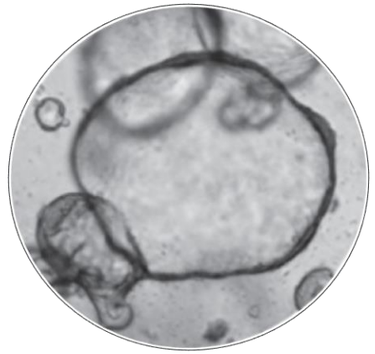
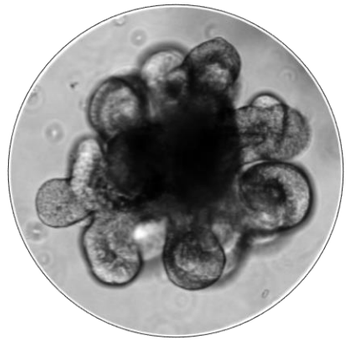
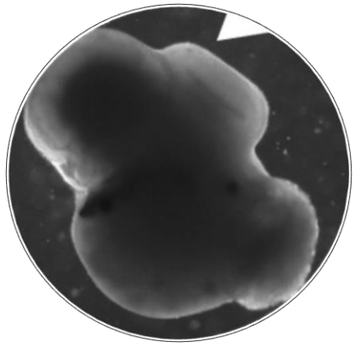




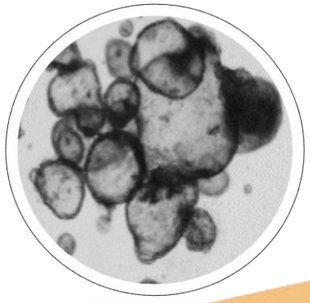
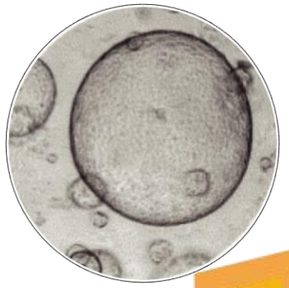
Organoids: "*Miniorgans*" That Are Revolutionizing Biological Research



2° Annual Meeting 3Rs in Italian Universities

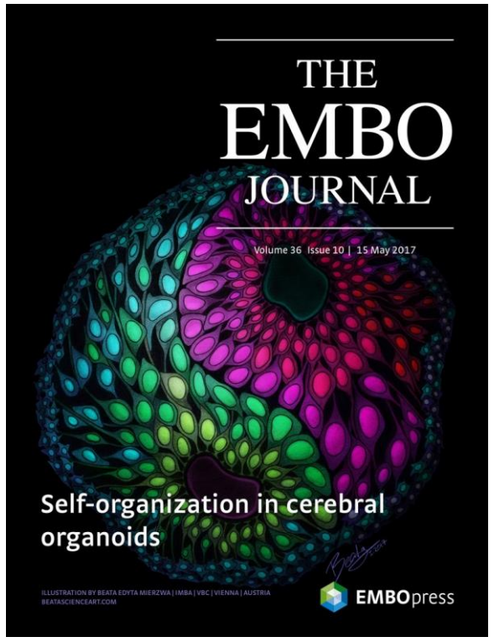
Genova

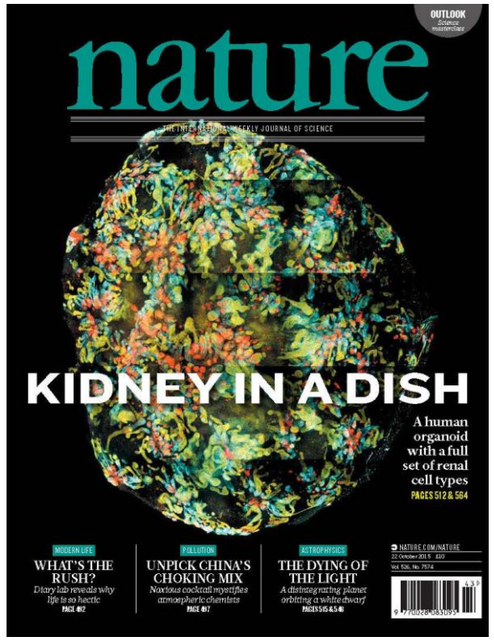
June 20th, 2019

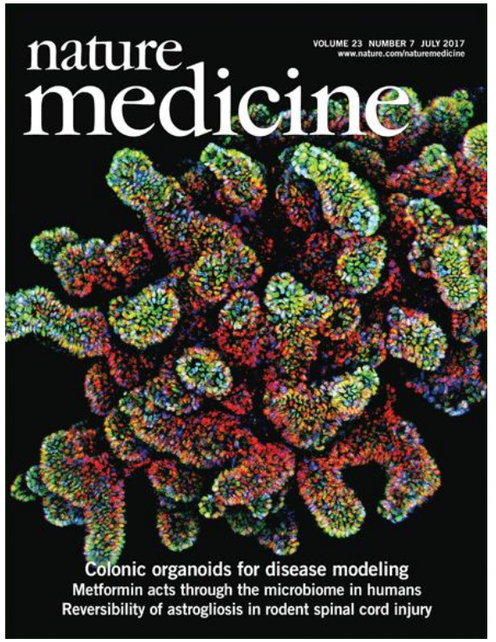



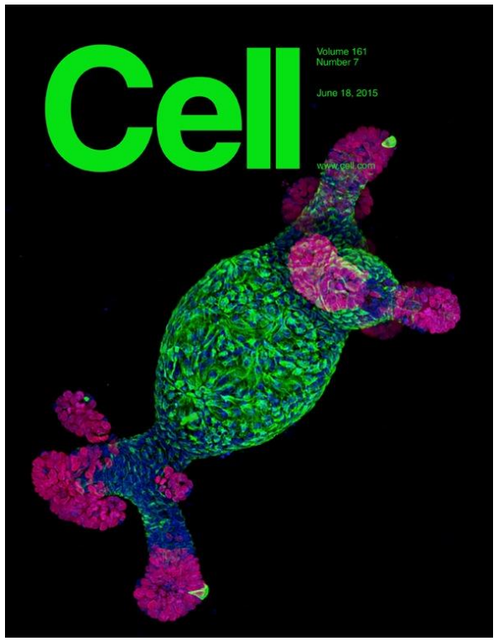
Salvatore Simmini, PhD
Scientist, R&D
STEMCELL Technologies, Cambridge UK
SALVATORE.SIMMINI@STEMCELL.COM

Organoids: Revolutionary Technology







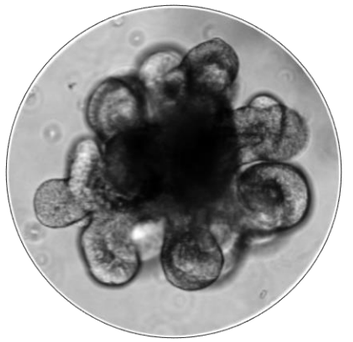


Method of the Year 2017: Organoids

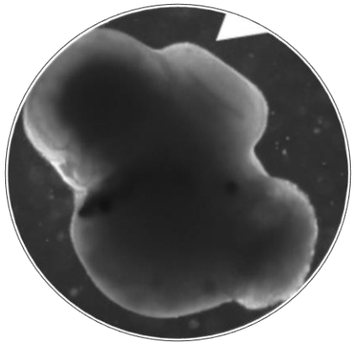
The ability to prod stem cells into three-dimensional tissue models makes for a powerful way to study human biology. But these exciting tools are still works in progress.

STEMCELL™ TECHNOLOGIES

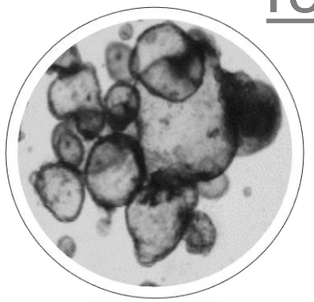
What is an Organoid?

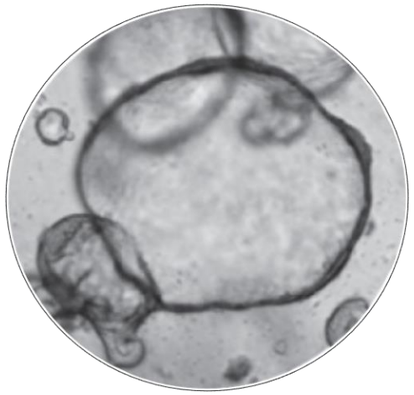


"A 3D structure derived from either PSCs, neonatal tissue stem cells or AdSCs/adult progenitors, in which cells spontaneously self-organize into properly differentiated functional cell types and progenitors, and which resemble their in vivo counterpart and recapitulate at least some function of the organ."



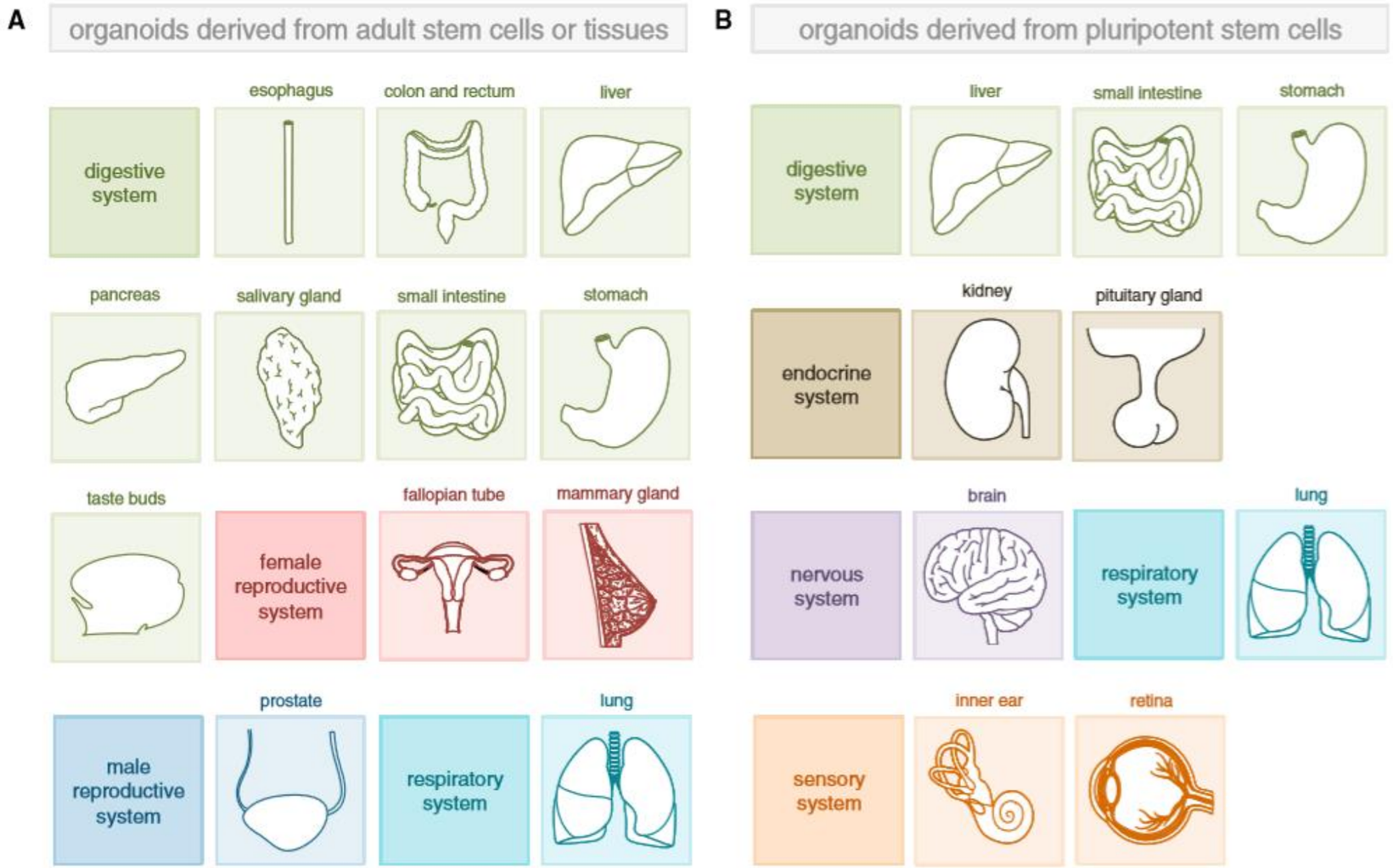
Huch & Koo, Development 2015





STEMCELL™ TECHNOLOGIES

Primary and hPSC derived Organoids Offer a Very Broad Set of Culture Systems

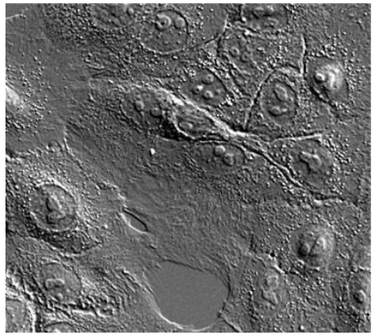


STEMCELL TECHNOLOGIES

Adapted from Kretzchmar K., 2016

Systems to Study Tissue Biology, Human Diseases and Drug Toxicity

Cell lines
(immortalized cancer cells, hPSCs)



Characteristics:

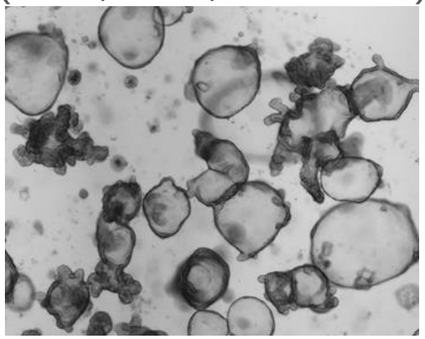
- Simple to maintain and passage
- Single cell type

- Inexpensive and no time consuming
- Easy high-throughput

- No variability
- Easy access to apical side

- Not physiologically relevant
- Does not allow personalized medicine
- Does not resemble the tissue of origin

Organoid cultures
(ADO, PDO, hPSCsDO)



Characteristics:

- Training is needed for maintaining and passaging
- Complex culture system: it contains multiple cell types and external ECM is needed
- Relatively expensive and time consuming
- Possible high-throughput

- Intra and inter culture variability
- Typically apical side is inside and basal side outside of the 3D structures
- Physiologically relevant
- Allow personalized medicine
- Resemble the tissue of origin

Animal models
(mouse, fish, rat, pig…)

Characteristics:

- A lot of training is needed for maintaining lines
- Very complex: it is an animal!

- Very expensive and time consuming
- High-throughput is very difficult or impossible depending from the model
- High variability
- All compartments and all tissues interactions are present
- Physiologically relevant
- Does not allow personalized medicine
- Most of the time it is the tissue of origin!

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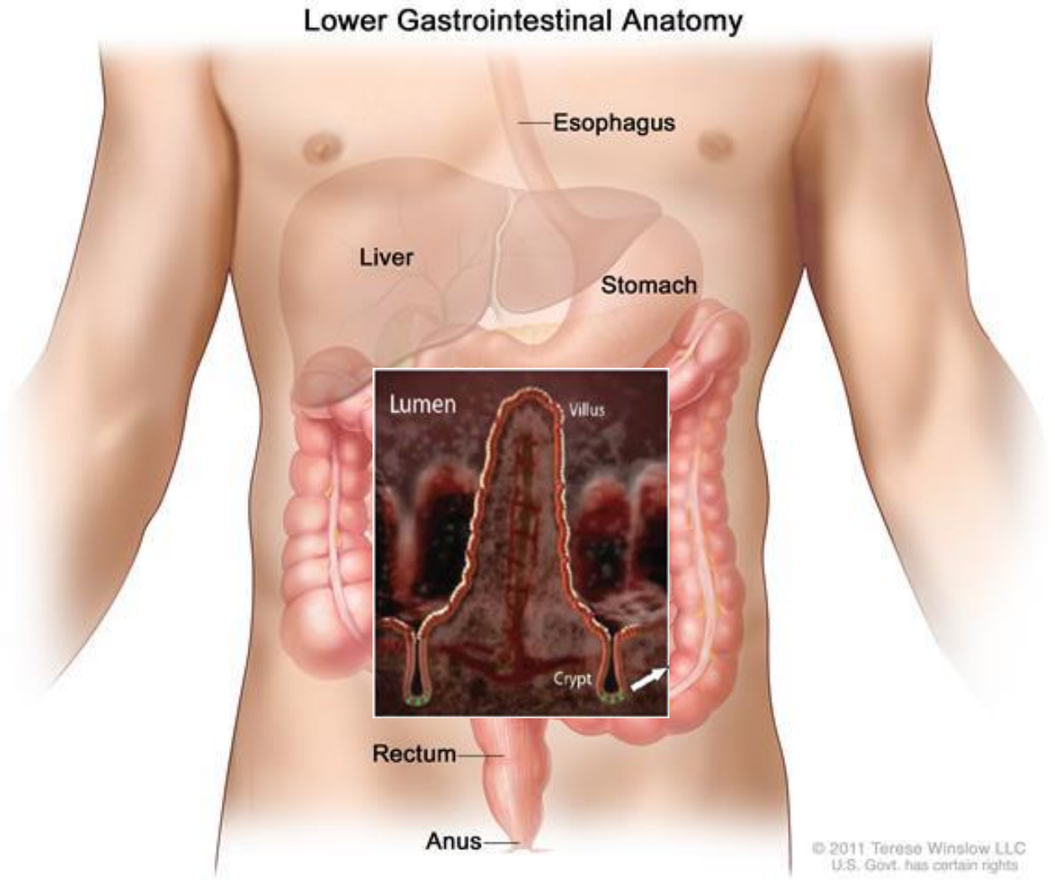
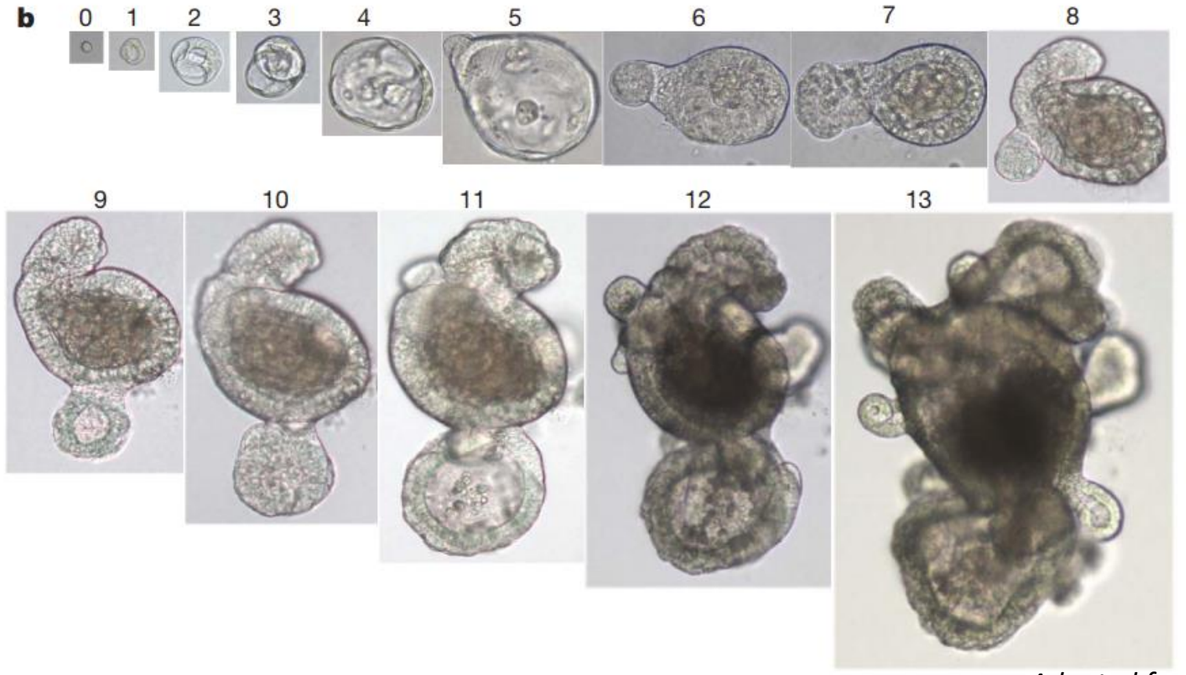
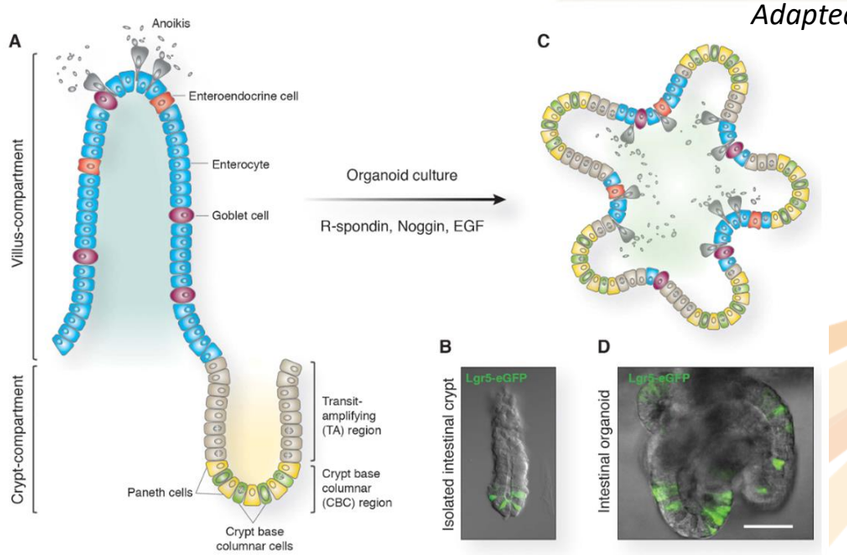
From the Gut to the “MiniGut” Organoids





Adapted from Sato T., 2009



Adapted from Leushacke & Barker, 2014

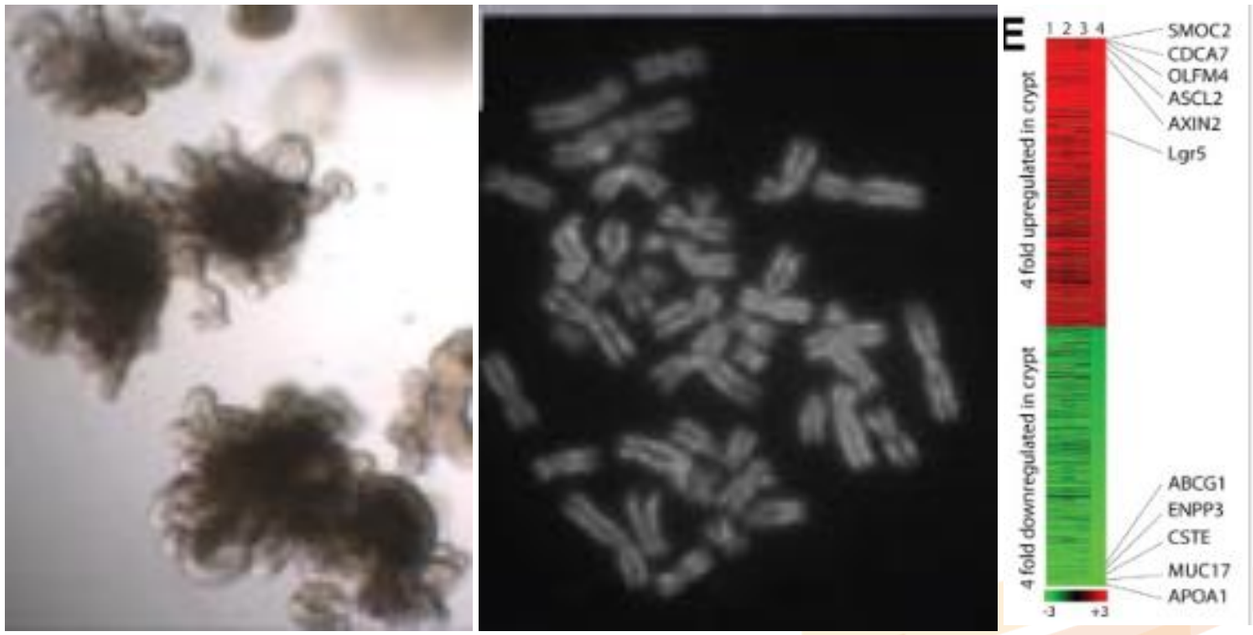
STEMCELL™ TECHNOLOGIES

Human Intestinal Primary Organoids Cultures Resemble Human Gut and Are Genetically Stable

Long-term Expansion of Epithelial Organoids From Human Colon, Adenoma, Adenocarcinoma, and Barrett's Epithelium

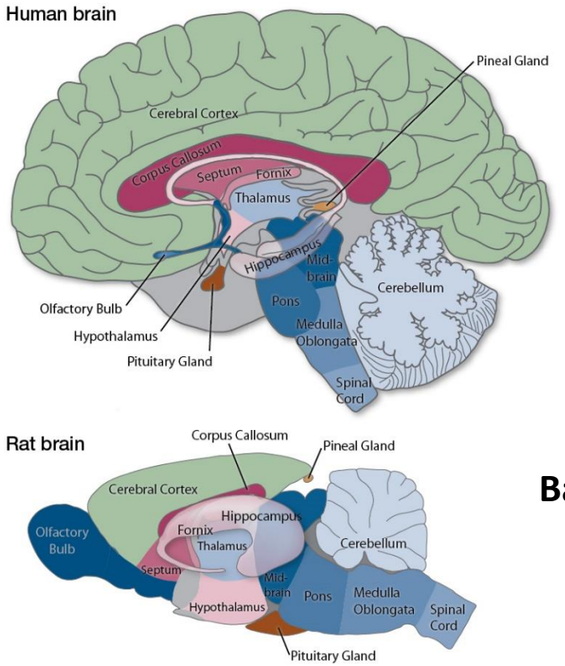
TOSHIRO SATO,* DANIEL E. STANGE,* MARC FERRANTE,*,‡,§ ROBERT G. J. VRIES,* JOHAN H. VAN ES,* STIENEKE VAN DEN BRINK,* WINAN J. VAN HOUDT,‖,¶ APOLLO PRONK,‖ JOOST VAN GORP,# PETER D. SIERSEMA,‡ and HANS CLEVERS*

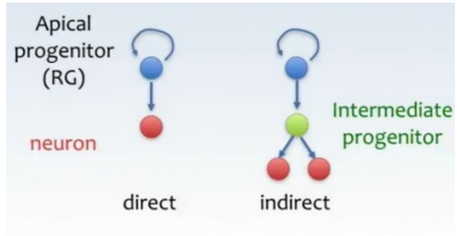
*Hubrecht Institute, KNAW and University Medical Centre Utrecht, Utrecht, The Netherlands; ‡Gastrointestinal Research Unit, Department of Gastroenterology and Hepatology, and ¶Department of Surgical Oncology, University Medical Centre Utrecht, Utrecht, The Netherlands; §Department of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium; and Departments of ‖Surgery and #Pathology, Diakonessenhuis, Utrecht, The Netherlands

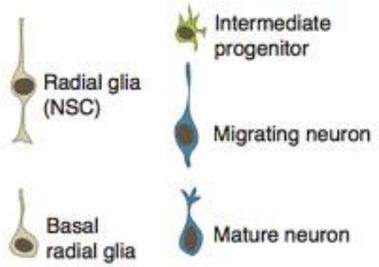


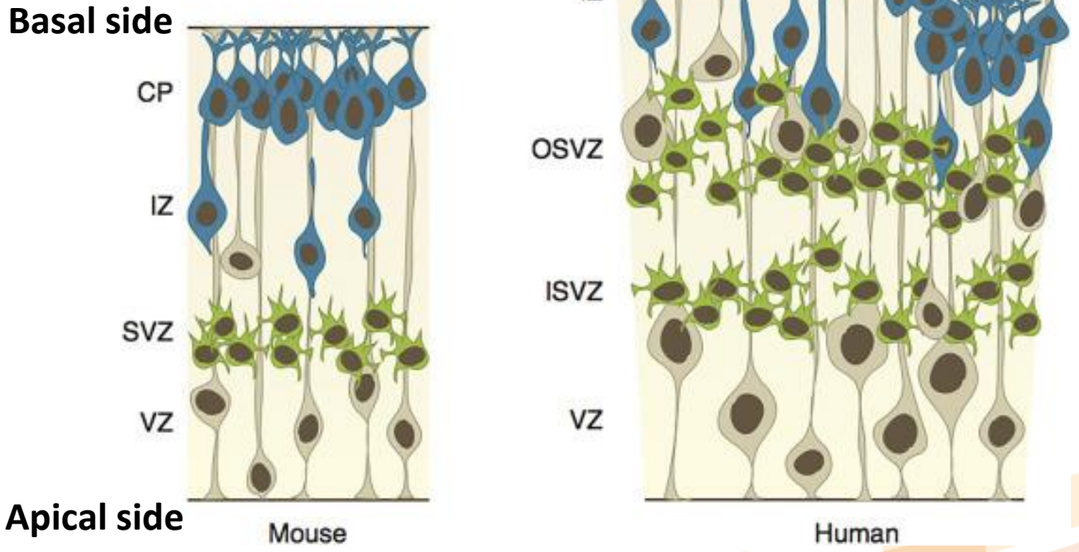
Adapted from Sato T., 2011

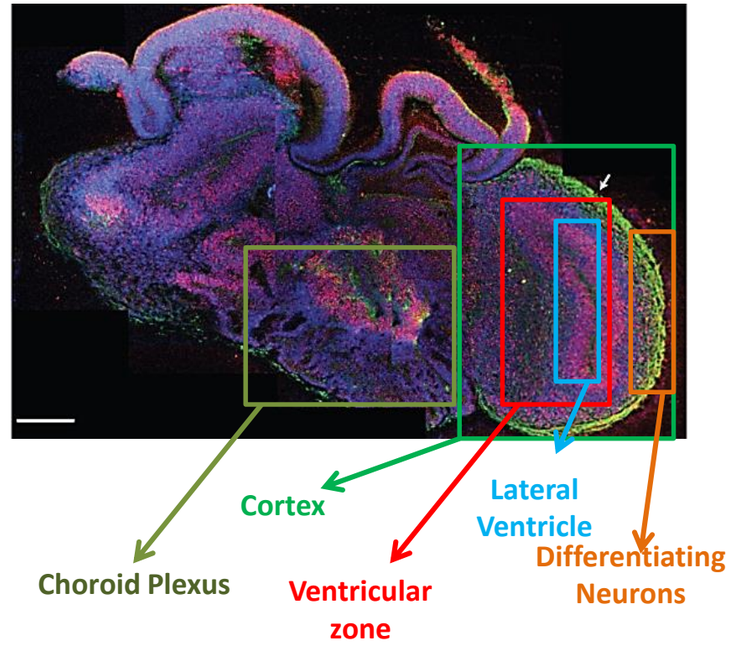
hPSCs Derived Cerebral Organoids for Modelling Development of Human Brain

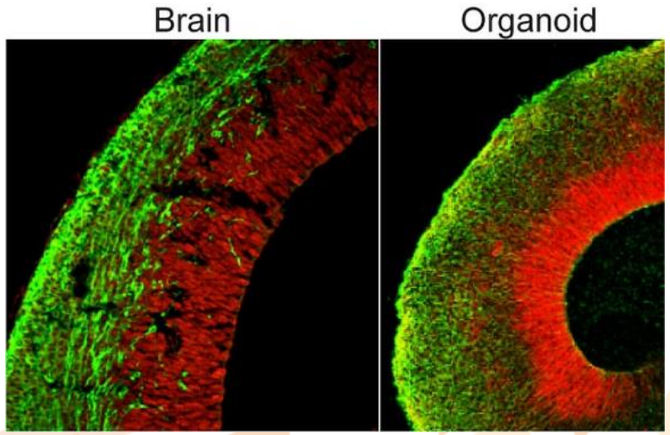












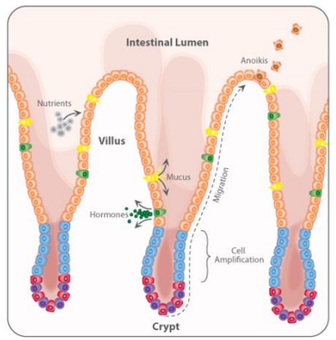
Adapted from Kelava I. and Lancaster M., 2016

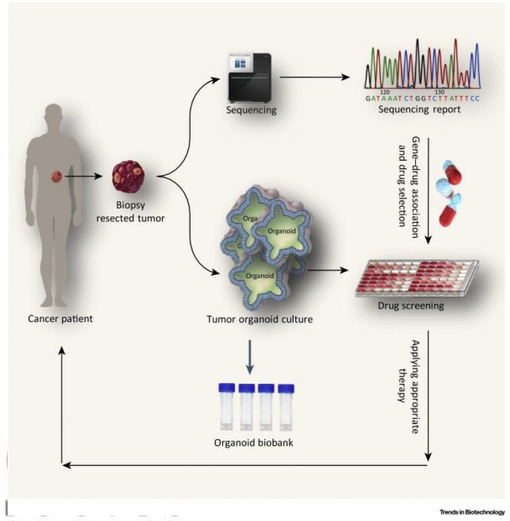
Adapted from Lancaster M., 2013

Applications of Organoids Cultures

Basic and Translational Research

- Development and function of organs
- Disease modelling
  - microcephaly
  - intestinal or more general epithelial diseases
  - cancer
- Host-microbe interactions
  - pathogenic and commensal organisms
  - Zika virus infections
- Mechanisms of epithelial cell and adult stem cell function





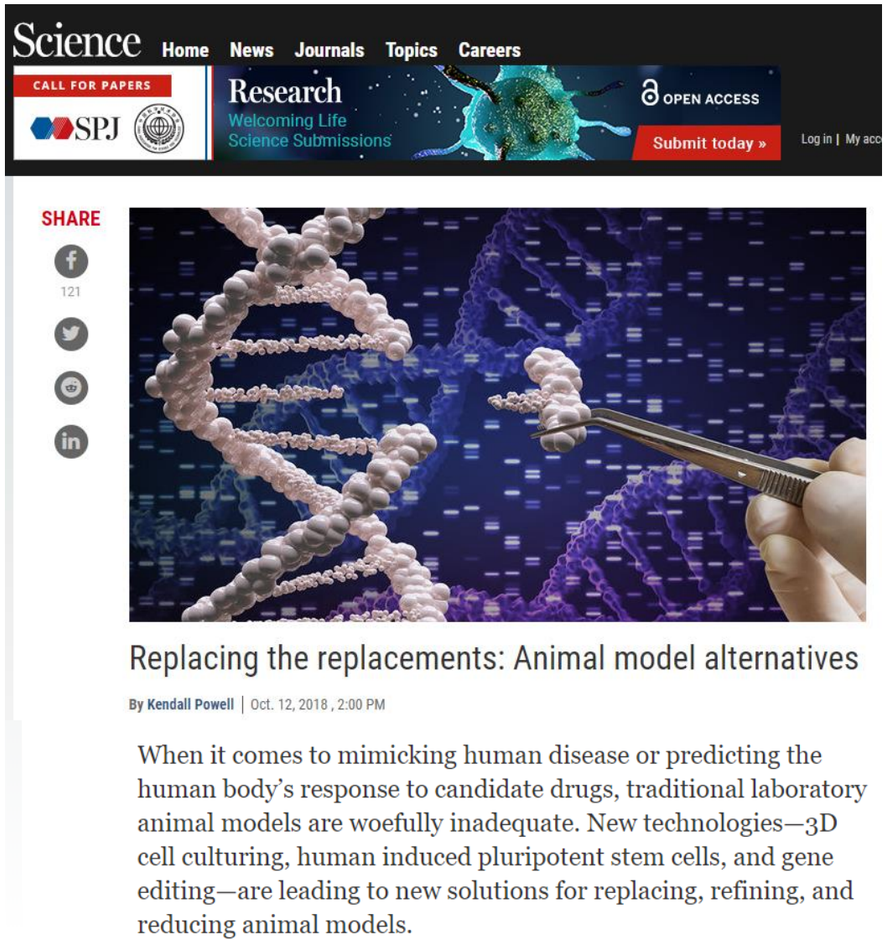
Drug Development

- Disease modelling
  - Crohn's, IBS, CF, colorectal cancer, etc.
  - either low- or higher-throughput depending on where in pipeline
- Absorption of drug candidates
- Toxicity of drug candidates
  - To narrow candidate funnel, not establish safety
- Clinical trial cohort selection
- Drug combination assessment in pre-clinical context
  - especially for cancer

Precision Diagnostics

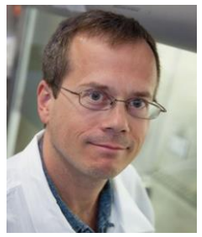
- Genetic diseases
  - e.g. cystic fibrosis
- Cancer

Could Organoids Reduce or Even Replace Animal Models? Answers From the Experts



Mouse and Human Primary derived Organoids
"I believe that [organoid models] will replace a lot of current animal experimentation". However, "a living organism is more than the sum of its parts. There will always be the need for confirmation of any finding . . . in vivo." [Hans Clevers]

hPSC-derived Cerebral Organoids
"Organoids are complementary rather than competing with animal research. It's an illusion to think they can be used to completely replace animal research." [Jurgen Knoblich]



hPSC-derived Definitive Endoderm Organoids
"The fact that [the cells are] human is really important. There can be very different responses to drugs in a mouse and a human." [James Wells]

hPSC-derived Kidney Organoids
"In addition, using the patient's own cells is going to give you all the genes that are modified [in the disorder]. You'll never get that in a mouse." [Melissa Little]

Adapted from The Scientist

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Scientists Helping Scientists™

Tools for Easily and Efficiently Generating Organoids

Intestine

IntestiCult™ Mouse

#06005

IntestiCult™ Human

#06010

Brain

STEMdiff™ Cerebral Organoid Kit

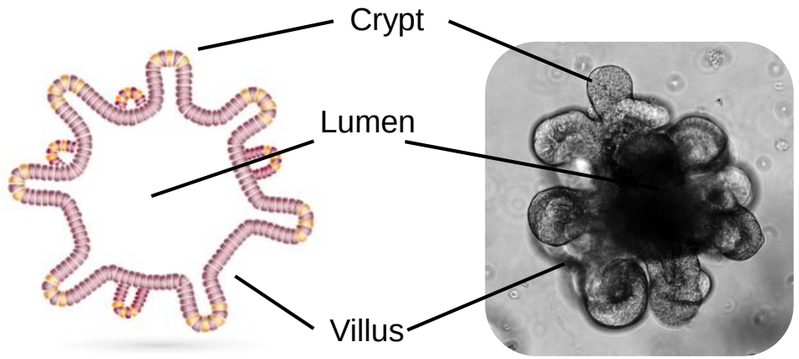
#08570 - #08571

STEMCELL™
TECHNOLOGIES

Efficient Formation of Mouse Intestinal Organoids from Primary Tissue

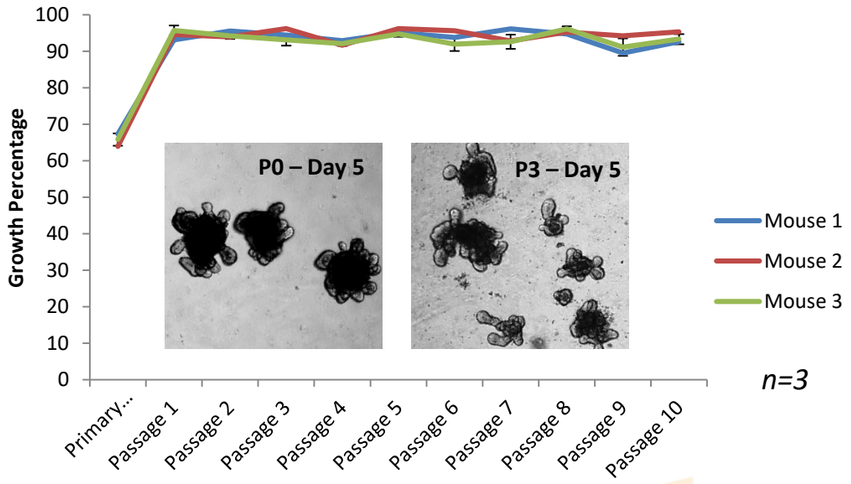
IntestiCult™ Mouse

#06005



Primary organoid culture – Day 5

IntestiCult™ Passaging Growth Percentage



n=3

Once established from crypt culture, > 90% of passaged organoids grow

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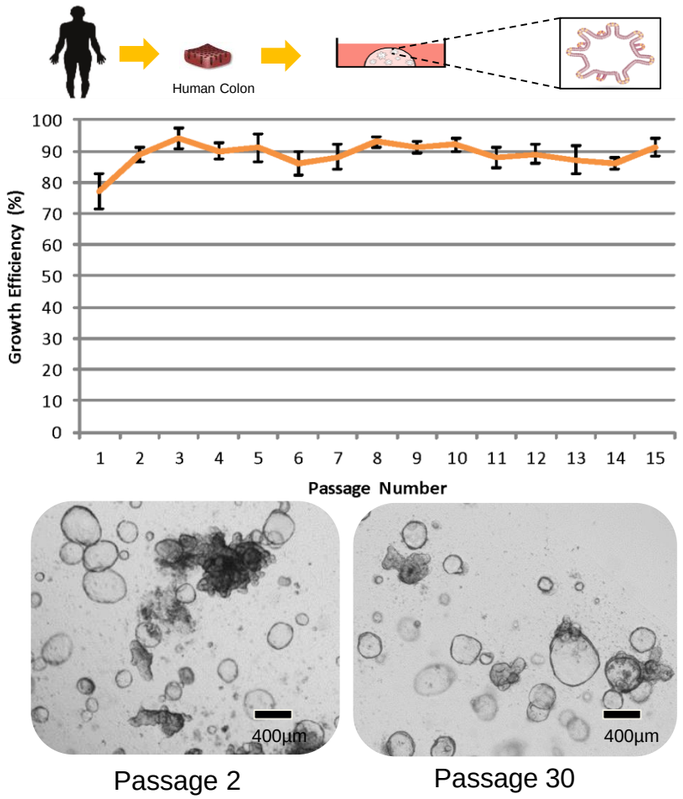
Efficient Formation of Human Intestinal Organoids from Primary Tissue

IntestiCult™ Human

#06010



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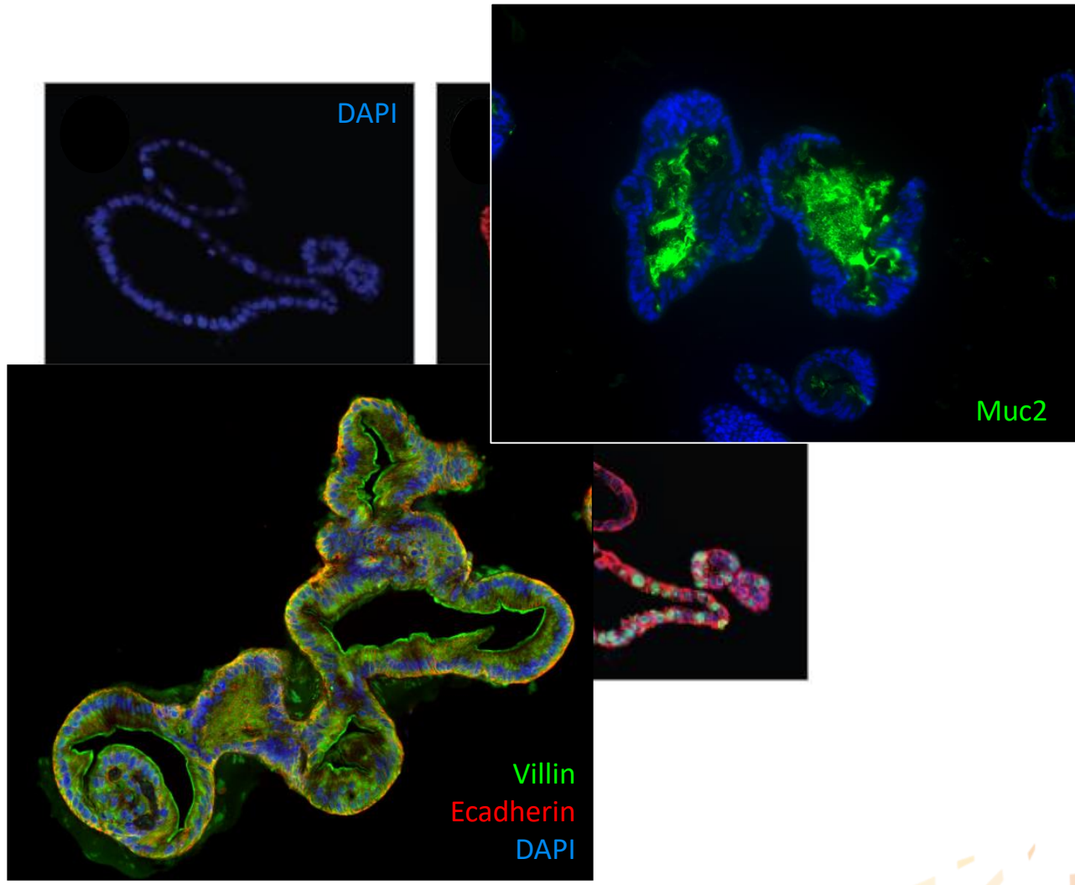


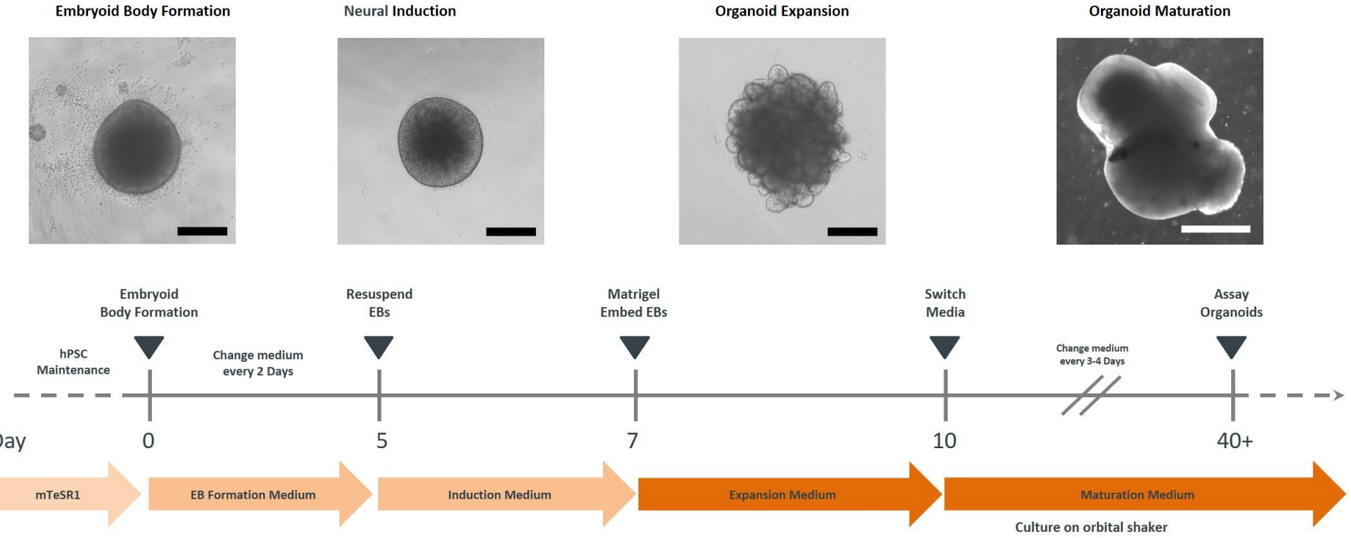
- IntestiCult™ supports the establishment and long-term maintenance of primary Intestinal organoids resulting in more standardized data acquisition
- Organoids can be cryopreserved

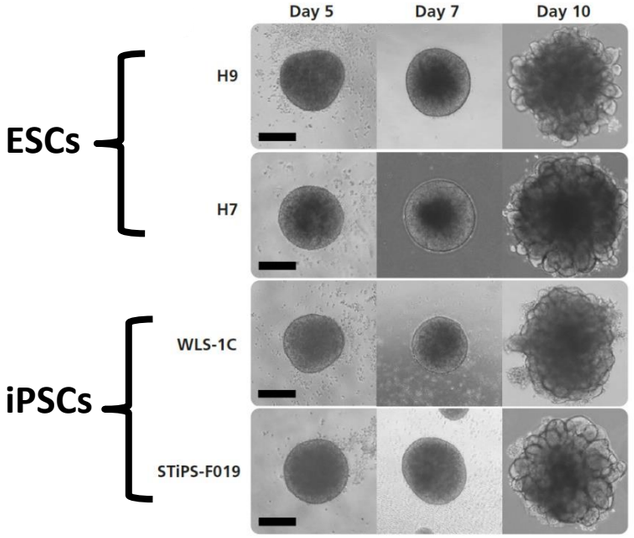
STEMCELL™ TECHNOLOGIES

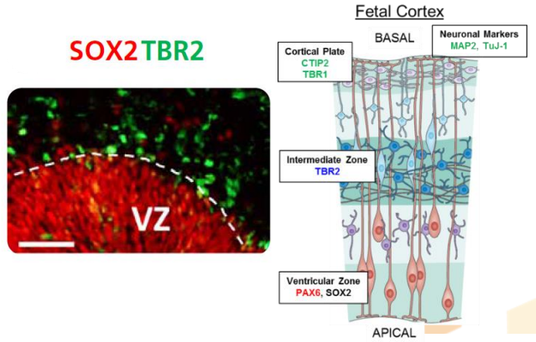
Efficient Formation of Cerebral Organoids from Multiple hPSC Lines

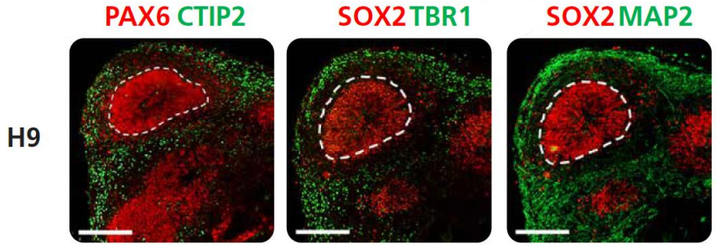
STEMdiff™ Cerebral Organoid Kit

#08570 - #08571



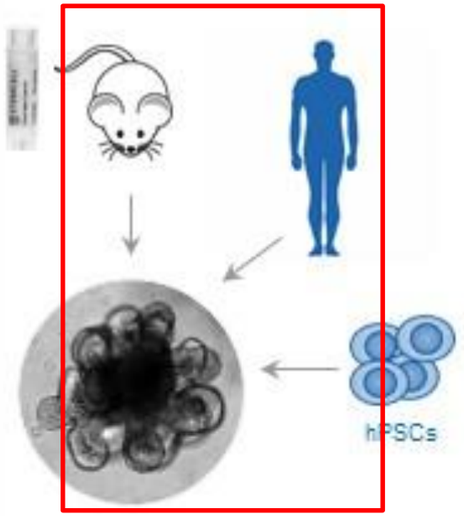






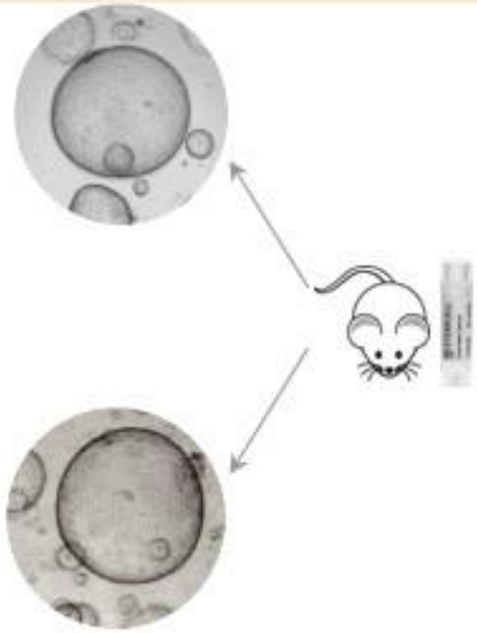
STEMCELL Expanding Organoid Product Lines Support Diverse Tissue Types

Intestinal



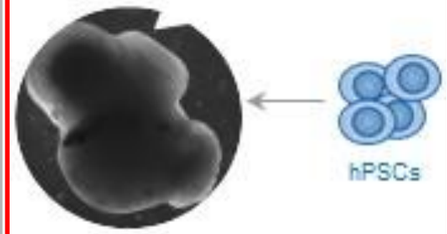
- Mouse Primary Tissue-Derived
- Human Primary Tissue-Derived
- Human ESC/iPSC-Derived

Hepatic Progenitor
Pancreatic Exocrine



- Mouse Primary Tissue-Derived

Cerebral



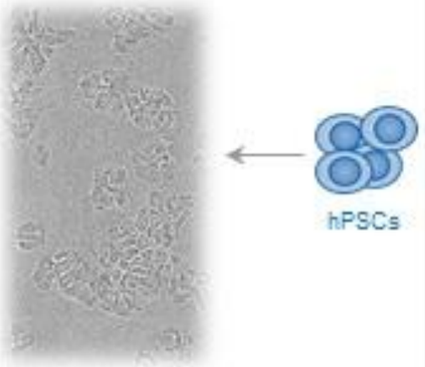
- Human ESC/iPSC-Derived

Airway

- Human Primary Tissue-Derived

Kidney

Coming Soon



- Human ESC/iPSC-Derived

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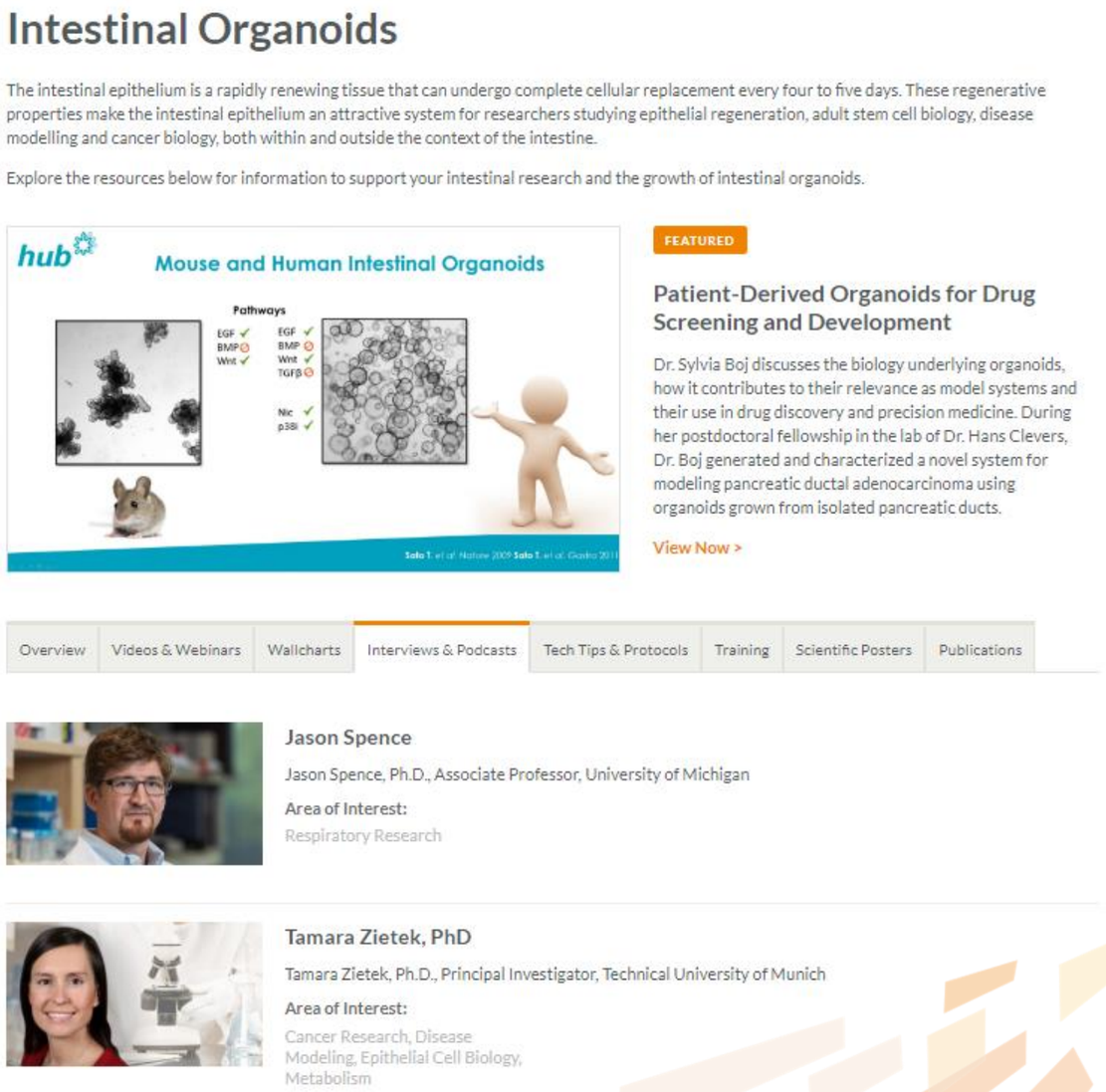
STEMCELL Website as Organoids Resource Center

A Collection of Educational Resources Including:

- Literature Reviews
- Videos and Webinars
- Wallcharts
- Interviews and Podcasts
- Technical Tips and Protocols
- Training Courses
- Scientific Posters
- Publications Sorted by Applications

www.stemcell.com/organoids

Intestinal, Liver and Pancreas Organoids Course in Cambridge (UK) Next October



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Scientists Helping Scientists™

Thanks!

Questions?

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