Biomics Lab Grenoble

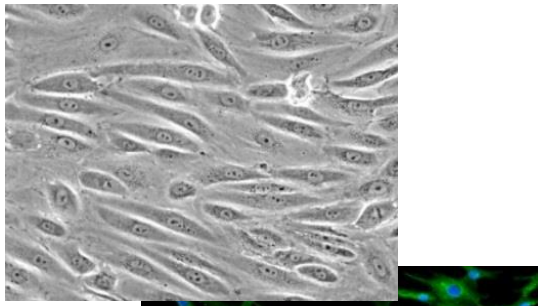
CEA/IRIG, INSERM, UGA

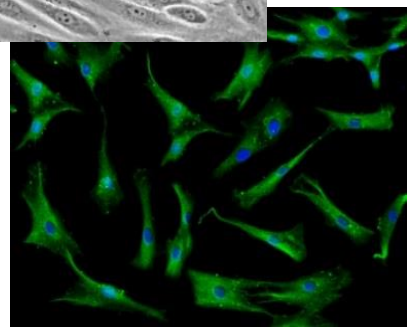
Xavier Gidrol, PhD

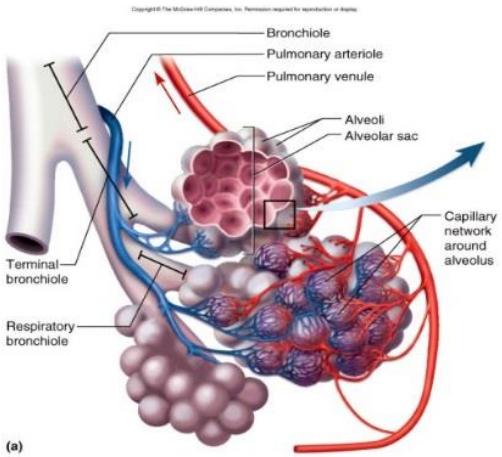


Life is in 3D

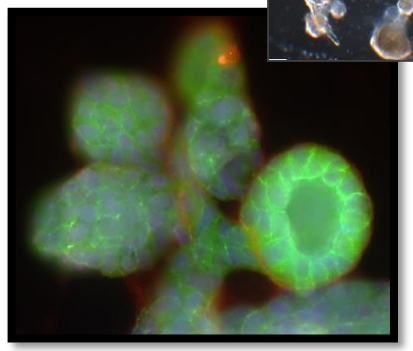
2D — **BETTER REPRESENTATION OF PHYSIOLOCAL REALITY** — **3D**







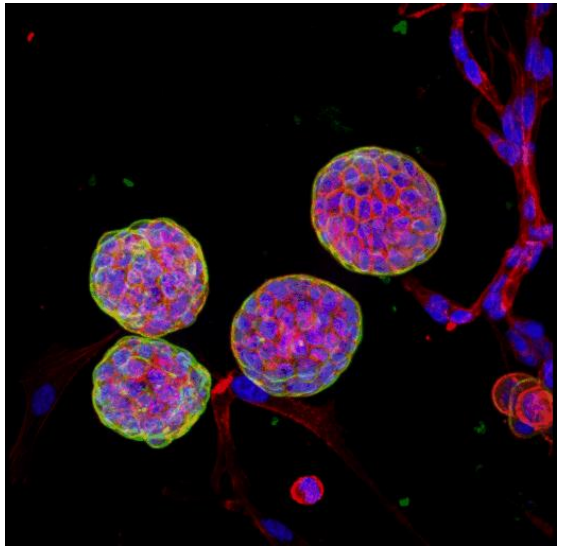




One needs physiologically relevant 3D models in human biology

Organ surrogates

What are the scientific issues?



Prostatic organoid

- ✓ **Basic Research Issues: Organ surrrogates could model organ development, organ physiology and pathology**
- ✓ **Pharmaceuticals Issues : Disease-modelling organs surrogates could improve discovery of new biomarkers, new therapeutics compounds. Could also improve the evaluation of their efficacy & toxicity**
- ✓ **Clinical Issues : Personalized pharmacodynamics and pharmacokinetics *ex-vivo* clinical trials, regenerative medicine**
- ✓ **Ethical Issues : Reducing and replacing animal testing**

Organ Surrogates : Definitions

DEFINITIONS

Organoids, Spheroids, Tumoroids
3D culture of human cells
Autoorganisation.

Organs on Chip
Structured or patterned biomimetic microsystems. Link microfluidic channel to cell layers in 2D or 3D. 3D Bioprinting of bioinks containing living cells in an hydrogel is possible

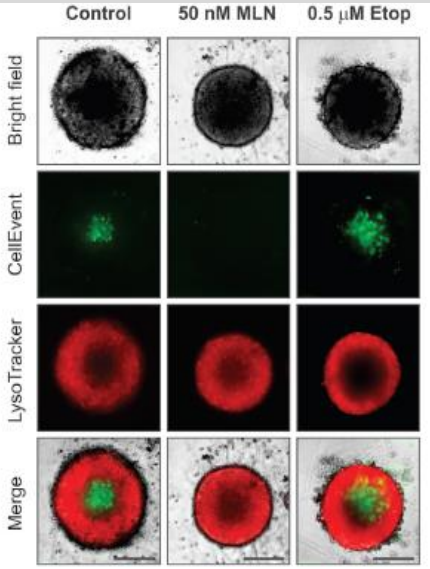
These two axes are converging Organoids-on-Chip

hESCells
iPSCells
Adult Stem Cells
(From patients or cell lines)

Spheroids

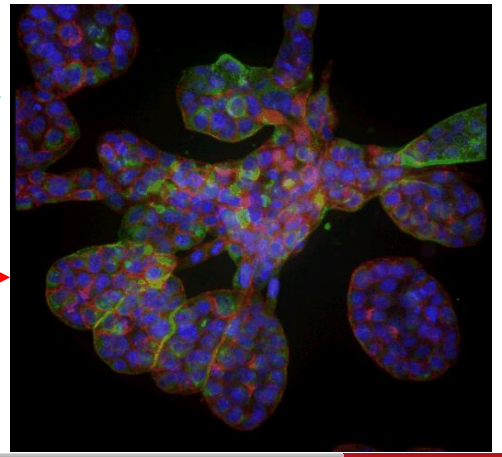


Tumoroids

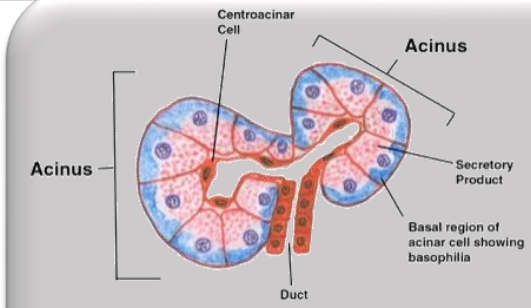


Organoids

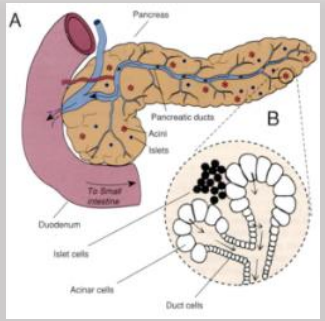
Nuclei
Laminin V
F-actin



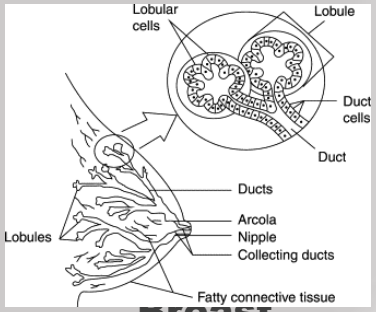
Modelling Glandular Epithelial Cancers



Prostate

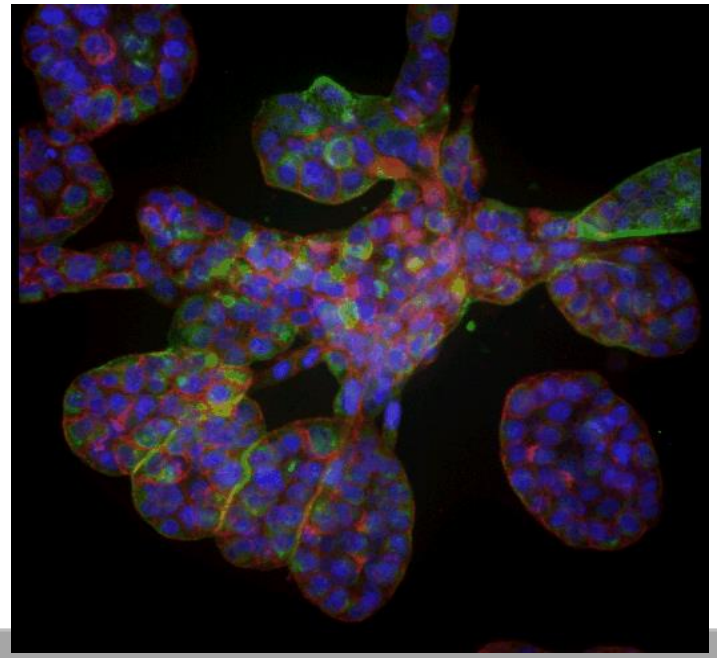


Pancreas



Breast

The Acinus: structural and functional unit of secretory gland



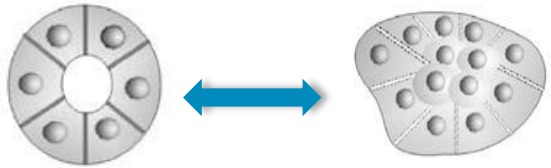
Acinar Development & Carcinogenesis

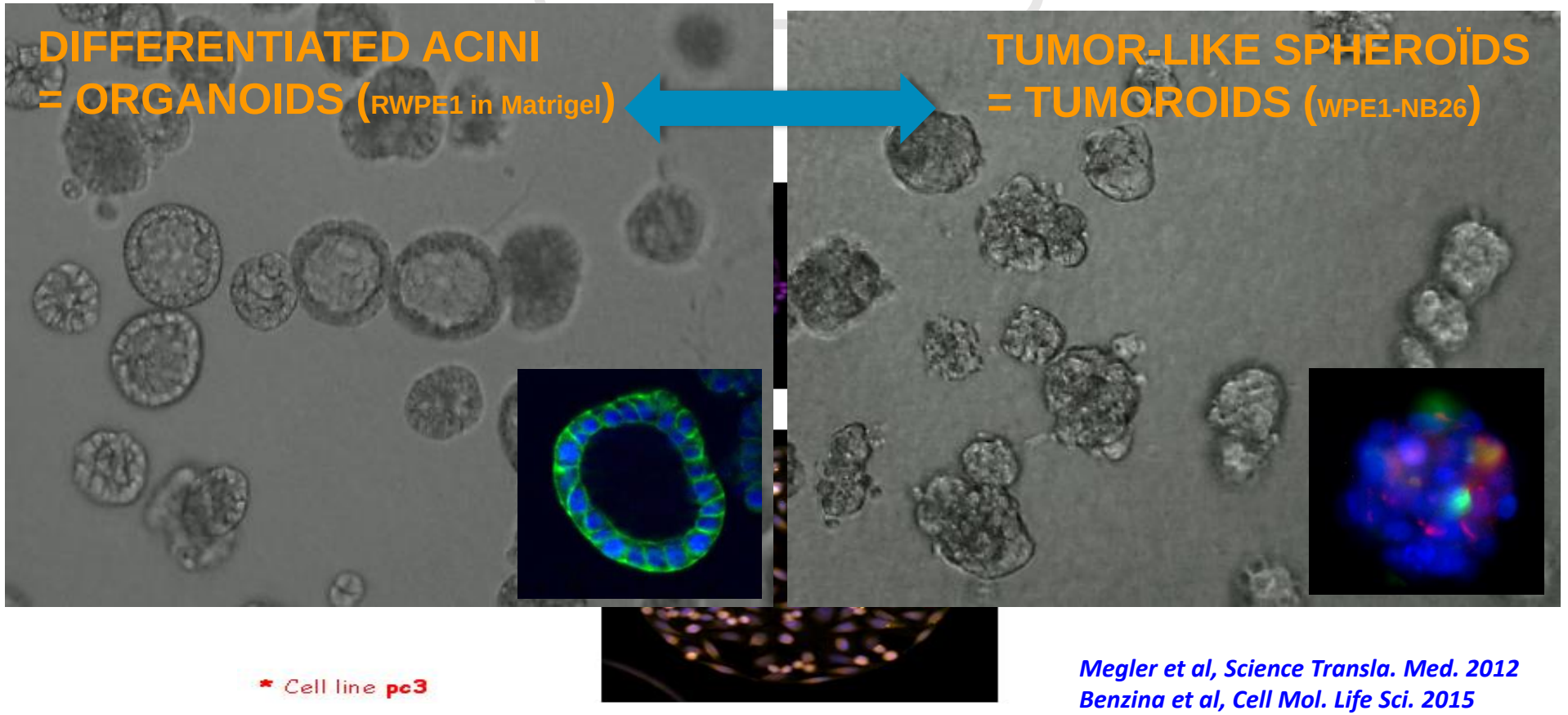
Prostatic Organoid

Nuclei
Laminin V
F-actin

Acinar Development & Carcinogenesis

RNAi-based functional screens to characterize genes which control the proliferation/differentiation balance as a source of new biomarkers and new therapeutic targets

DIFFERENTIATION  **PROLIFERATION**

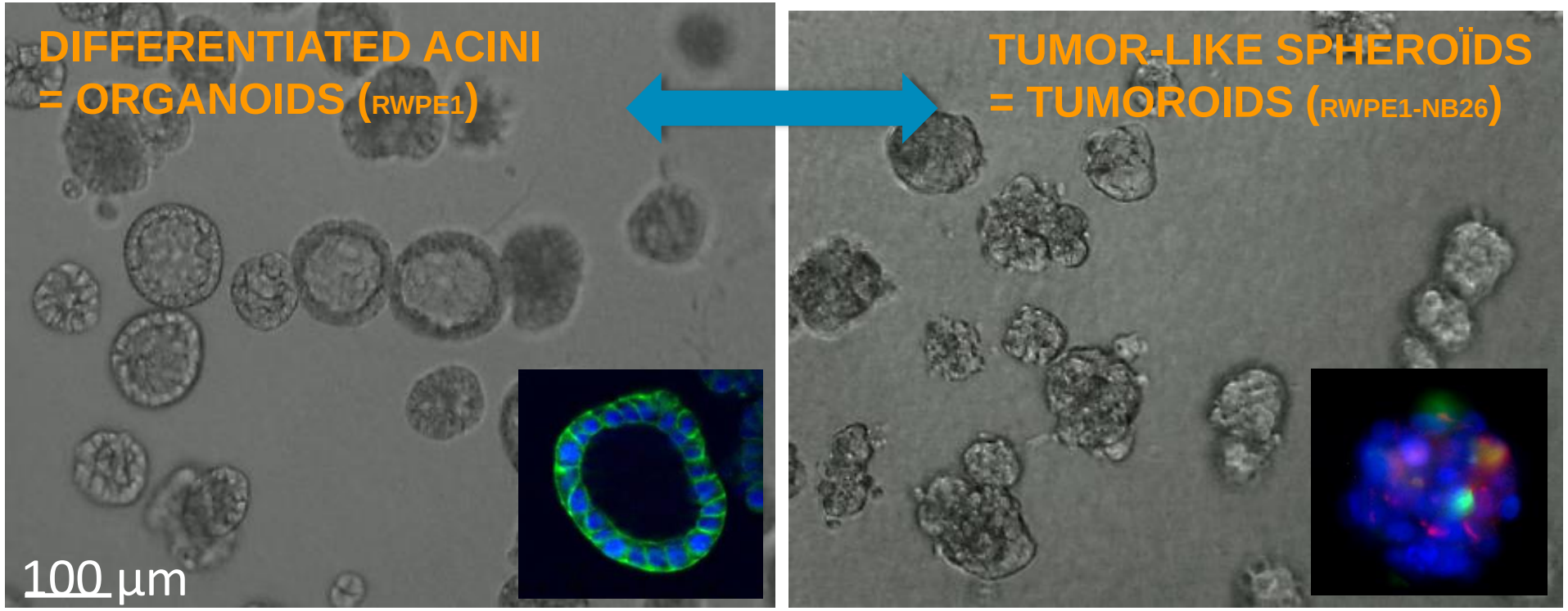


* Cell line pc3

Megler et al, Science Transla. Med. 2012
Benzina et al, Cell Mol. Life Sci. 2015

Acinar Development & Carcinogenesis

RNAi-based functional screens to characterize genes which control the proliferation/differentiation balance

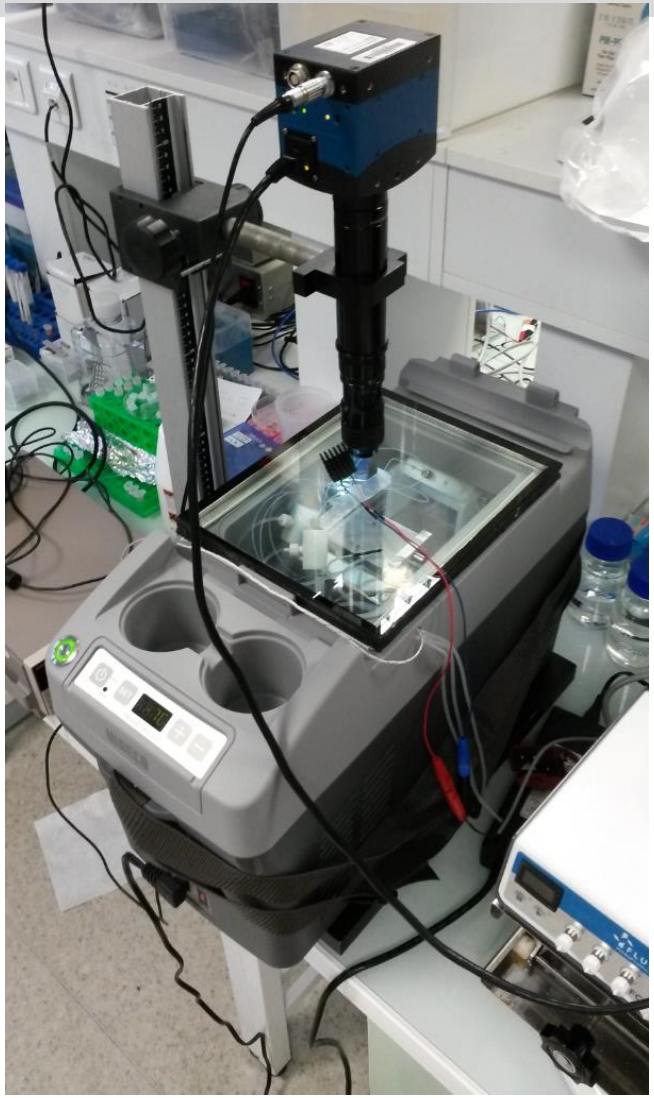


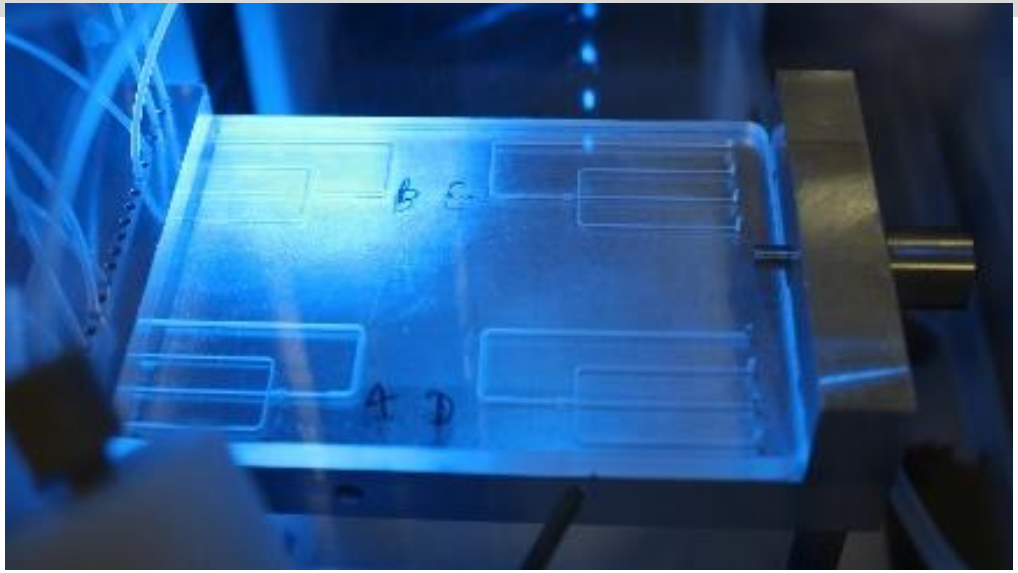
- Because of the heterogeneity of 3D structures
- Because one single tumor is made of several proliferating clones
- Because of the difficulty in recovering 3D structures

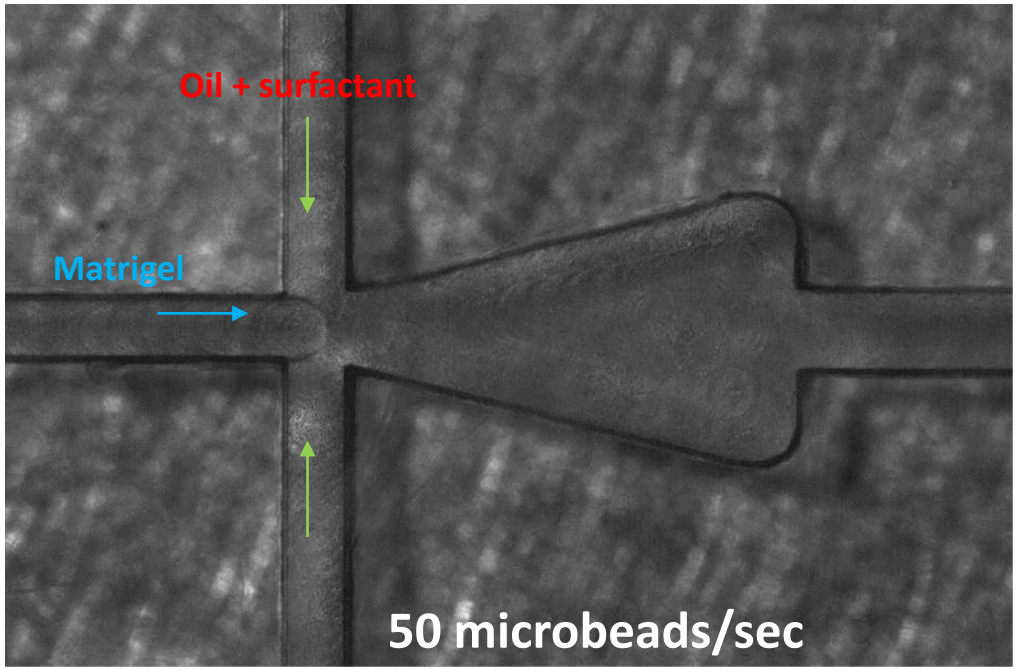
A new way of generating 3D structures to improve control, clonality and recovery

Encapsulation of Organoids/Spheroids/Tumoroids

S. Porte, M Dolega, B Laperoussaz





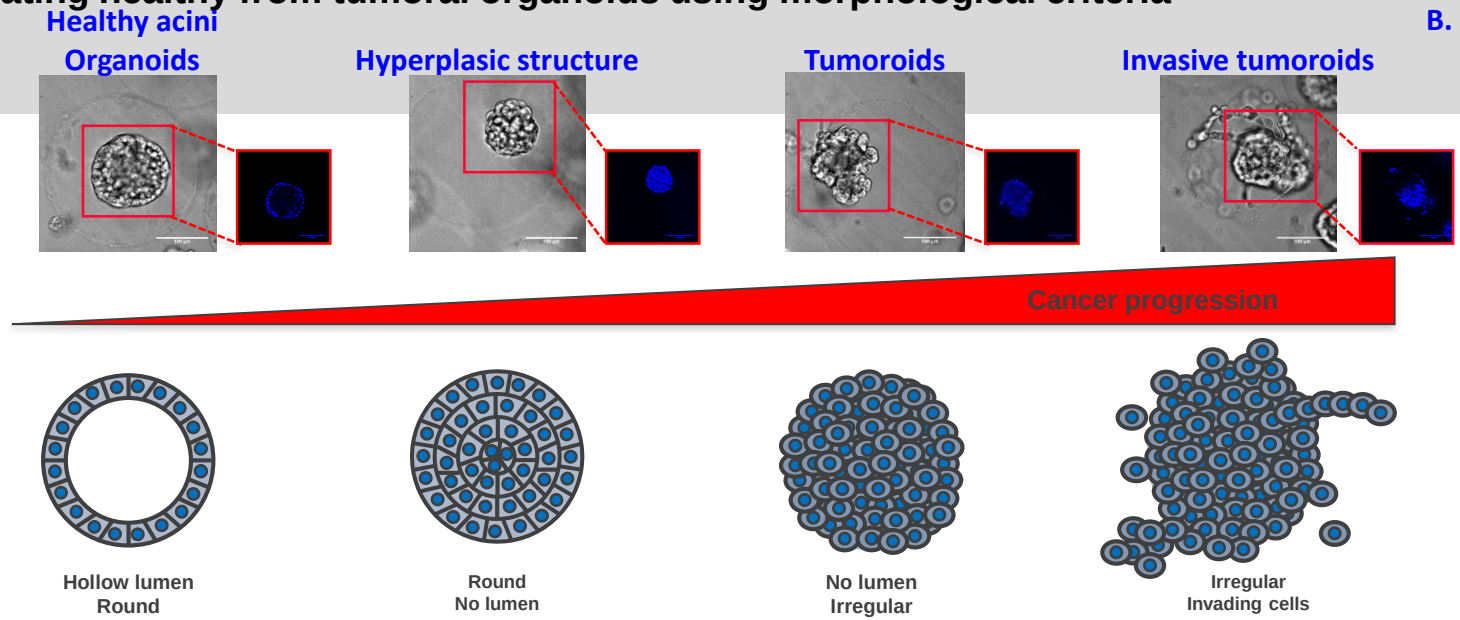


Dolega et al, Biomaterials, 2015

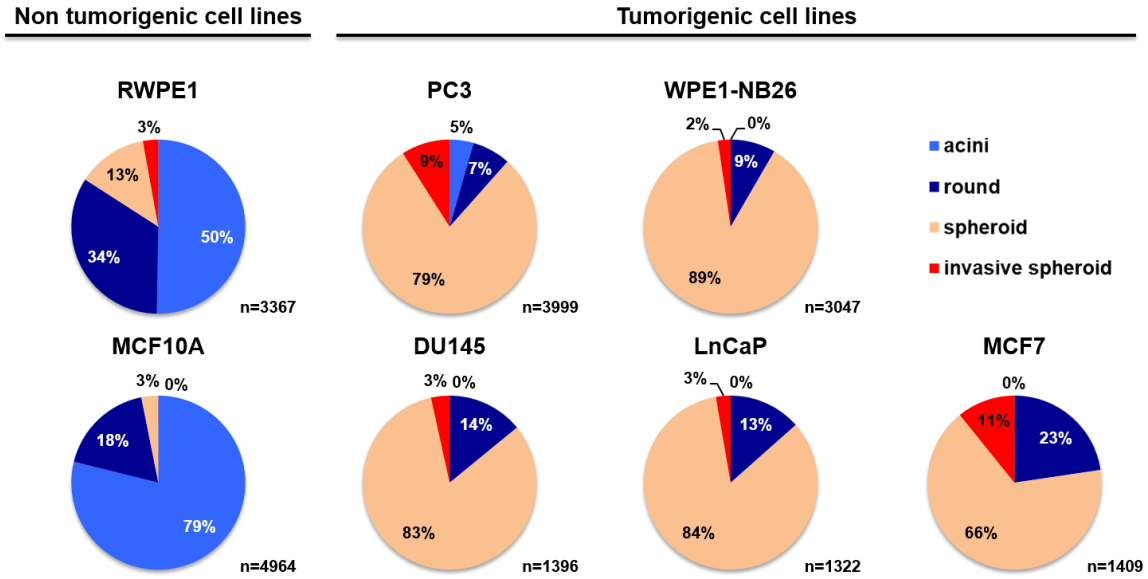
Laperoussaz et al., NAR 2018

A) Discriminating healthy from tumoral organoids using morphological criteria

B. Laperrousaz, S Porte, F Kermarrec



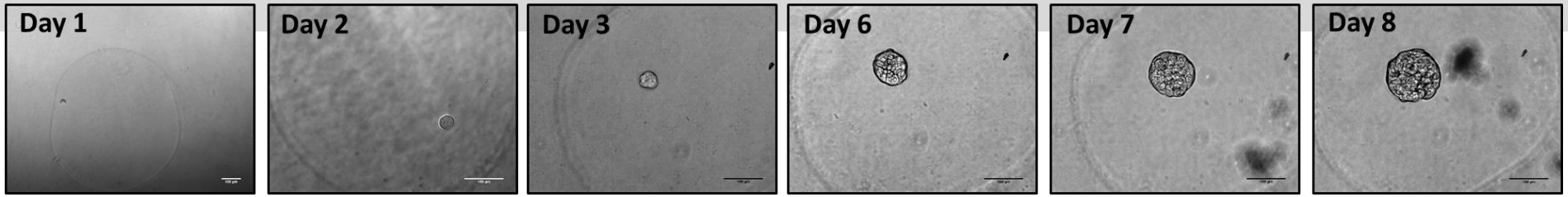
B) Organoid discrimination in different cell lines



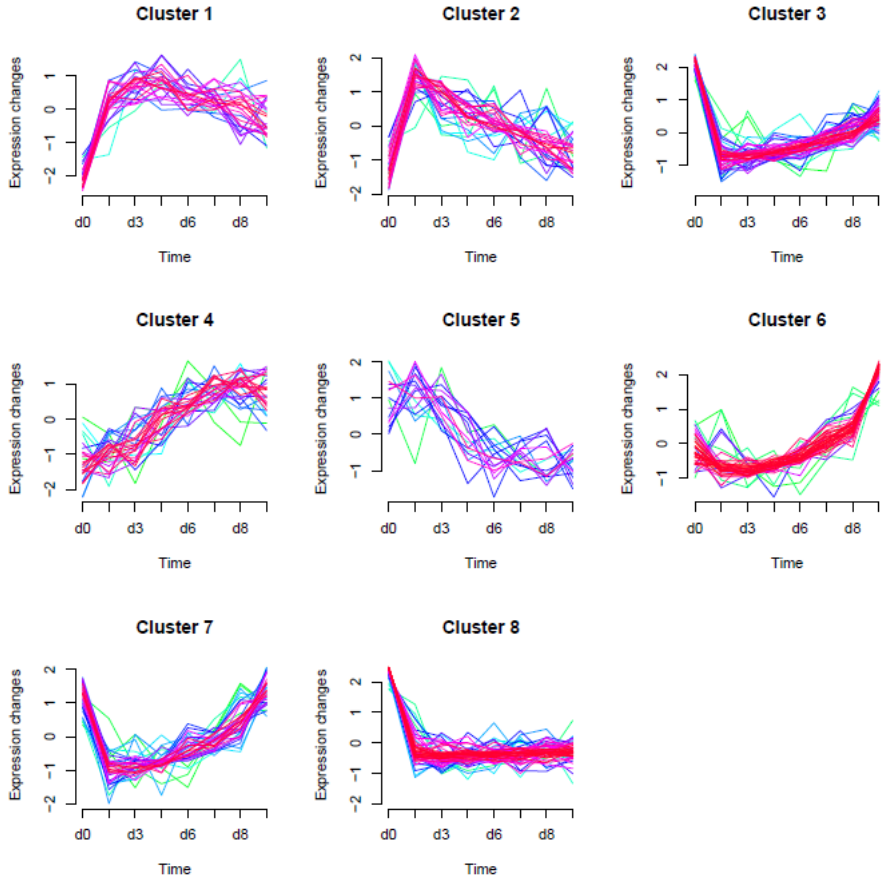
Laperoussaz et al., NAR 2018

RNA-Seq of 4D Clonal Organoid Development

S Porte, P Obeid



Prostatic Cell Line
RWPE1
VS
Prostatic Cell Line
WPE1-NB26



Nuclei
Integrin β1
Giantin

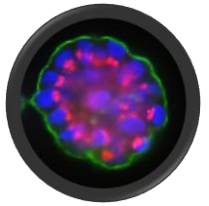
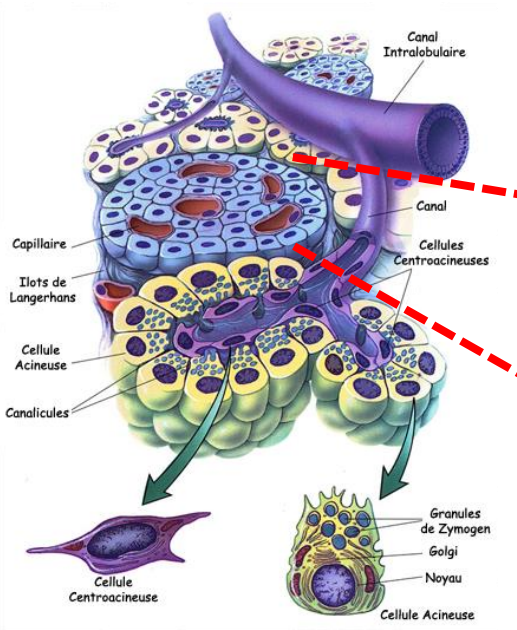


Figure 12: **Soft clusters of significant genes identified in the RWPE1 vs WPE1-NB26 between each stage analysis.** The genes are gathered in function of their fluctuation over the time. The x-axis represents the different time points and the y-axis the standardized normalized mean count from samples belonging to a given time point.

Pancreatic Islets Spheroids (InSphero)

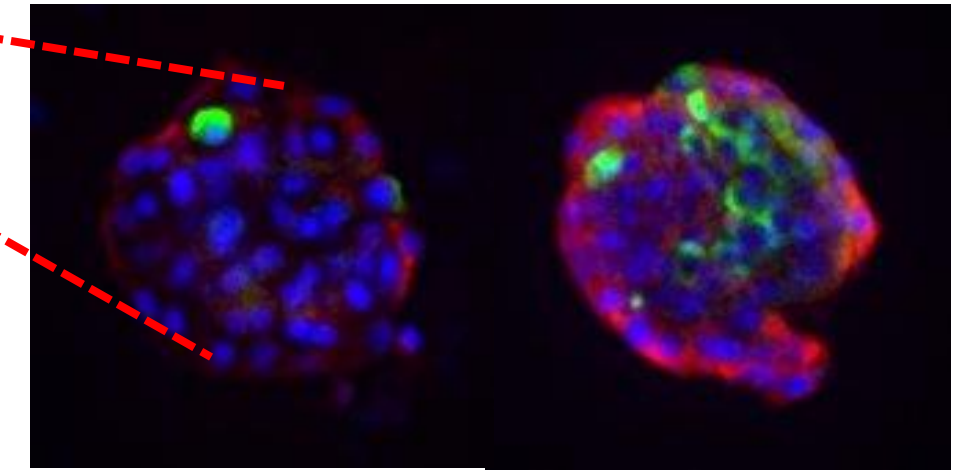
A. Pitaval, C. Laporte



Human primary cells from cadaveric donors reaggregated into spheroids

Low glucose

High glucose

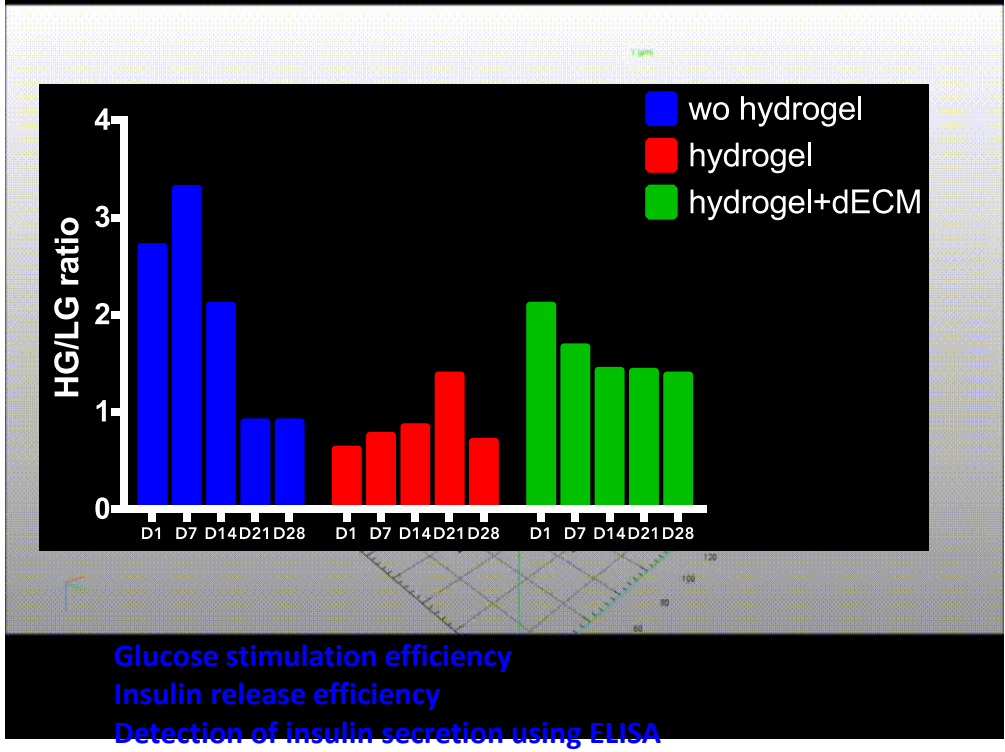


Insulin

Glucagon

DAPI

Quantification of insulin secretion after glucose stimulation



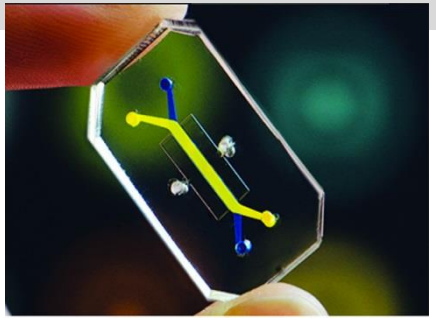
Glucose stimulation efficiency

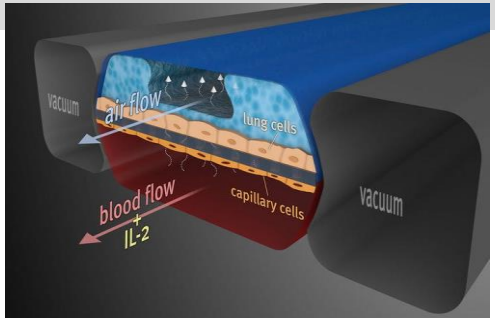
Insulin release efficiency

Detection of insulin secretion using ELISA

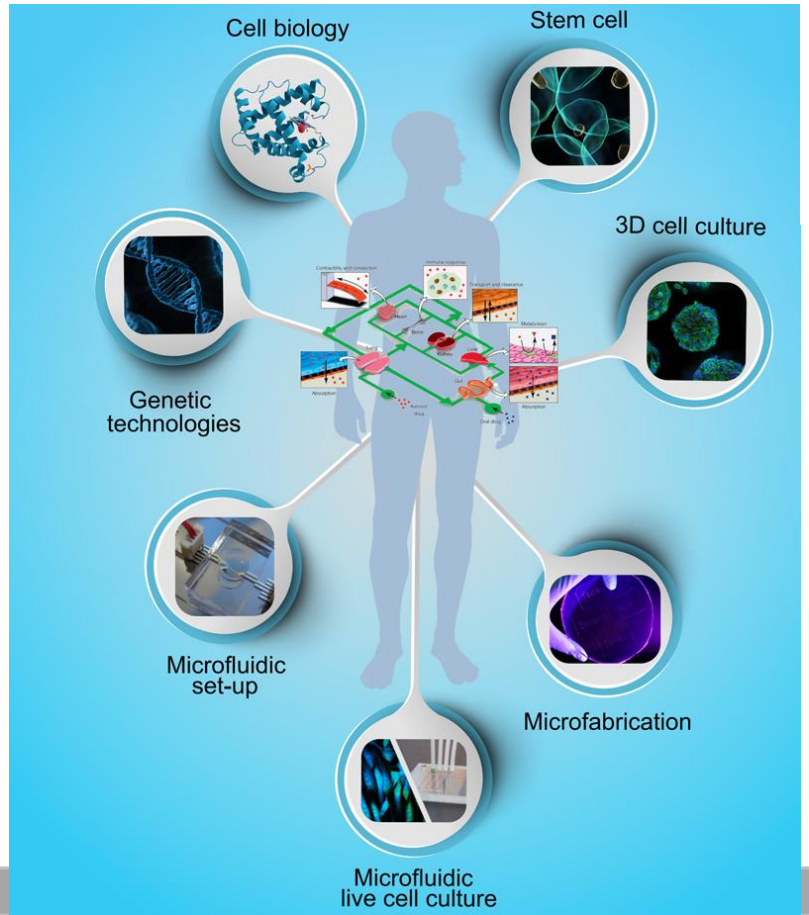
Beneficial effect of dECM at D21/D28

Organs-on-chip



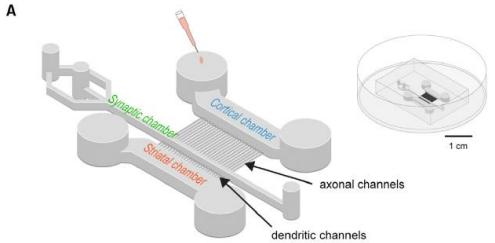


Huh et al. Reconstituting organ-level lung functions on a chip. Science, 2010





TISSUSE
Emulating Human Biology

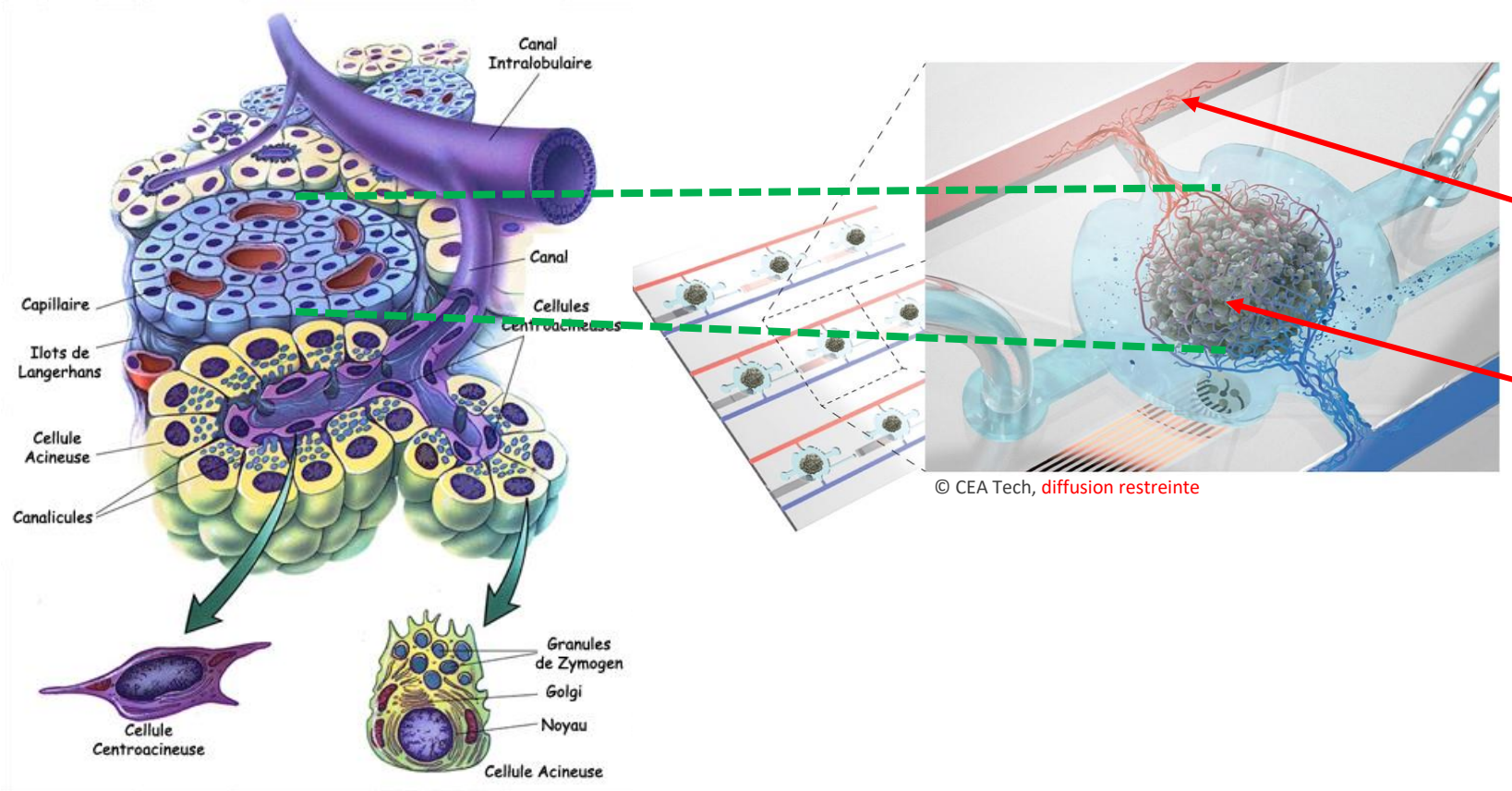


Huntington on Chip
GIN, Grenoble



3D printed
Heart on Chip
with integrated sensing
Harvard University

Vascularized Islet-on-Chip



© CEA Tech, diffusion restreinte

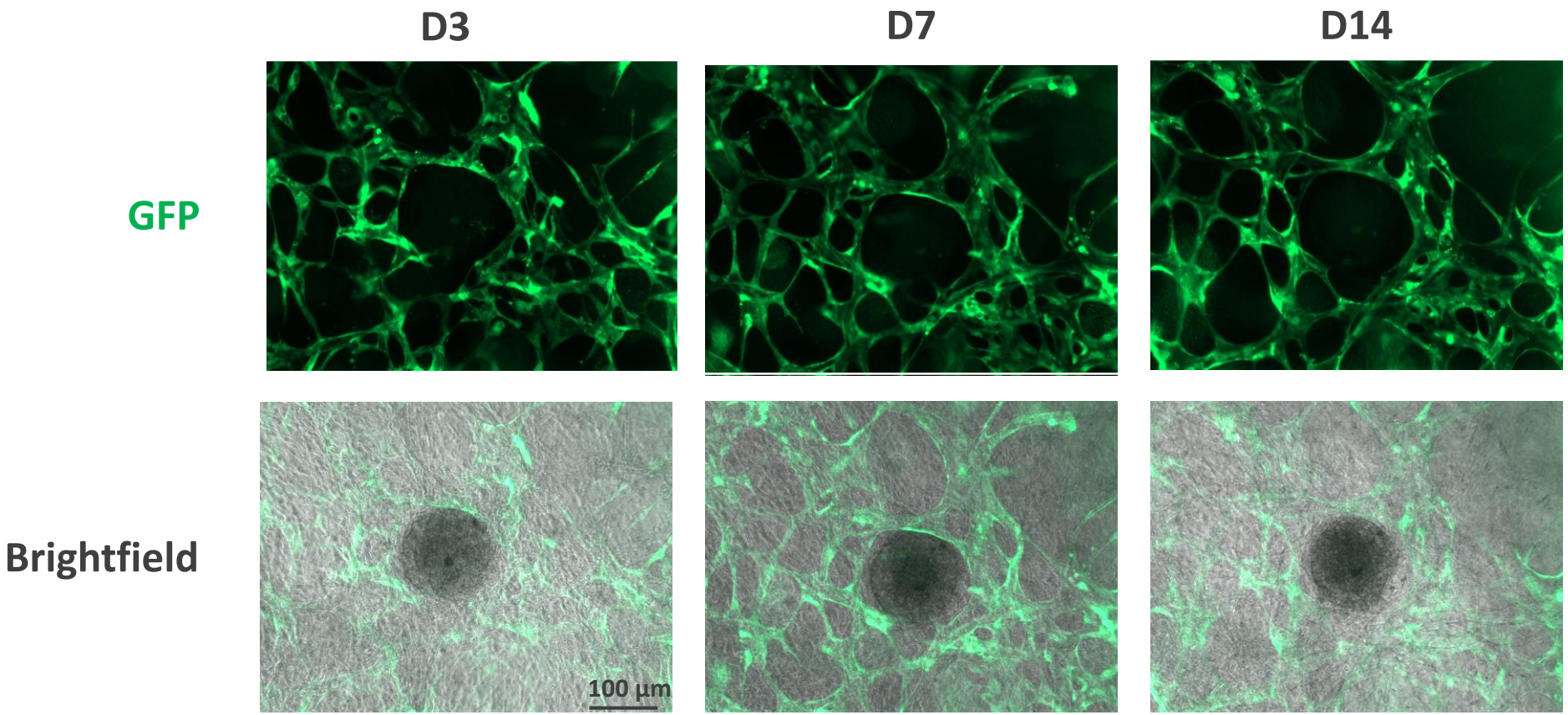
Guided vascularization

Self-Organized vascularization

Pancreatic Islets with a surrounding vascular network

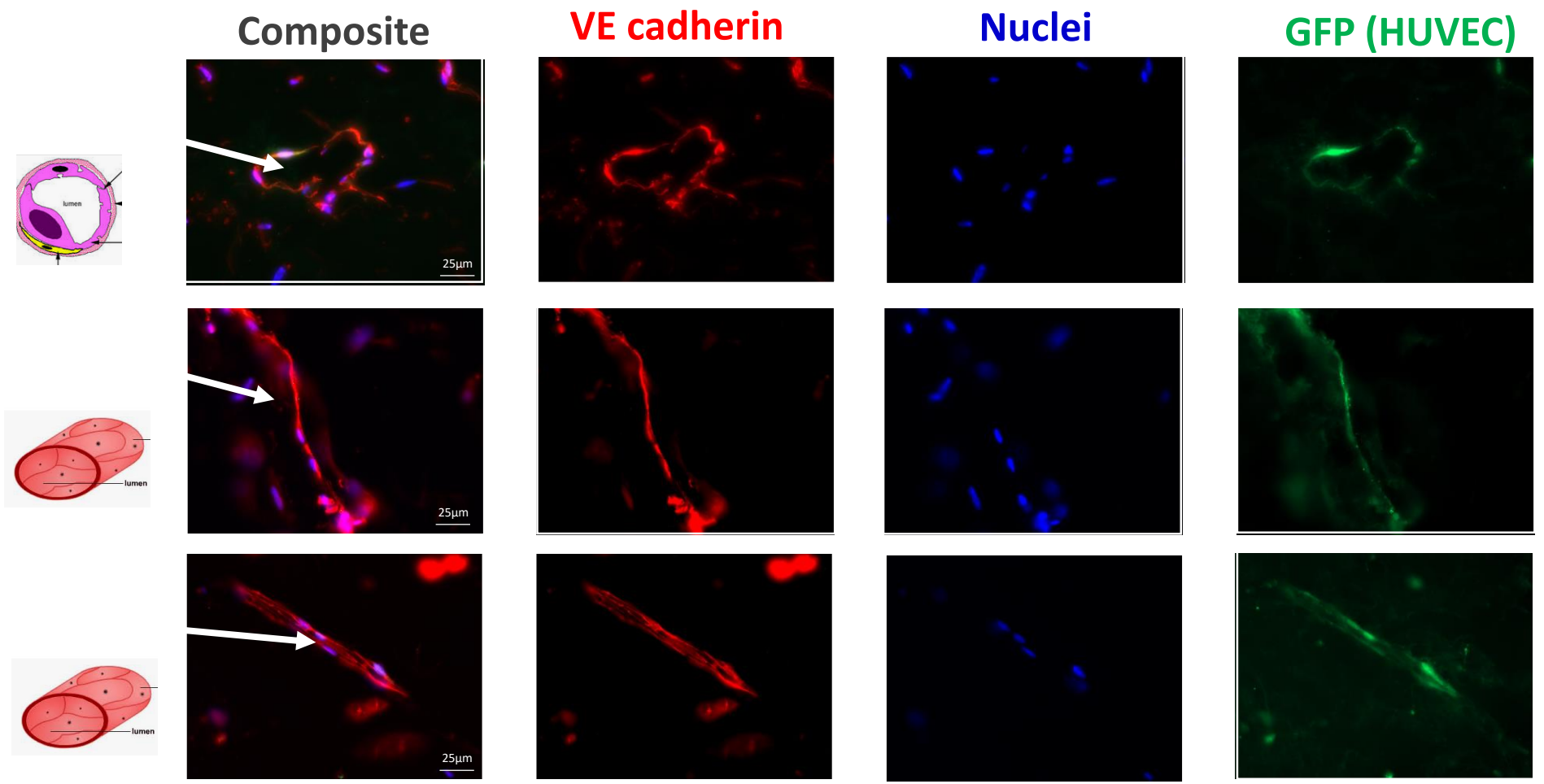
A. Pitaval

HUVECs-GFP + Primary Fibroblasts + InSphero Islets in a fibrin gel

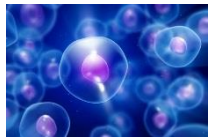


Vascular network ; lumen

A Pitaval

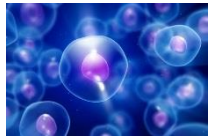


Organ Surrogates (Avatars) Applications:



hES Cells
iPS Cells
Cell lines

- ✓ **Basic Research Issues: organogenesis, pathogenesis, organ physiology, etc….**
- ✓ **Pharmaceutical Issues : Optimizing biomarkers discovery, Drug discovery, Drug efficacy & toxicity with pathology-mimicking avatars**



Primary Cells
from donors

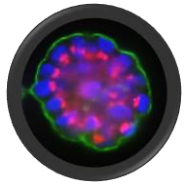
- ✓ **Clinical Issues : personalized or precision medicine avatars**



- ✓ **Clinical Issues : Ex vivo clinical trials ; e.g children, pregnant women**



- ✓ **Clinical issues : Regenerative medicine**





- ✓ **Ethical Issues : Reducing and replacing animal testing, but still necessary**

Acknowledgements



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