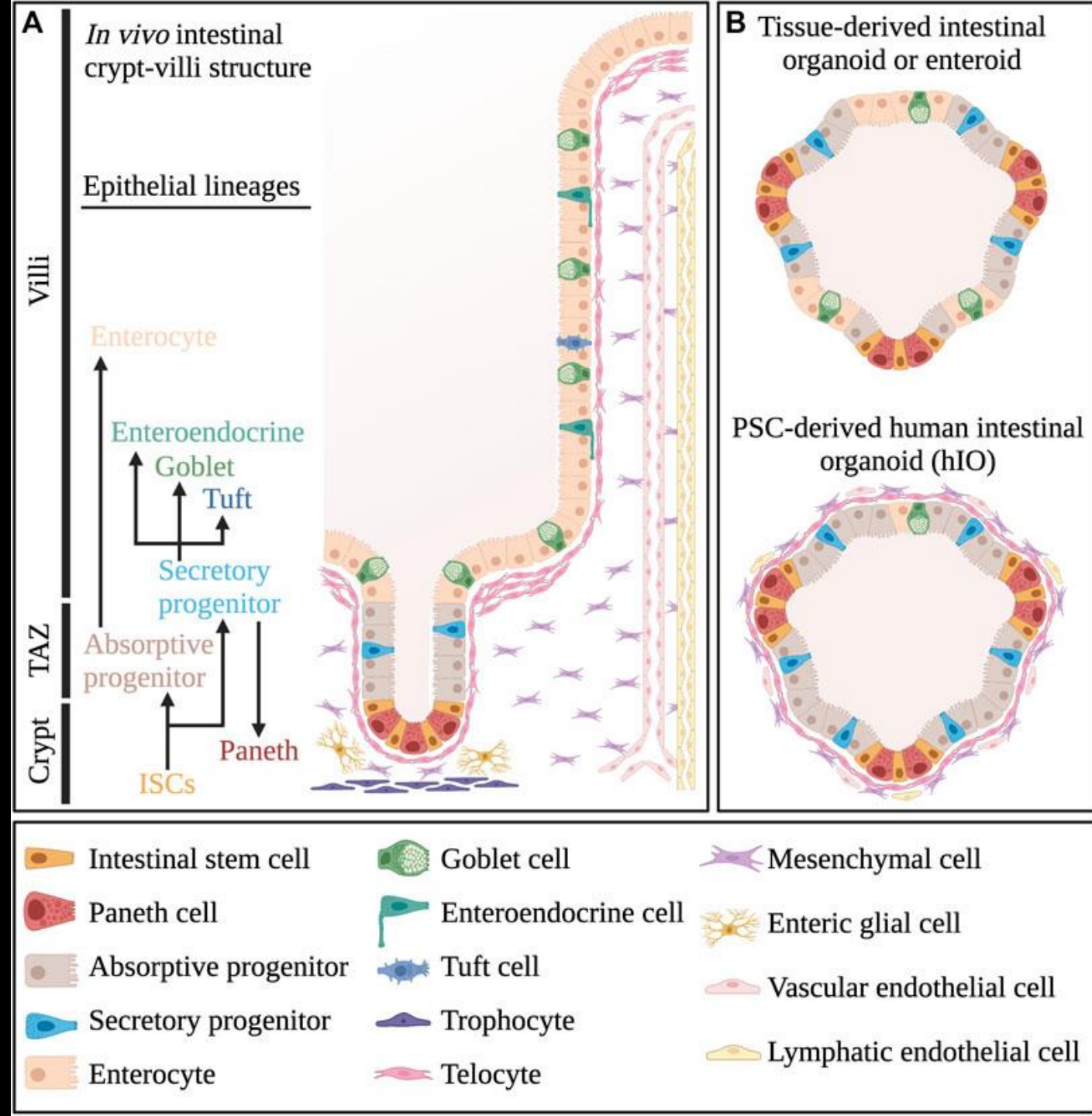
Introduction

2 major types of human organoids:

- Adult stem- or tissue-derived organoids
 - Epithelial cell only
- iPSC-derived organoids
 - Epithelial + mesenchymal cells

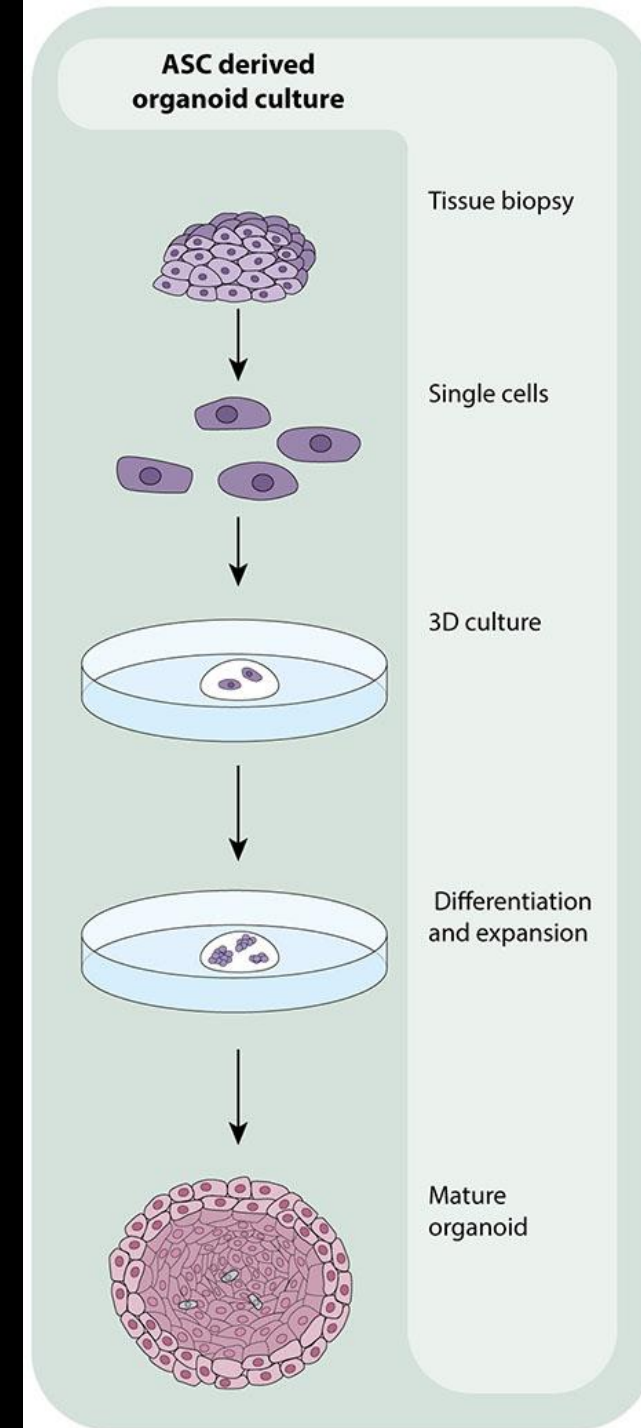
How are organoids made:

- Cultured in matrix enriched in extracellular matrix proteins (Matrigel)
- Media containing the suitable exogenous growth factors (e.g., Wnt, EGF)
- Ingrained genetic instructions promote self-organization into functional structures



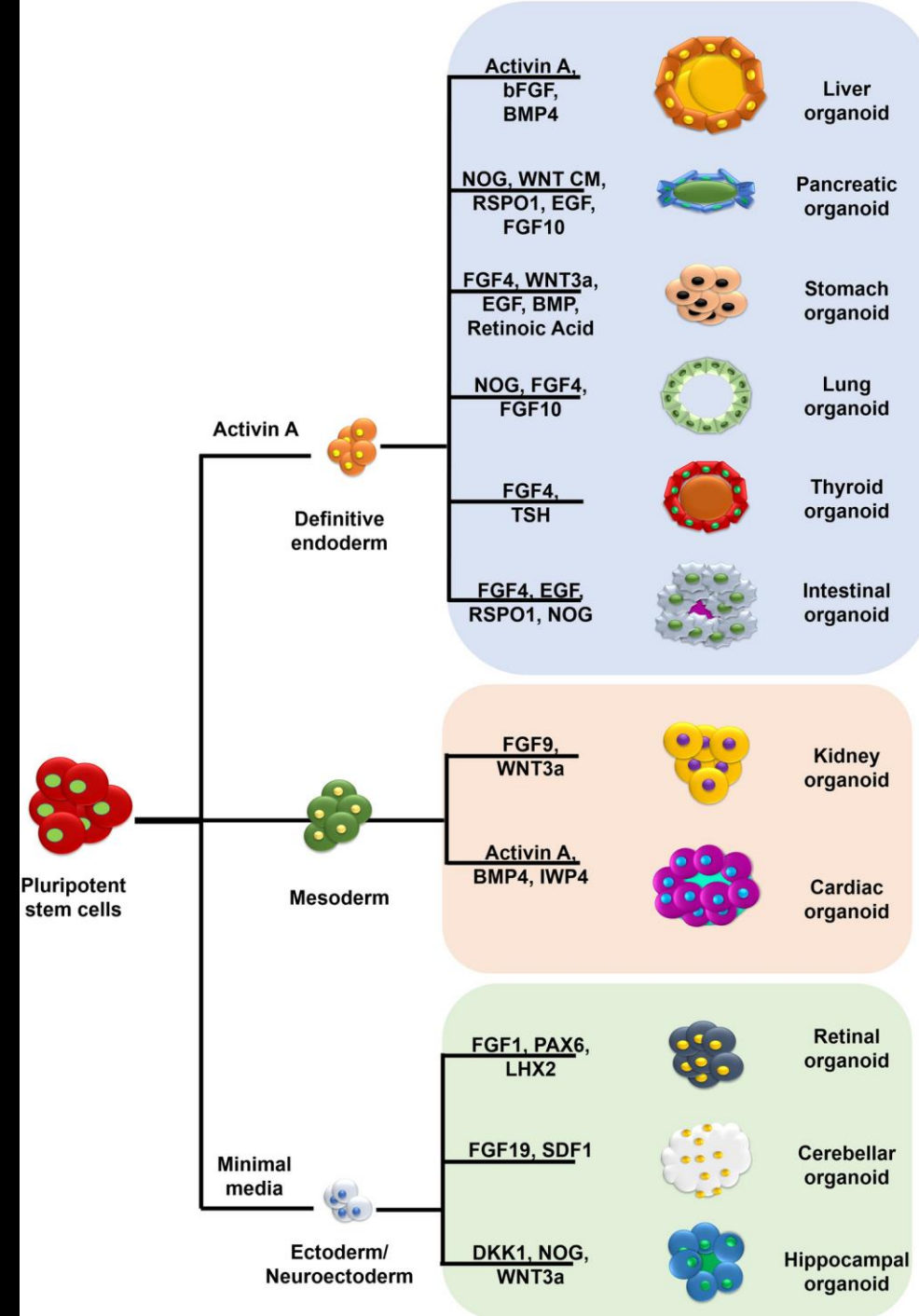
Adult Stem Cell-Derived Organoids

- Adult stem cell- or tissue-derived organoids are generated from biopsies or surgical resections from patient donors.
- Retain tissue-specific phenotypes and functions.
- Preserve disease-related pathologies.
- Can be indefinitely propagated and maintain normal karyotype.
- Highly reproducible.
- Easy to scale and culture in multiple conformations.

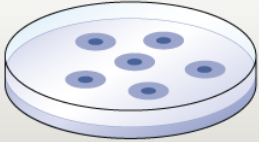
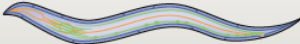
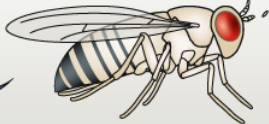



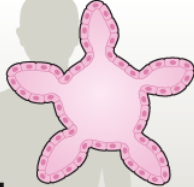


iPSC-Derived Organoids

- iPSC organoids are generated from established embryonic cell lines or reprogrammed from patient somatic cells.
- More complex cultures than ASC organoids.
- Can model any gastrulation layer.
- Preserve patient genotypes.
- Used to model human organ development due to fetal-like transcriptome.
- Increased maturation and cell types can occur when engrafted into animal models.

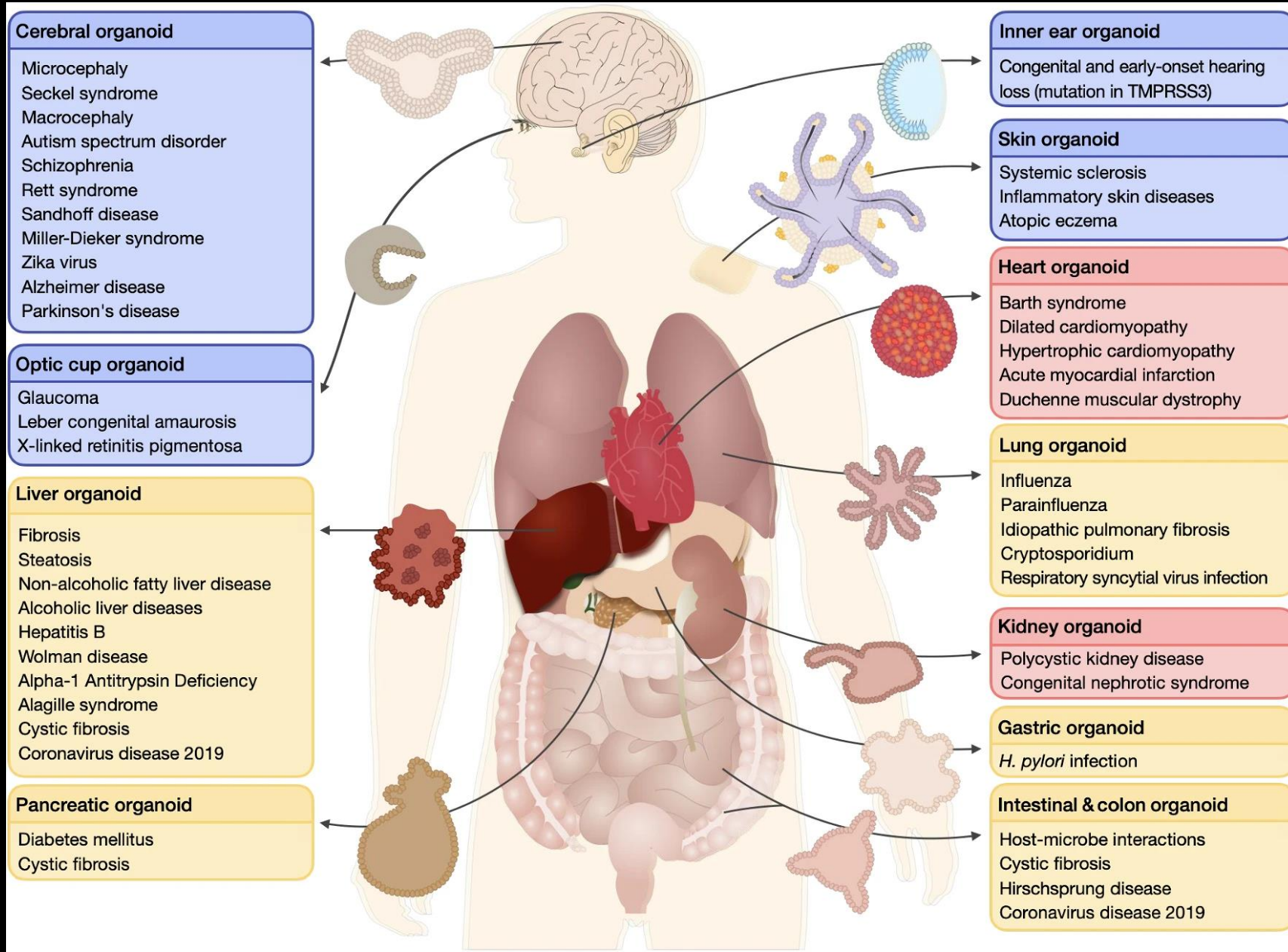


How do organoids compare to other models?

	 2D cell culture	 <i>C.elegans</i>	 <i>D. melanogaster</i>	 <i>D. rerio</i>	 <i>M. musculus</i>	 PDX	 Human organoids
Ease of establishing system	✓/✗	✓	✓	✓	✓	✓	✓
Ease of maintenance	✓	✓	✓	✓	✓	✓	✓
Recapitulation of developmental biology	✗	✓	✓	✓	✓	✗	✓
Duration of experiments	✓	✓	✓	✓	✓	✓	✓
Genetic manipulation	✓	✓	✓	✓	✓	✗	✓
Genome-wide screening	✓	✓	✓	✓	✗	✗	✓
Physiological complexity	✗	✓	✓	✓	✓	✓	✓
Relative cost	✓	✓	✓	✓	✓	✓	✓
Recapitulation of human physiology	✓	✓	✓	✓	✓	✓	✓

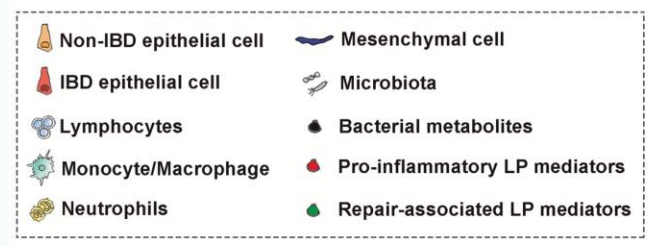
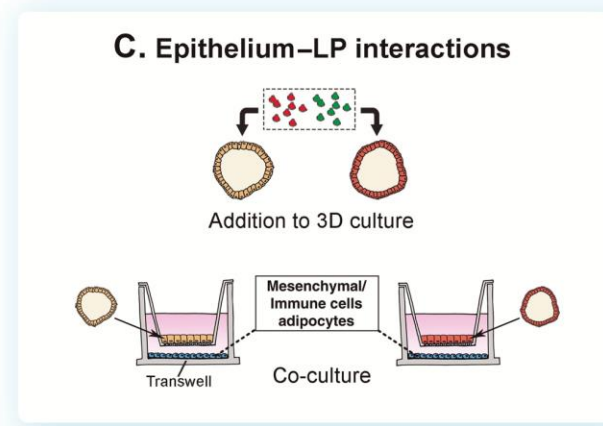
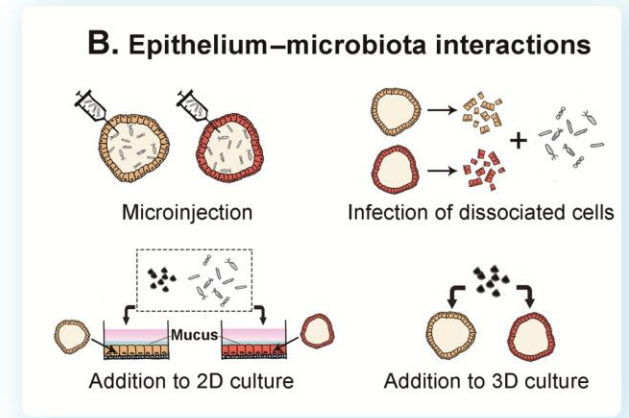
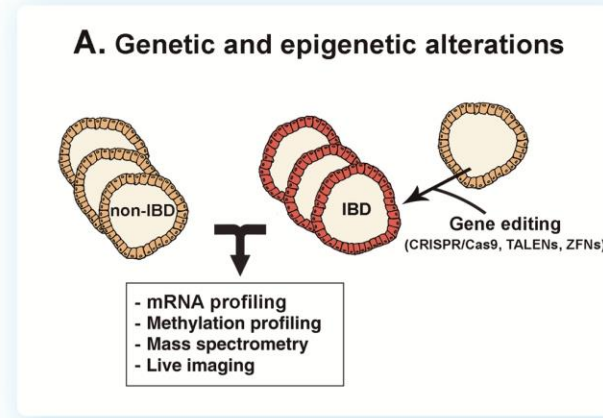
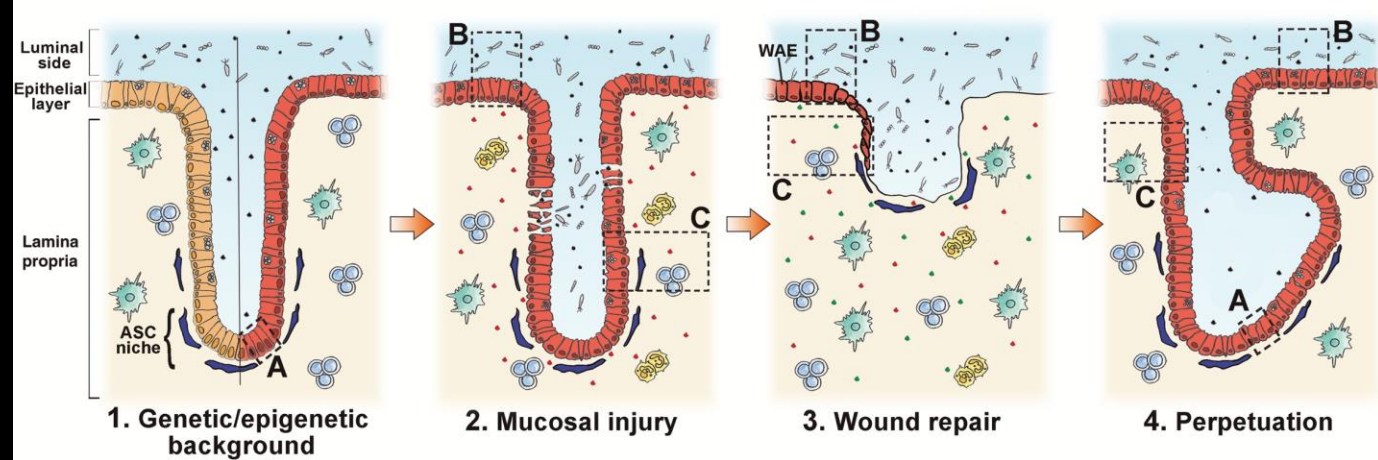
✓ Best
 ✓ Good
 ✓ Partly suitable
 ✗ Not suitable

Studying human diseases with organoids

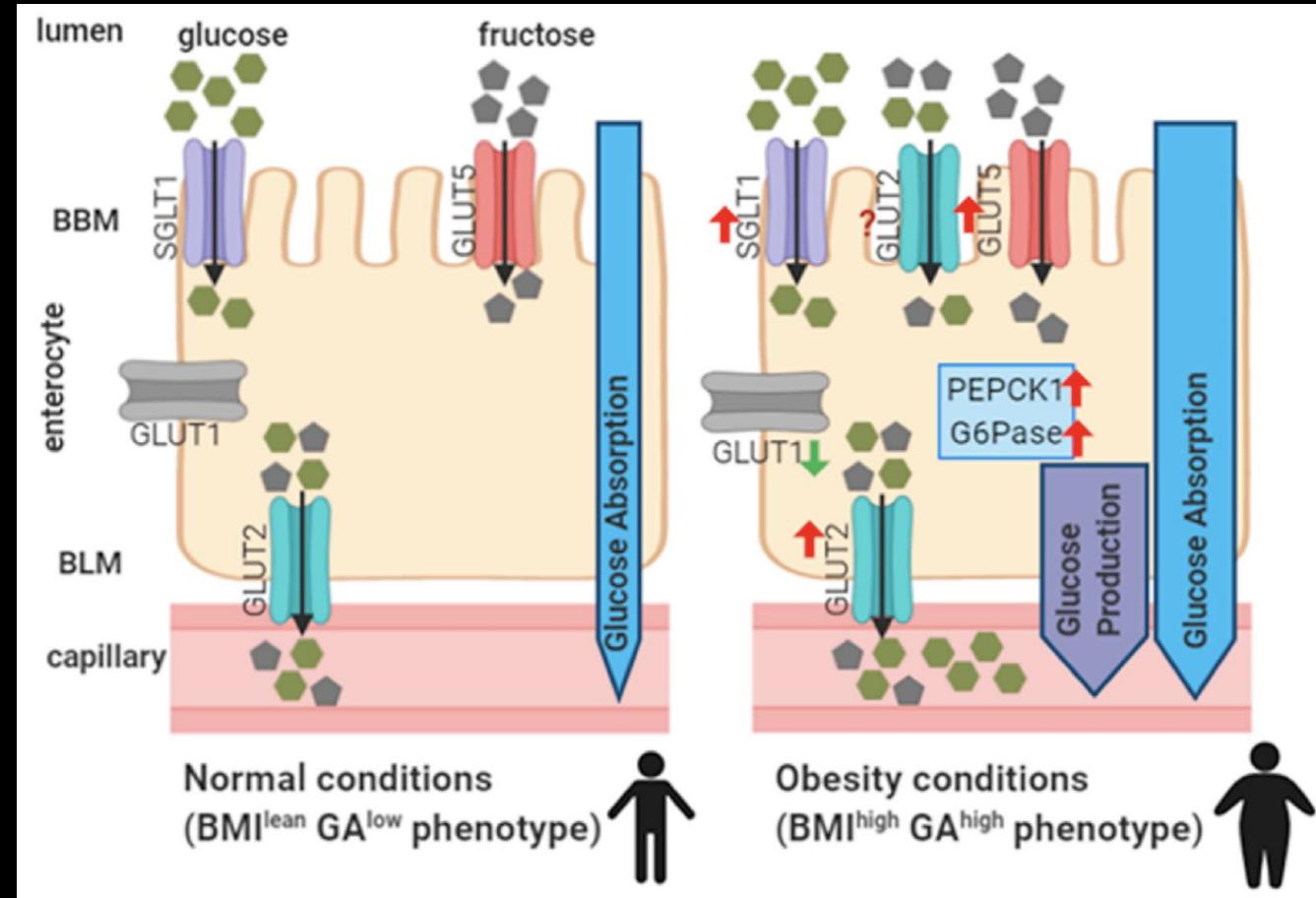
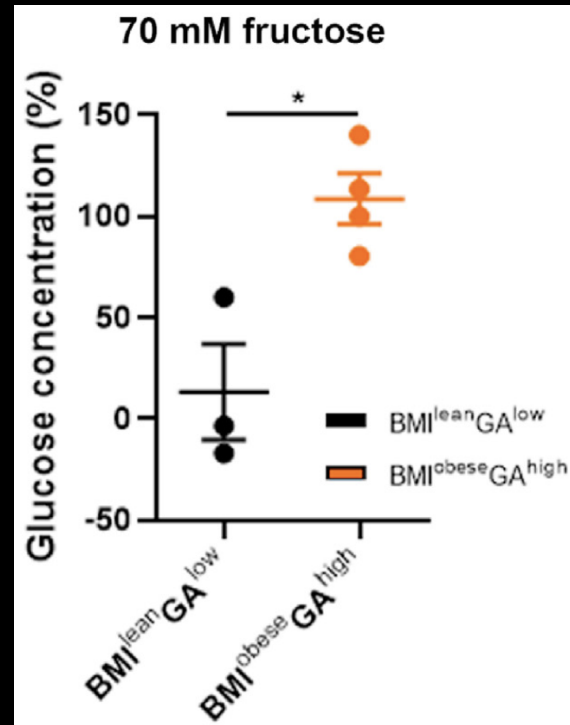
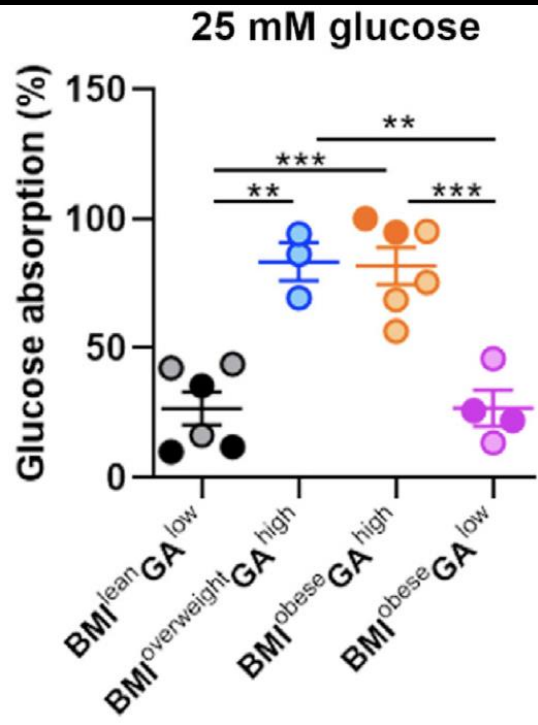


Modeling Organoids to Study IBD

- Patient-derived organoids (A) can be used to obtain in-depth profiles of the epithelial genetic/epigenetic disease-related background or the effect of engineered genetic mutations (Panel 1).
- “Omics” approaches can be applied to interrogate the effects persistent exposure to pro-inflammatory signals in IBD perpetuation (Panel 4).
- 2D organoid monolayers used to study the effects of the direct or indirect (e.g. secreted mediators) interactions of the epithelium with the microbiota (B) and LP cells (C) during the different stages of IBD pathophysiology (Panels 2, 3, and 4)

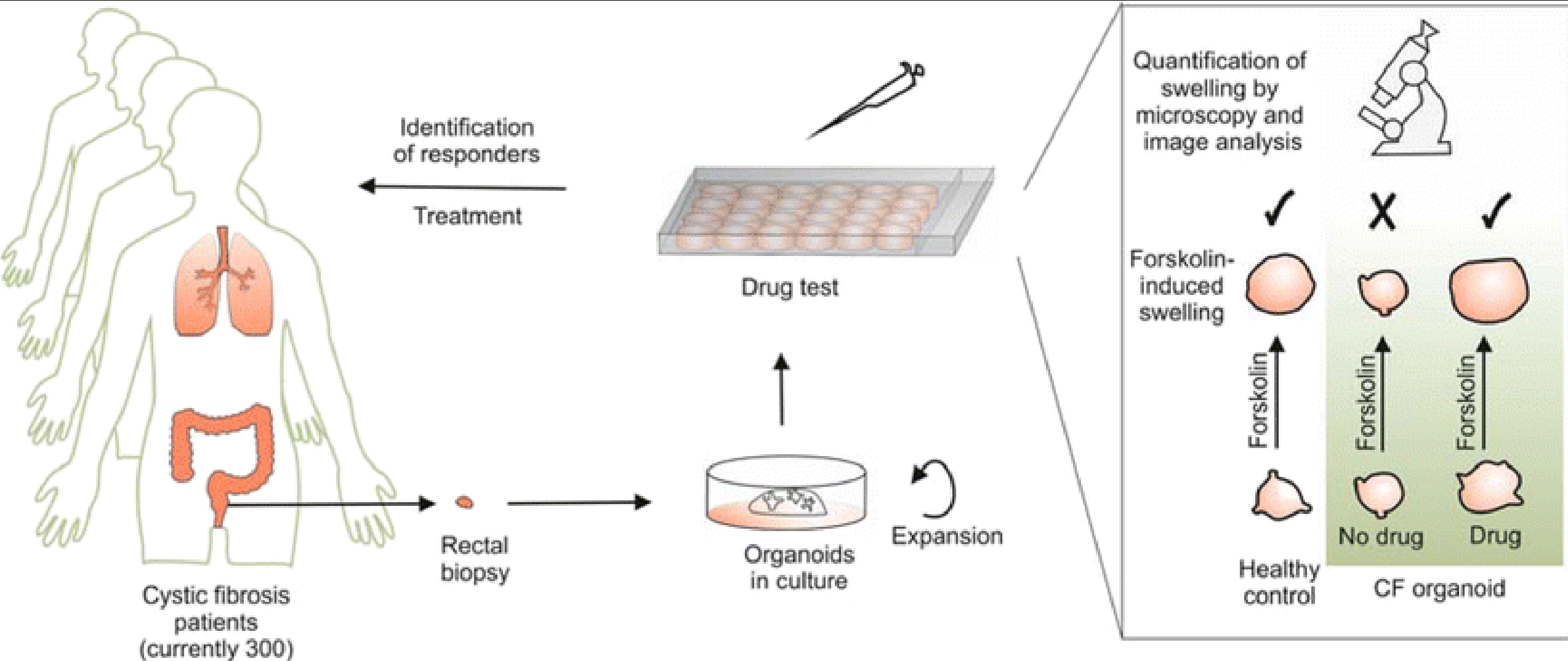


Human Organoids to Study Obesity/T2DM



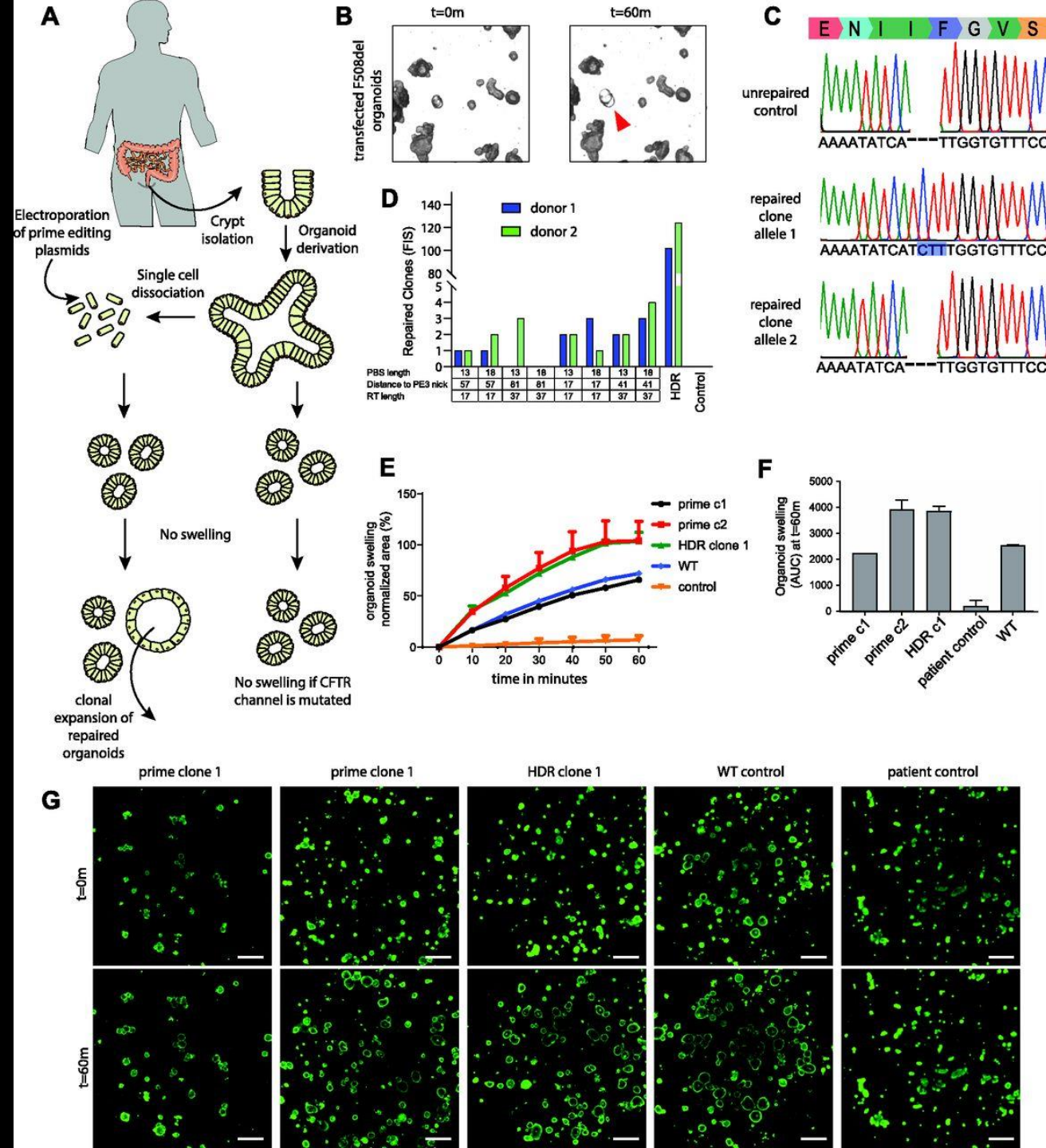
- Patient-derived organoids retain disease-related functional phenotypes.
- Organoids from obese patients exhibit increased glucose absorption and are gluconeogenic.

Precision Medicine for Cystic Fibrosis



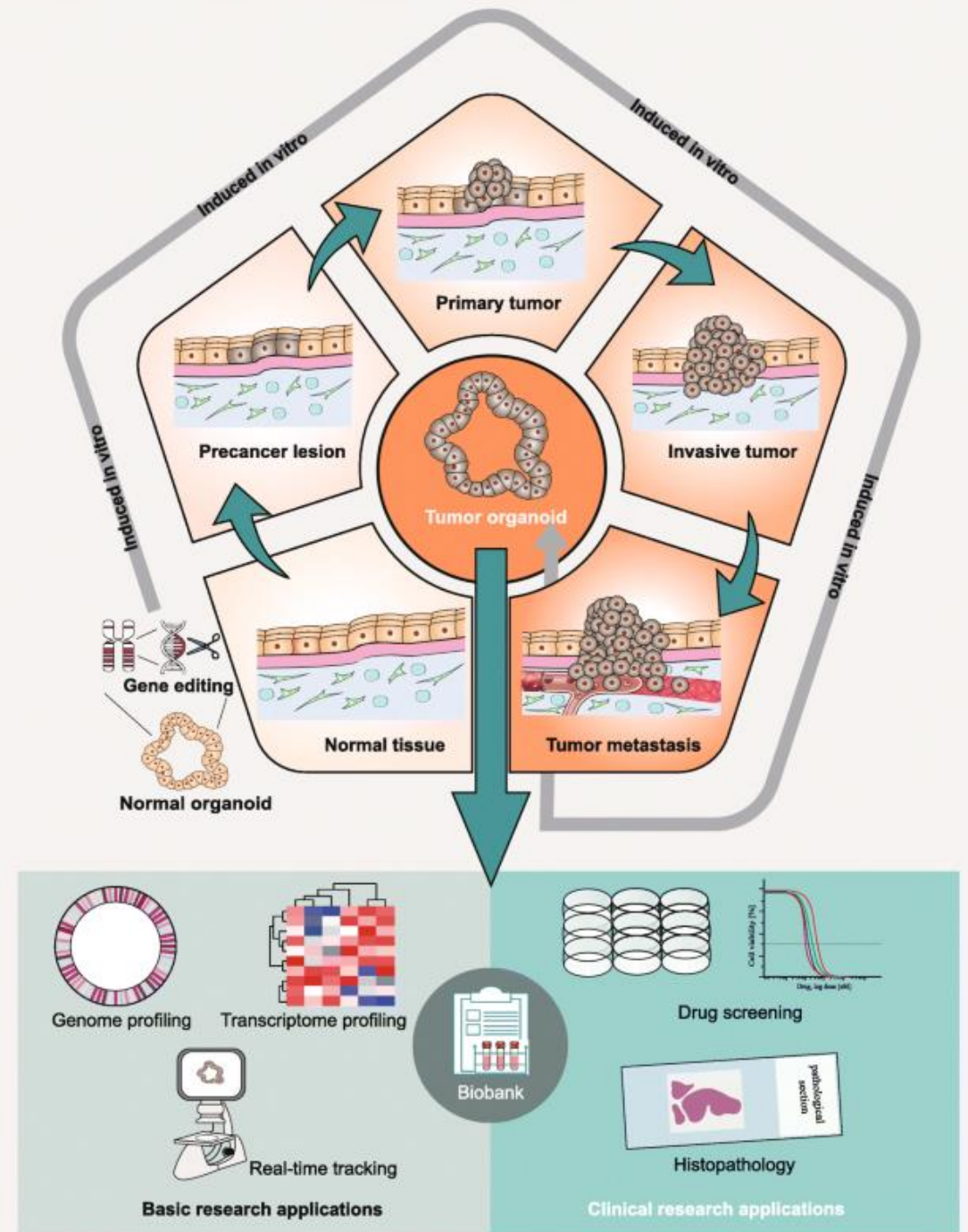
Functional repair of the *CFTR*-F508del mutation in patient-derived organoids

Experimental design of prime editing-mediated repair of *CFTR* mutations in human intestinal organoids.



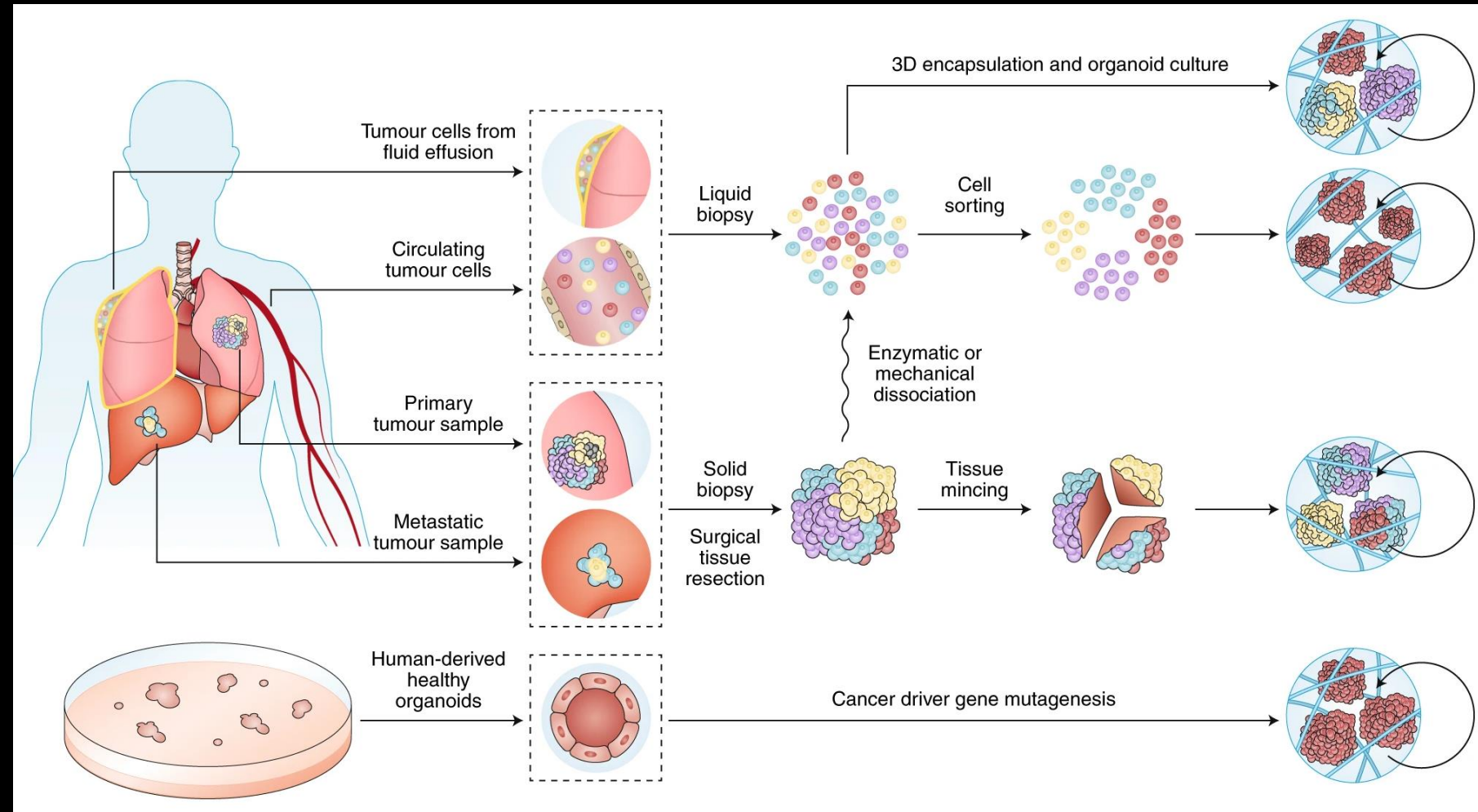
Strategy to study carcinogenesis in patient-derived organoids

- Cancer organoids can be derived from patients with diverse cancer grades and subtypes.
- Patient-derived organoids can possess patient-specific genetic and epigenetic contexts for preclinical cancer research and theranostics.
- Normal organoids can be used to model cancer evolution after the introduction of oncogenic mutations.
- Tumor cell behaviors can be monitored by time-lapse microscopic imaging.
- Cancer organoid lines can be expanded and cryopreserved to establish a biobank



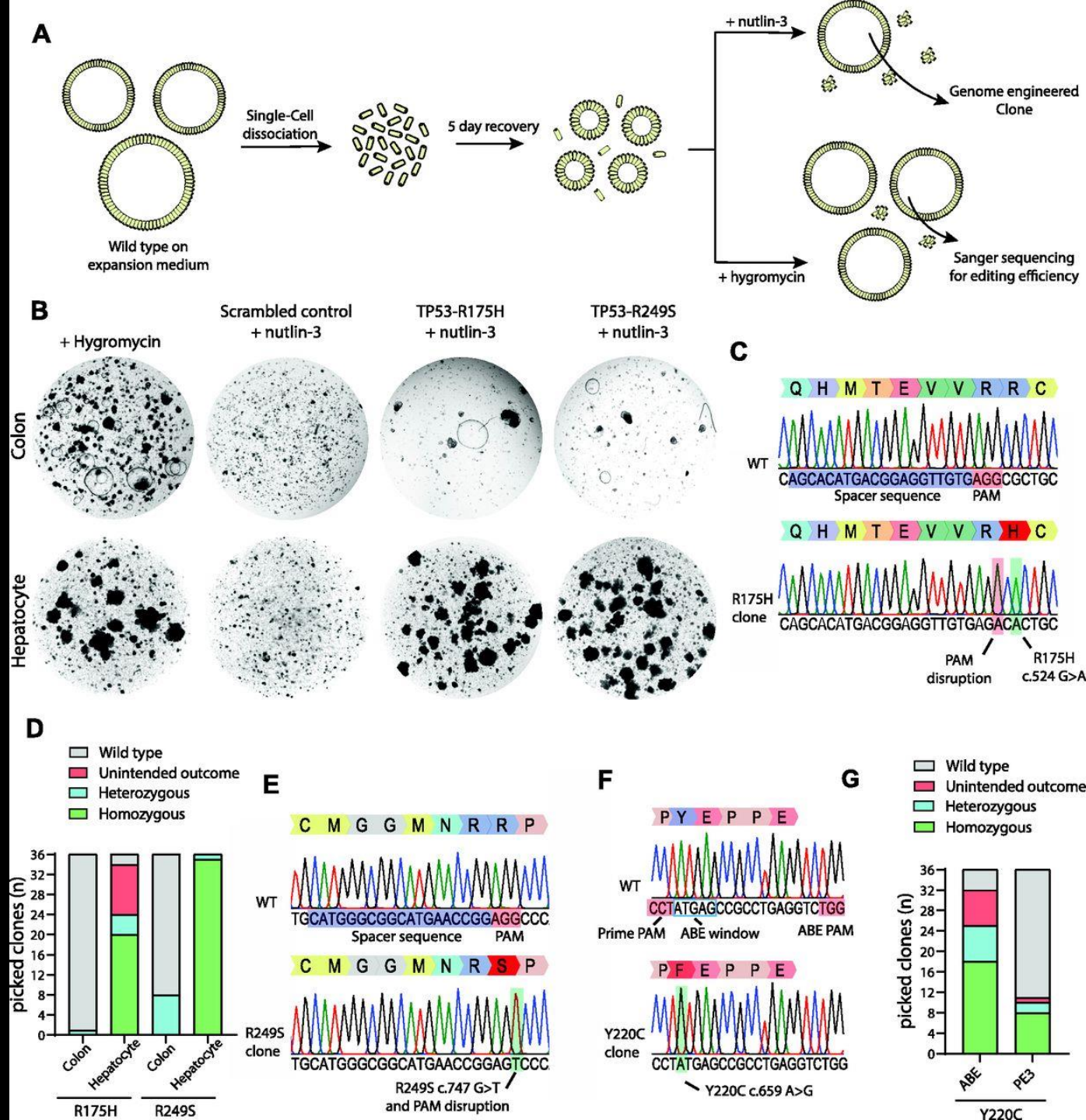
Current methods of cancer organoid derivation

Several sources of tumor tissue from distinct stages of cancer progression, including primary tumors, circulating tumor cells and secondary metastatic lesions, have been collected to generate patient-specific cancer organoid models.

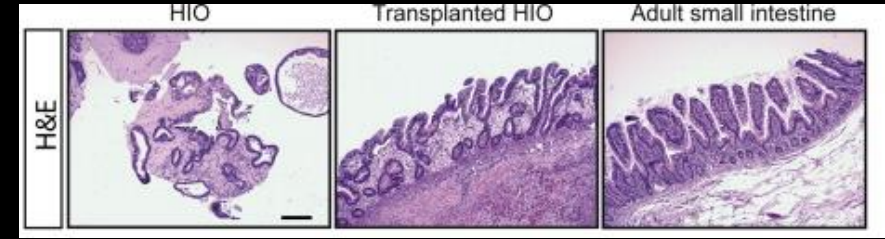
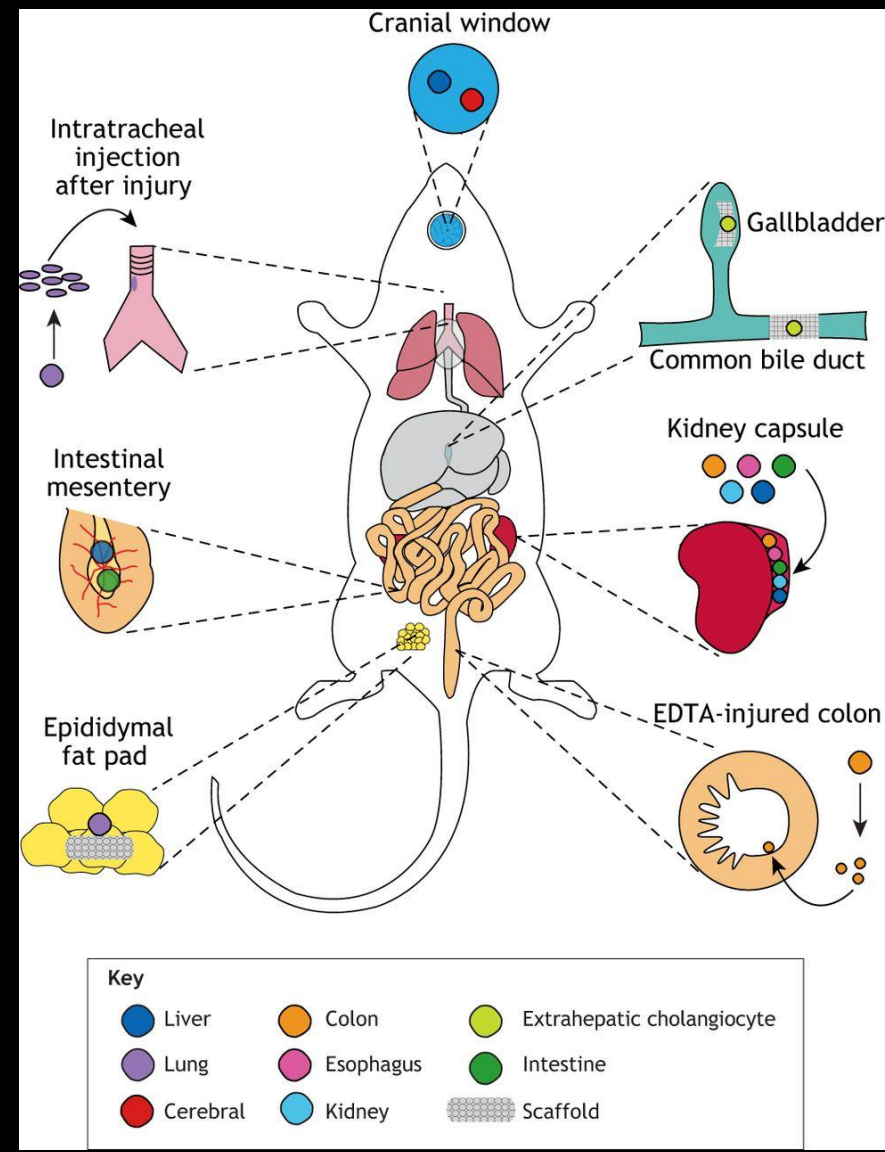
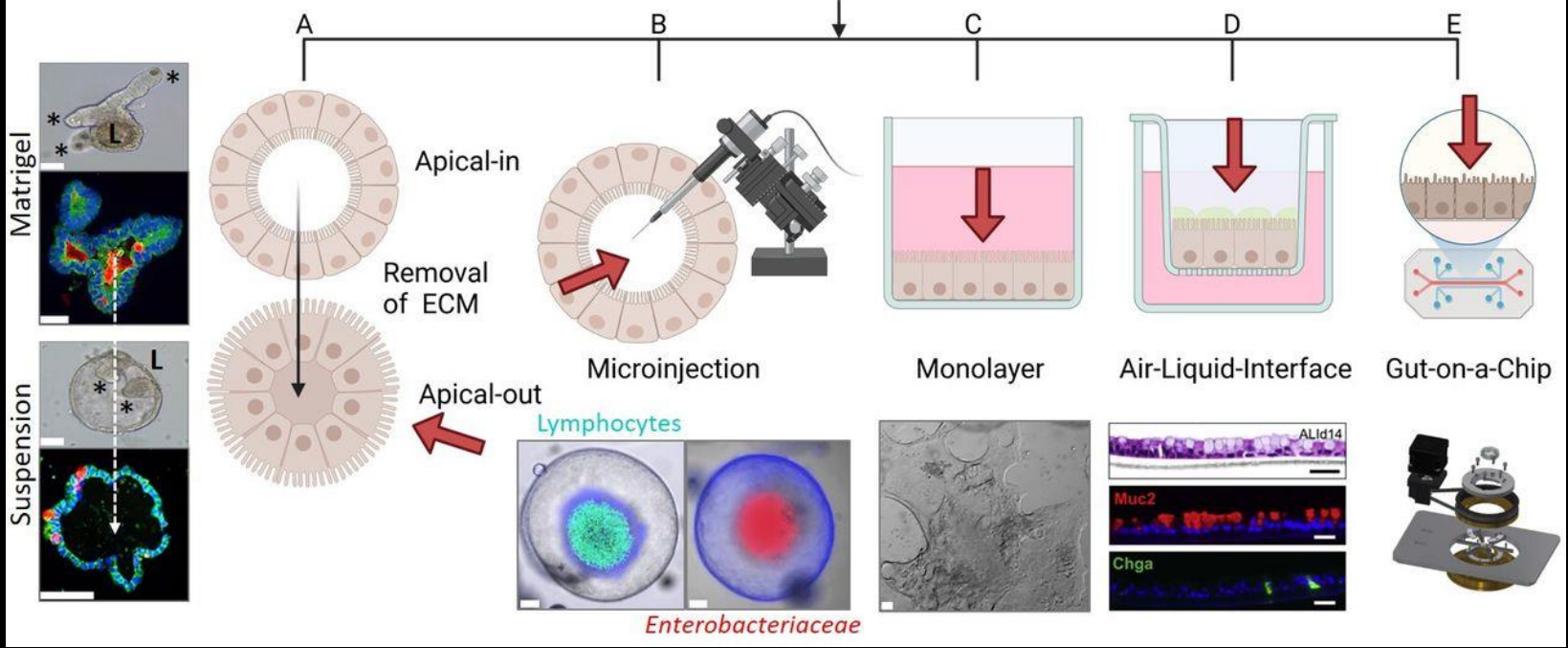
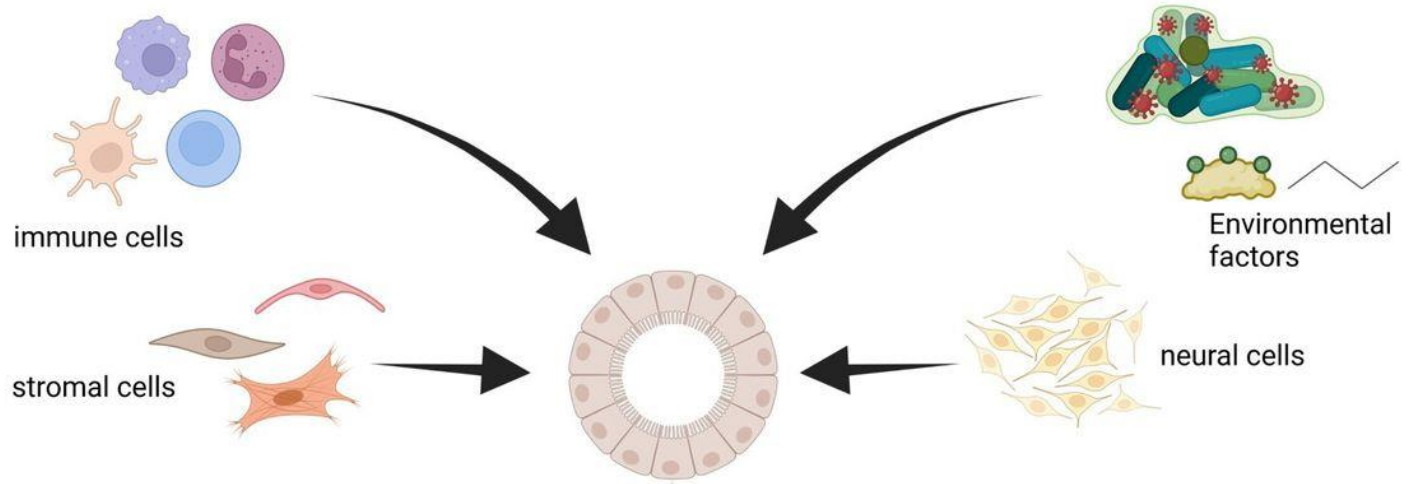


Prime editing enables generation of oncogenic mutations in organoids

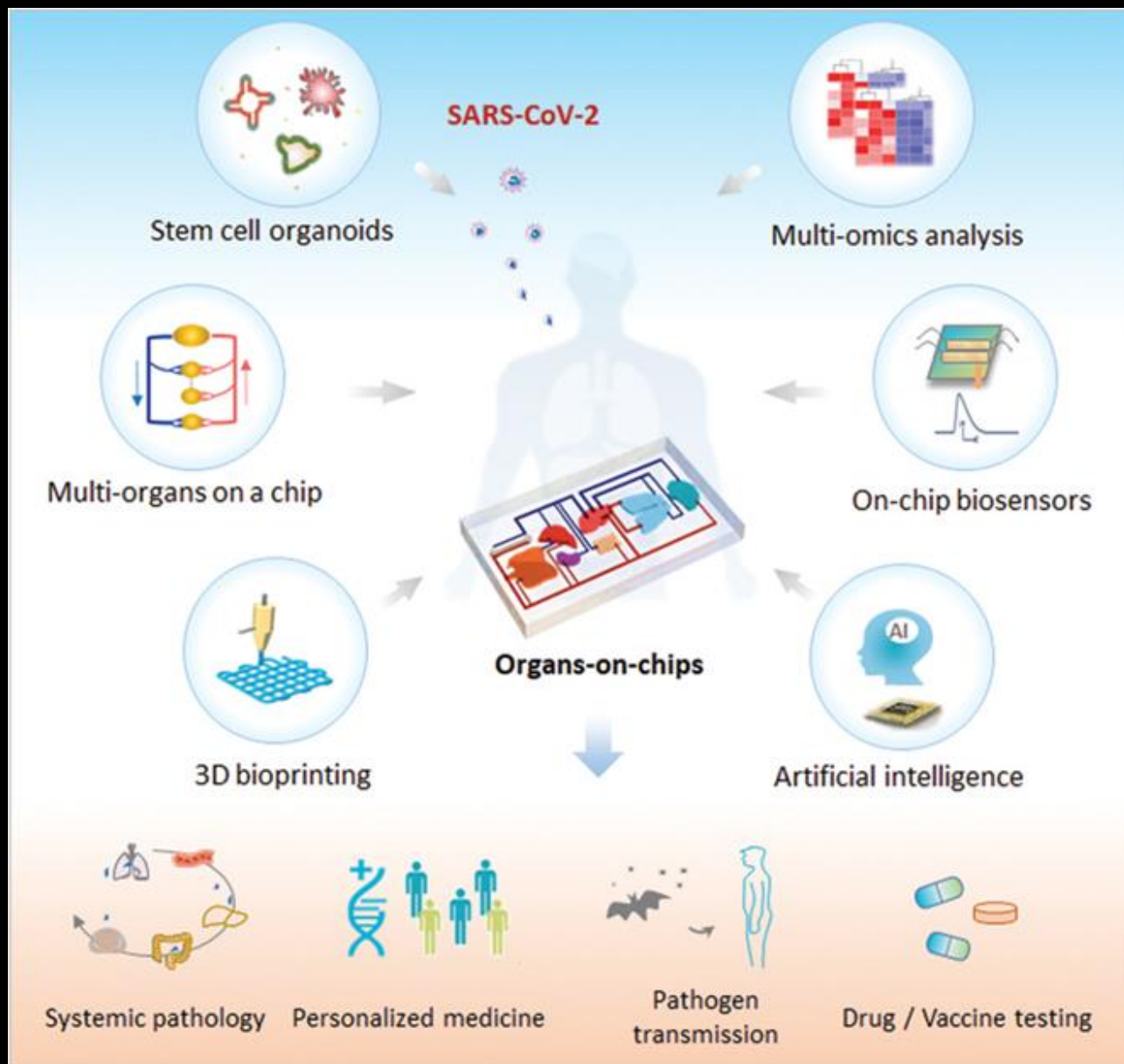
Generate *TP53*-mutated organoids



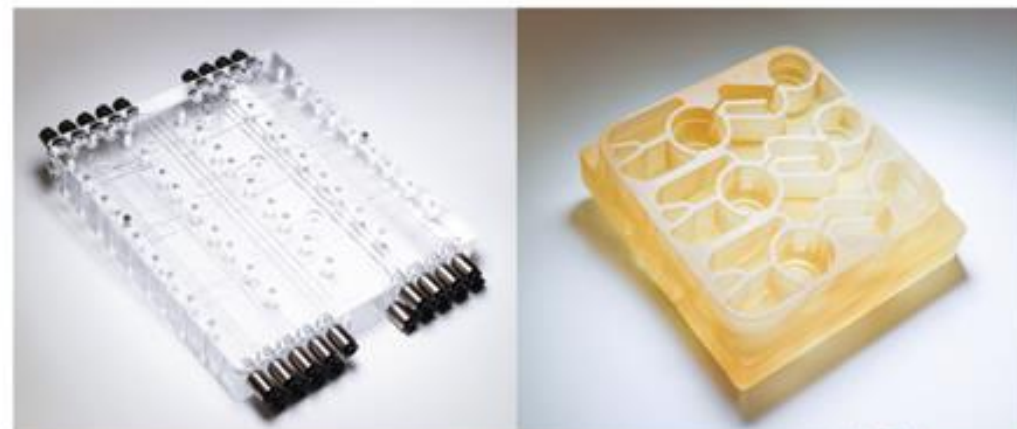
Biologically inspired approaches to enhance human organoid complexity



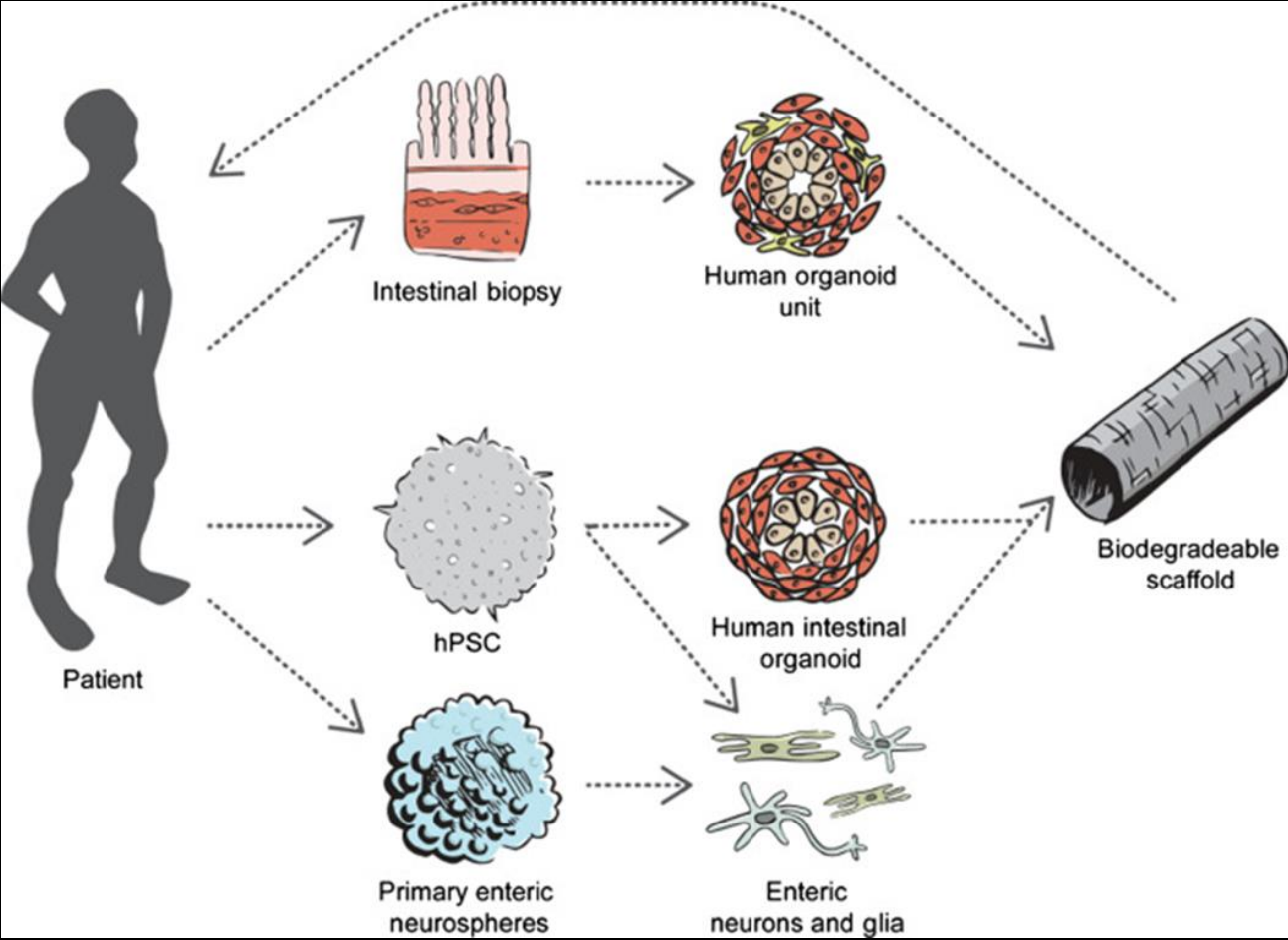
Microphysiological Systems: Organs-on-a-chip



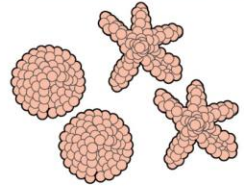
3XGLB physiomimetic platform



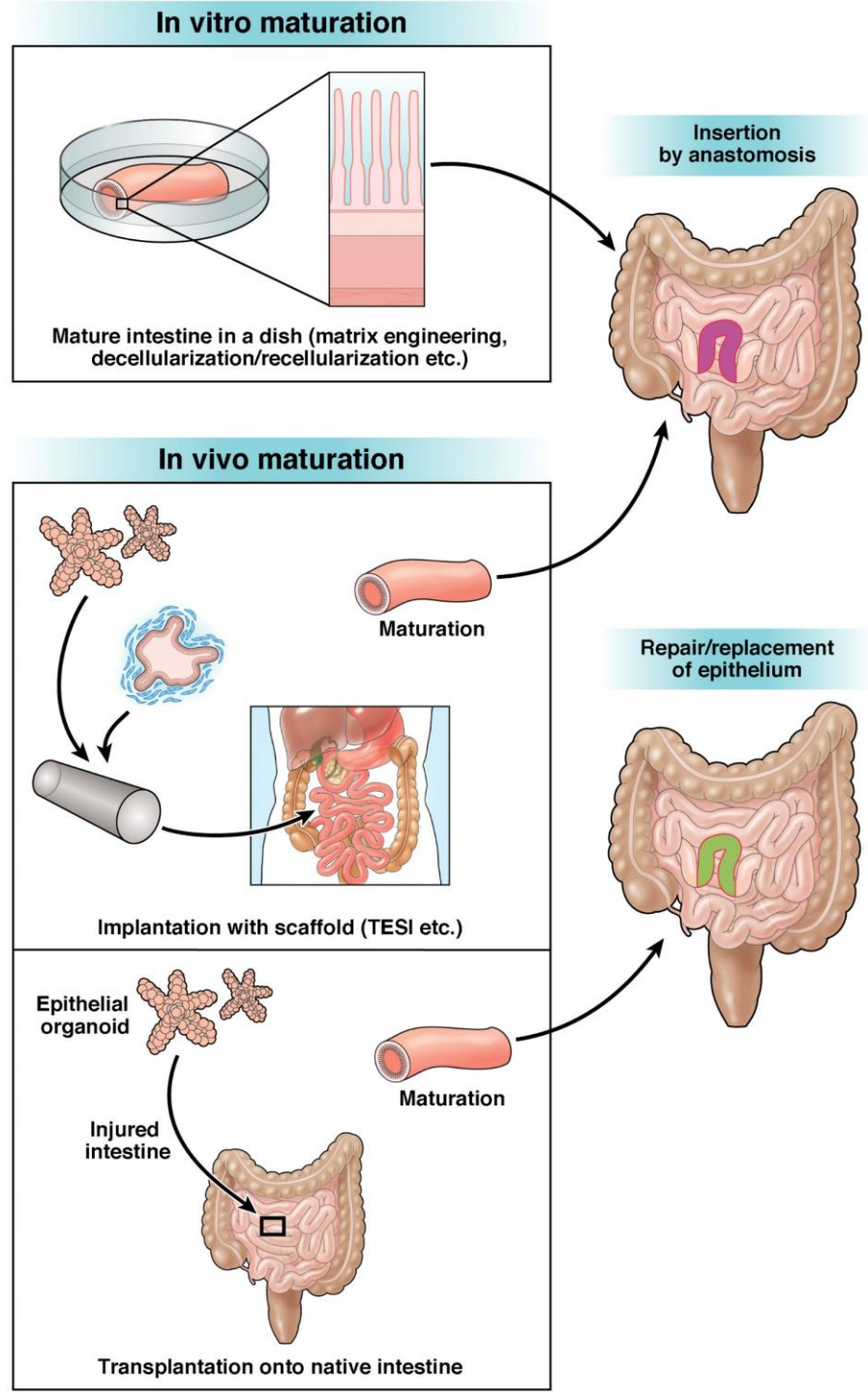
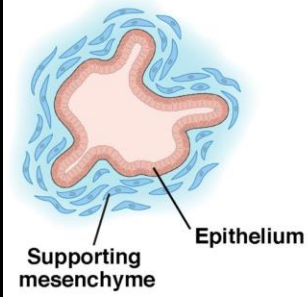
Organoid Engraftment/ Transplantation



Epithelial organoid

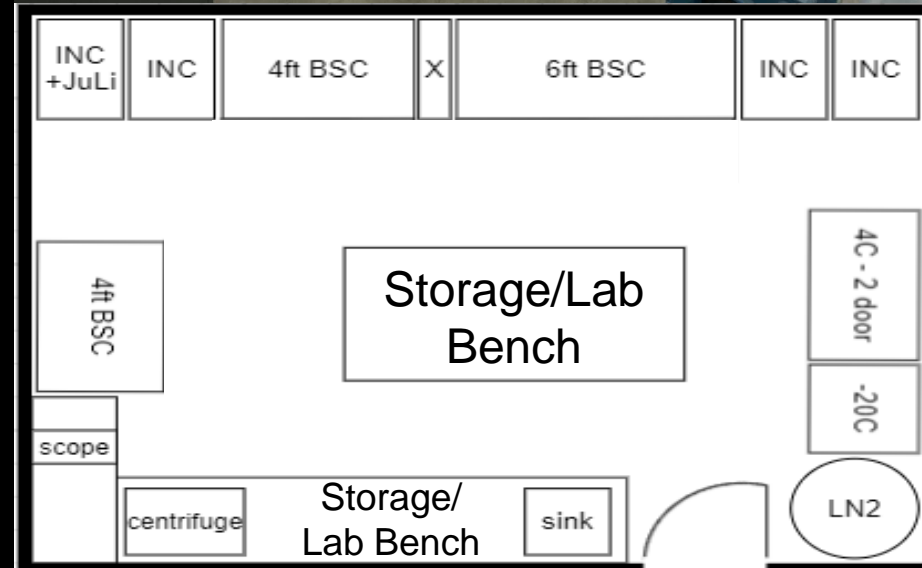
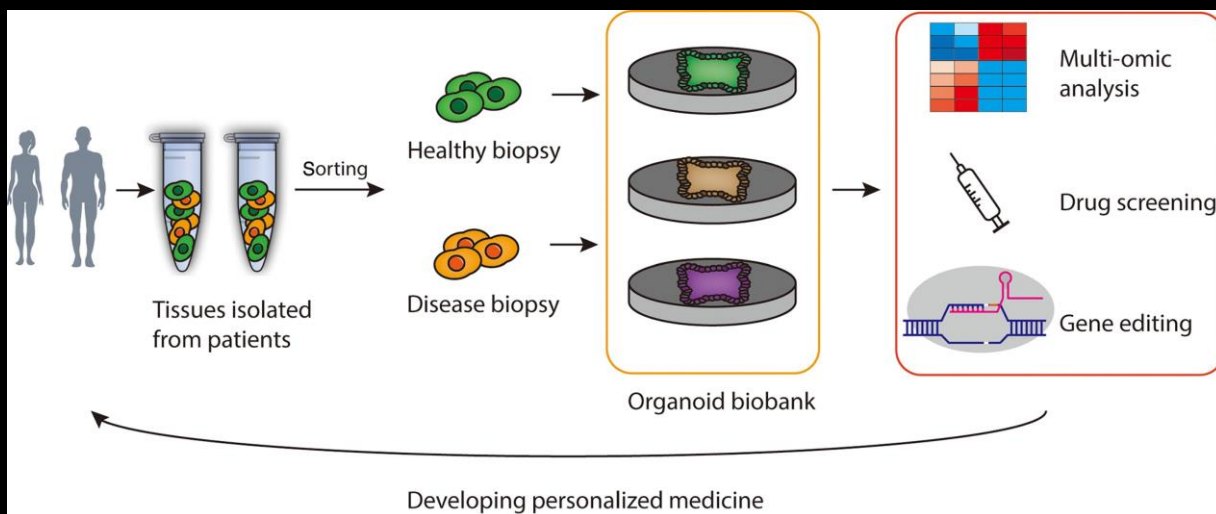


Epithelial/mesenchymal organoid (HIOs etc.)



“The VUMC Organoid Factory”

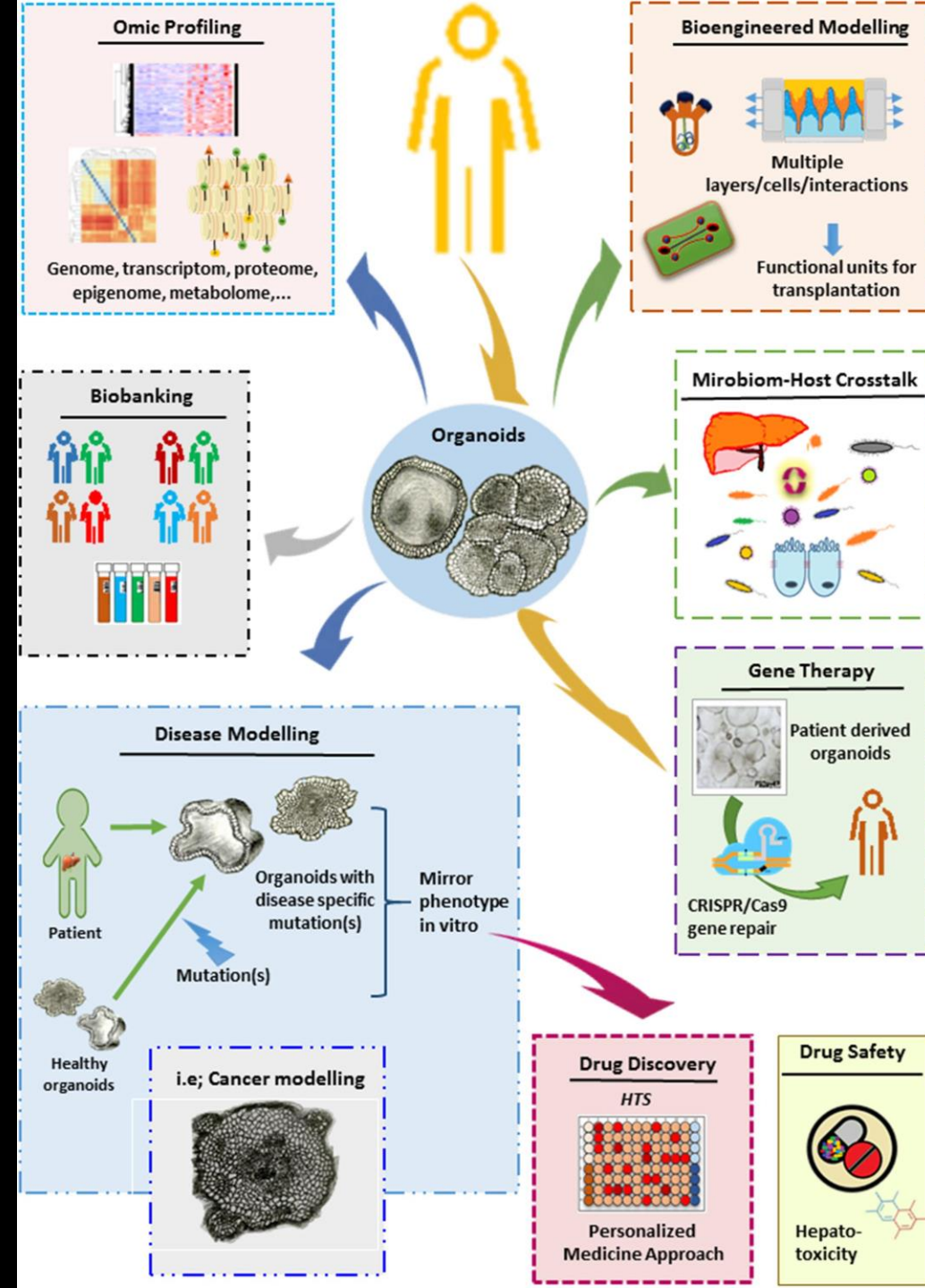
- Medical Center North, Room CC-2311
- Light Surgical Research & Training Lab
- Biosafety Level 2 Facility
- Normal and disease organoids
- Organoid biorepository (11,000+ lines)



“The VUMC Organoid Factory”

MISSION:

- To enhance intra- and inter-departmental translational research programs.
- Increase translational research opportunities for surgical residents/fellows and faculty.
- Combine multi-omics and advanced imaging approaches to develop novel protocols to culture organoids from understudied cancers.
- Develop comprehensive organoid biobank to include clinical metadata, pathology, and blood/tissue specimens.



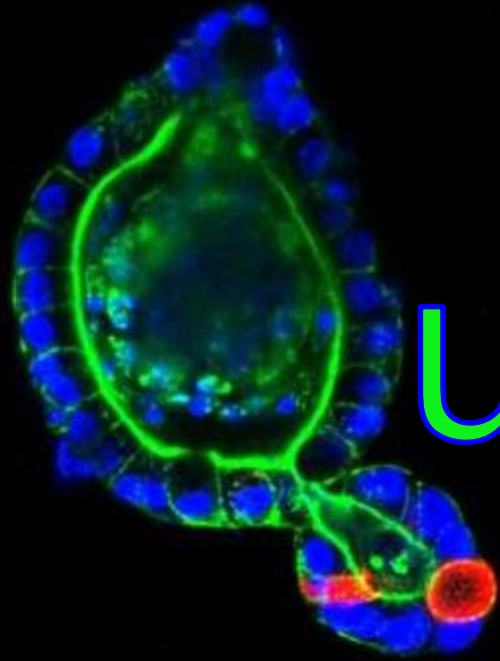
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