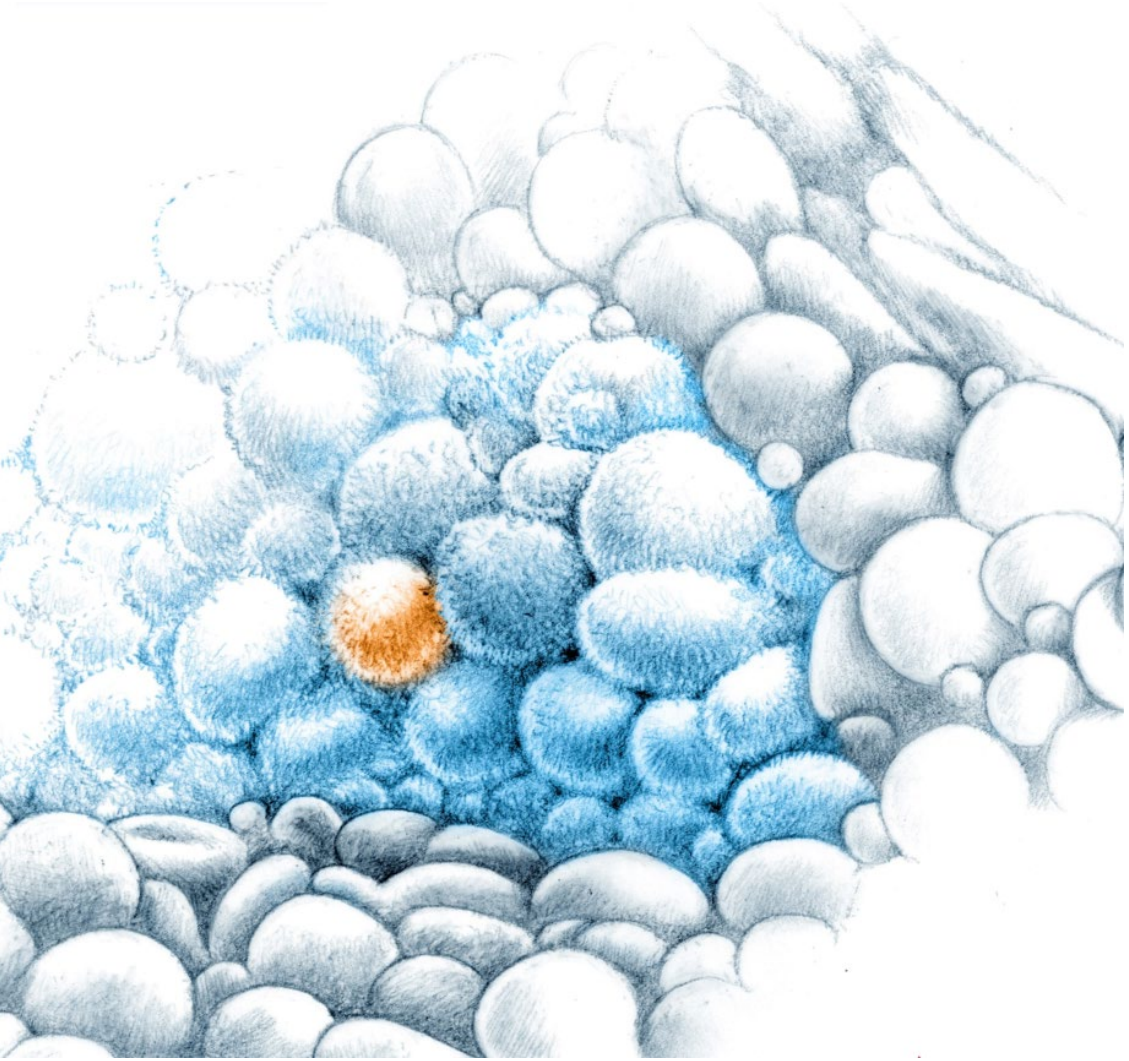
Cancéropôle Île-de-France

FÉDÉRER LA RECHERCHE ET L'INNOVATION
MÉDICALE EN CANCÉROLOGIE



# Advances in tumor on chip development


Descroix Stéphanie,

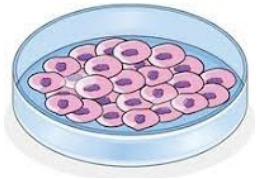
UMR 168

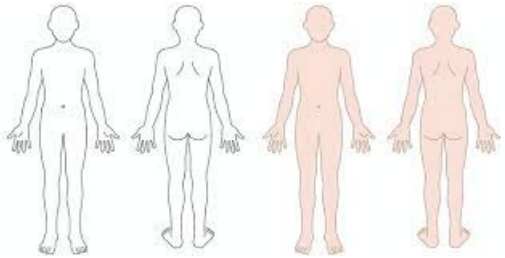
Institut Curie

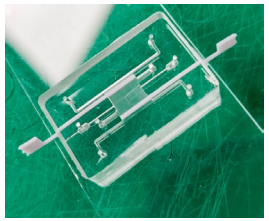
Institut Pierre Gilles de Gennes (IPGG)

# Organ-on-a-chip technology

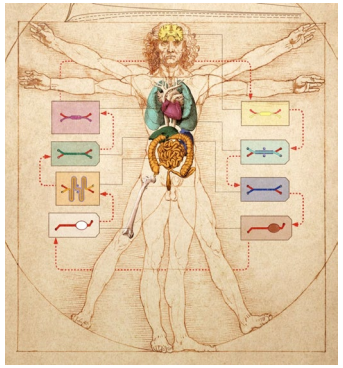
**Conventional models**



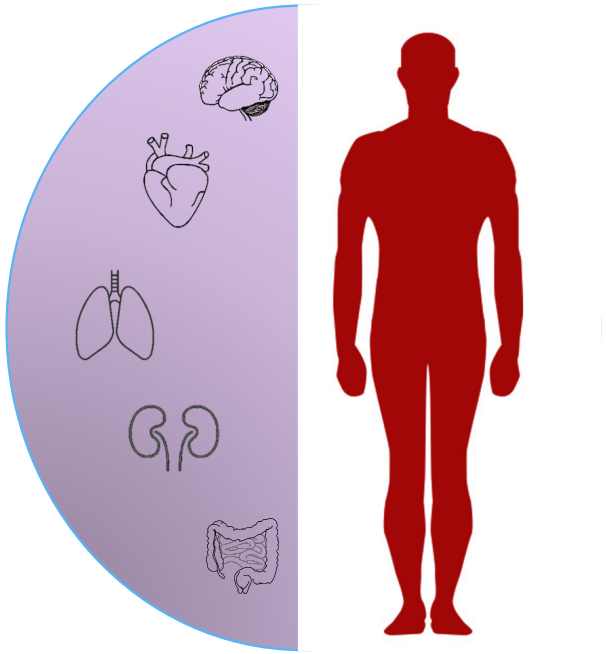




***Organ-on-chip***

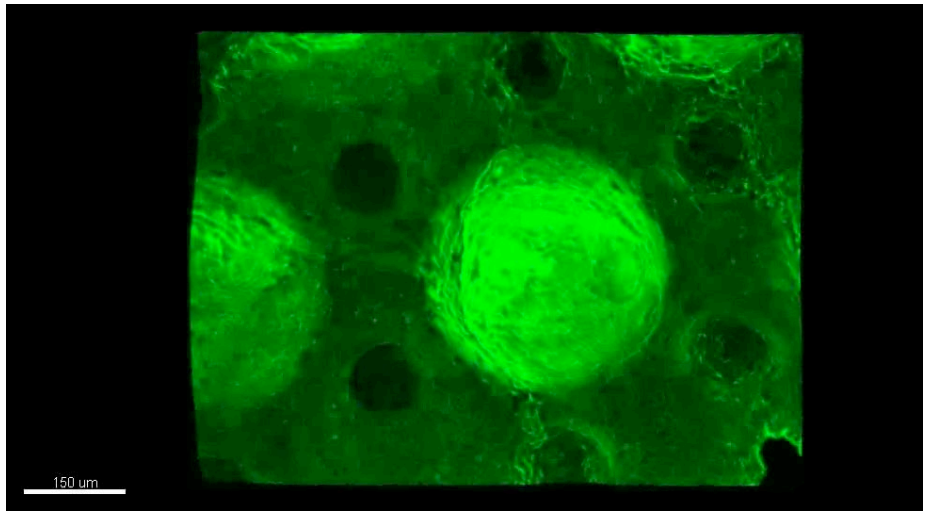


- Miniaturization
- Fine control over cellular microenvironment
- Fully humanized
- Direct visualization of cell dynamics (3D)

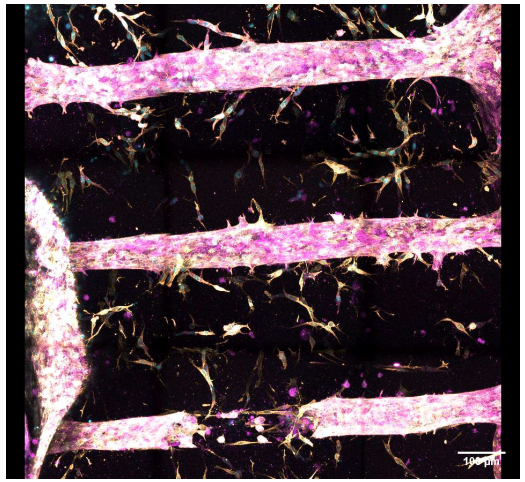


# Organ on chip in our team - Institut Curie /IPGG

Gut



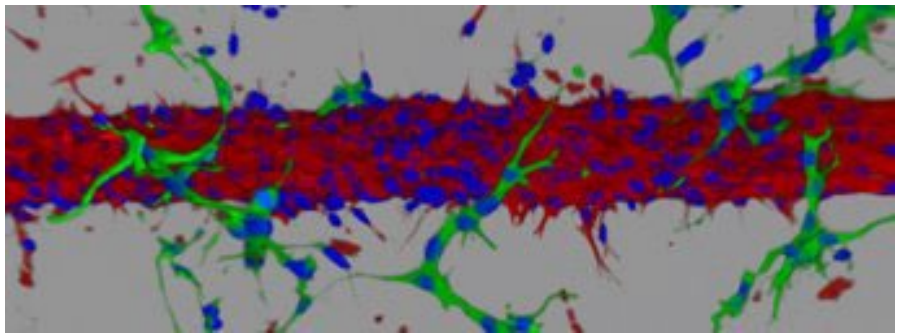

With D. Vignjevic



With S. Coscoy

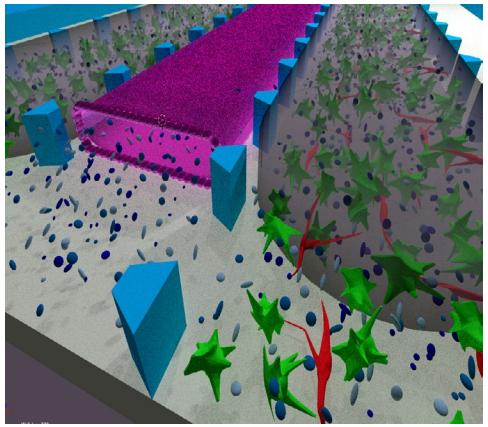
Kidney pathology

Muscle



MyoChip

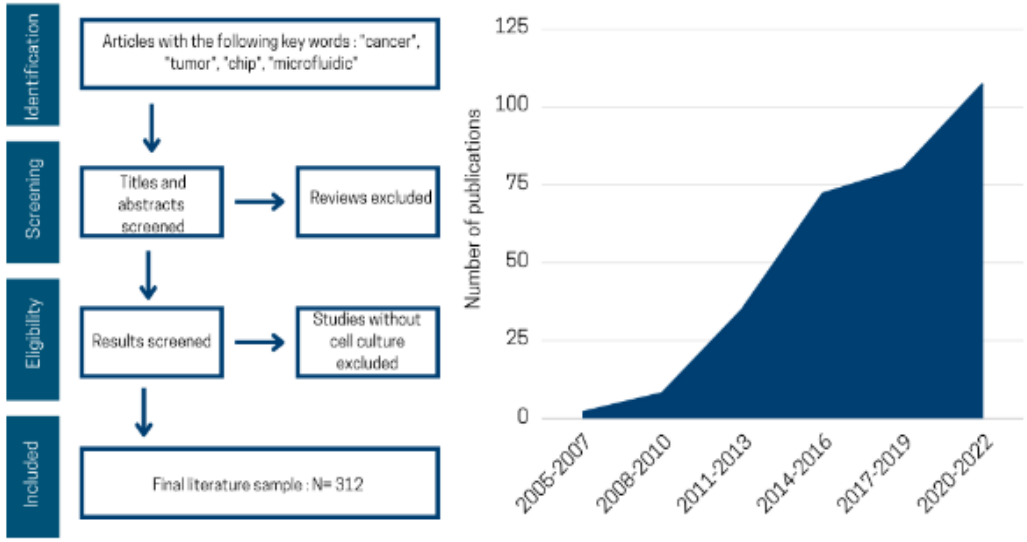
With E. Gomes

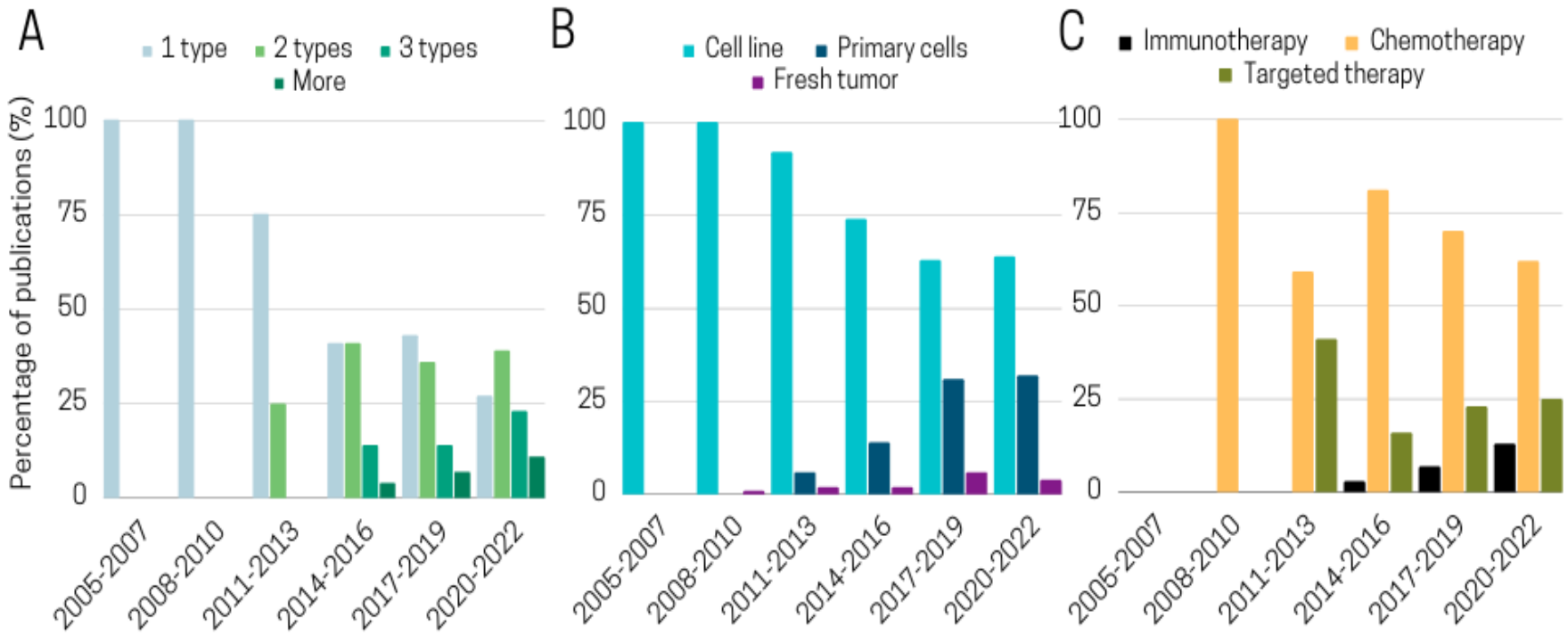


With MC. Parrini

Tumor (TME)

# Tumor on chip, where are we today ?

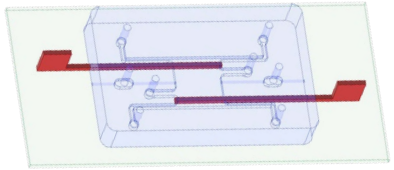


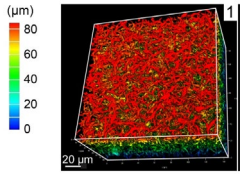

Bouquerel et al., Bridging the gap between tumor-on-chip and clinics: a systematic review of 15 years of studies, Lab On Chip 2023

# Developing tools to control 3D cell culture on chip

## . ECM on chip : Controlling gel positioning in 3D : sliding walls



A. Yamada Lab Chip 2016

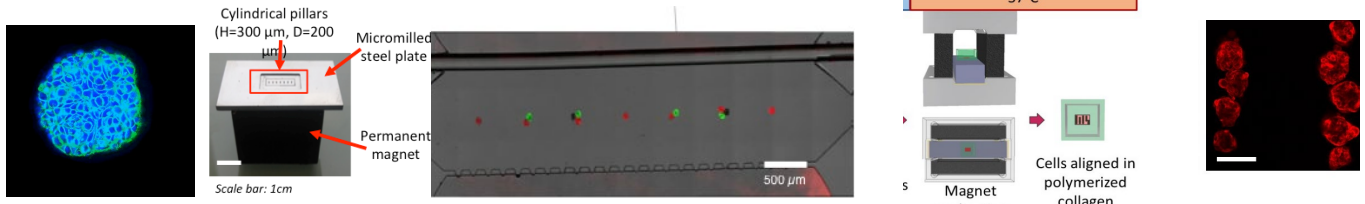



Patented Technology

B. Venzac, Nat Microsyst Nanoeng 2020

## . Cells in the Tumor on chip : Controlling cell position in gel : Magnetic Spheroids

(A. Yamada, M. Serra, N. Demri, C. Wilhelm)




Demri et al Adv Func Mat, 2022

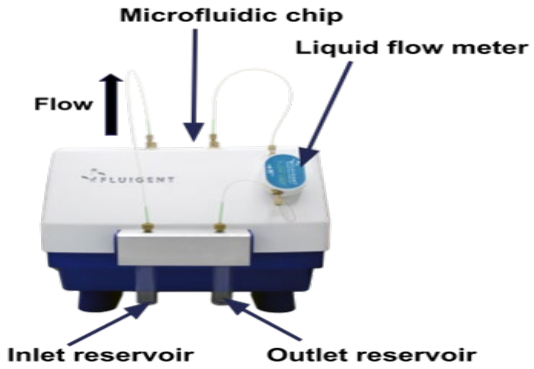
## . Control of the liquid and gas environment

(**C. Bouquerel,** MC Parrini - Fluigent Collaboration)

Oxalys Technology - Patented

FLUIGENT
SMART MICROFLUIDICS

Bouquerel et al , Lab Chip 2022

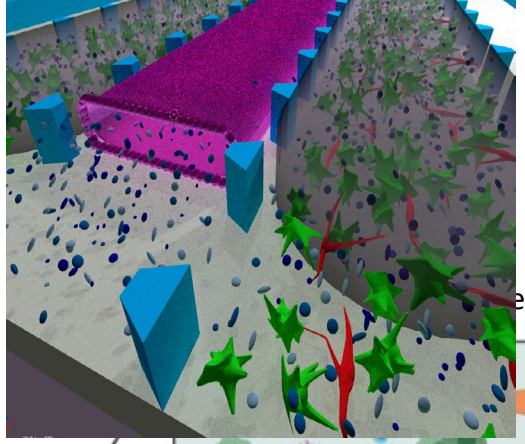


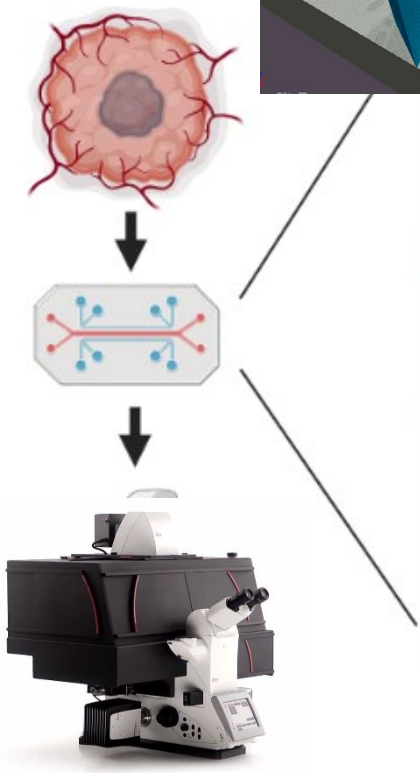
# Two main approaches

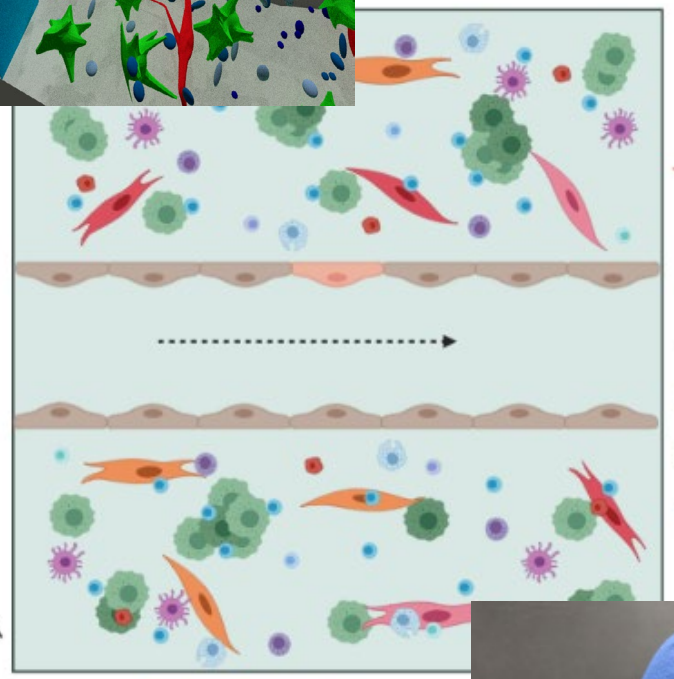
- Based on cells co-culture and self-assembly in a 3D matrix

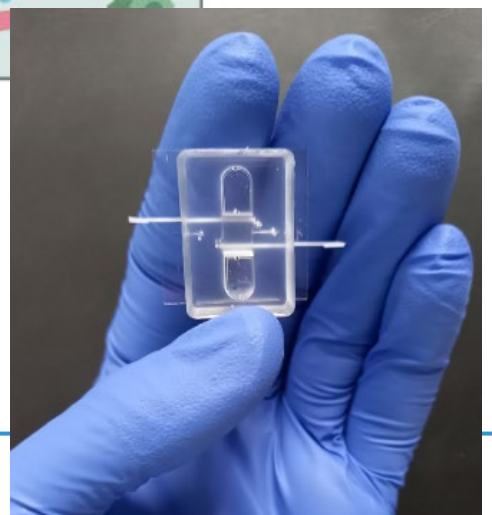
- Based on 3D scaffold mimicking the organ geometry

# On chip self assembling





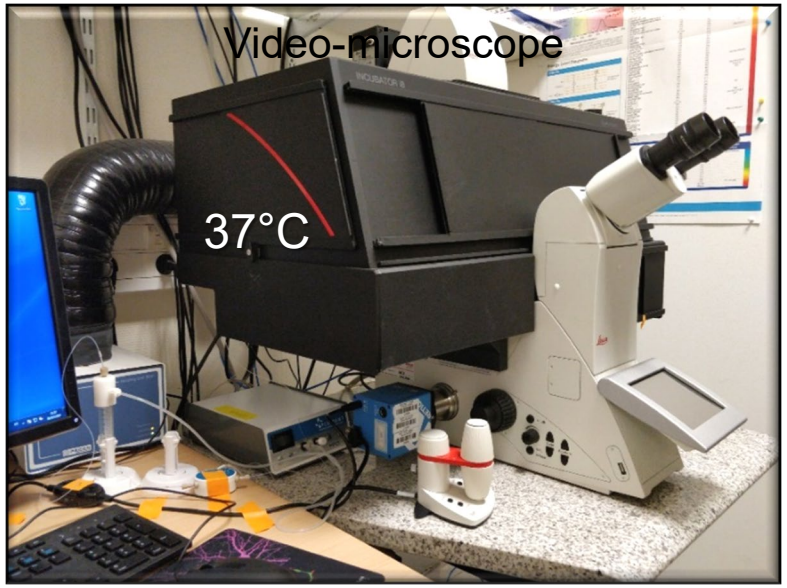


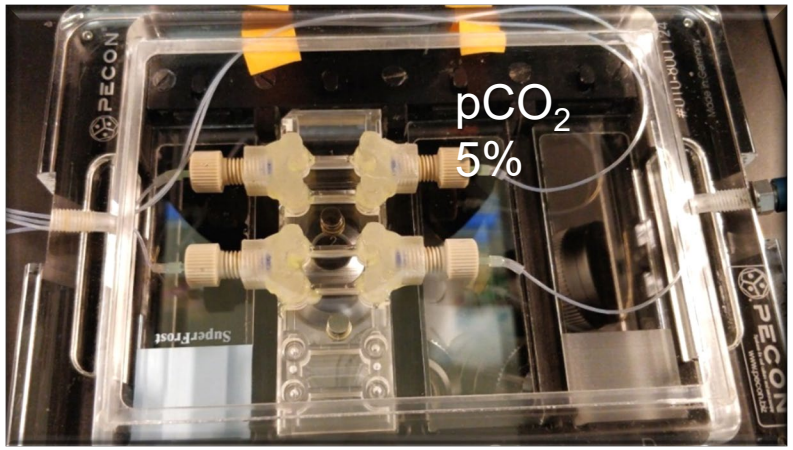



**Maria Carla Parrini,**
U830 Institut Curie

**Anti-cancer treatments**
**Chemotherapies**: doxorubicin, paclitaxel…
**Targeted therapies**: trastuzumab, Yap inhibitor…
**Immunotherapies**: nivolumab…
**Oncolytic virus**
**Nanoparticles-mediated therapies**
**…**

# Our experimental setting



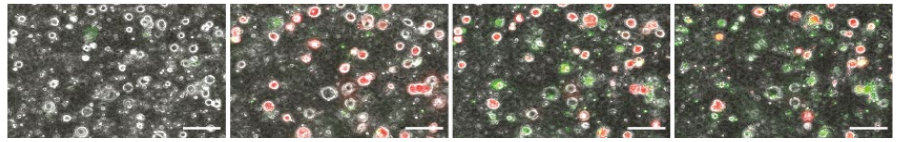




**Microfluidic setting for drug injection**

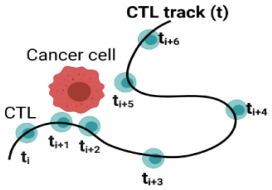
**Data acquisition and analysis**

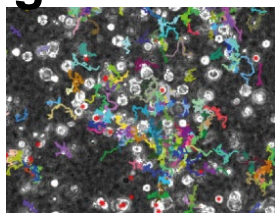
## Data acquisition and advanced analysis

Quantification of cellular processes using flurescent reporters



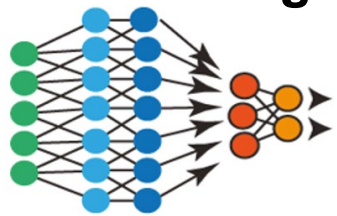

## Cell tracking and cell-cell intera



## Machine learning methods

AI

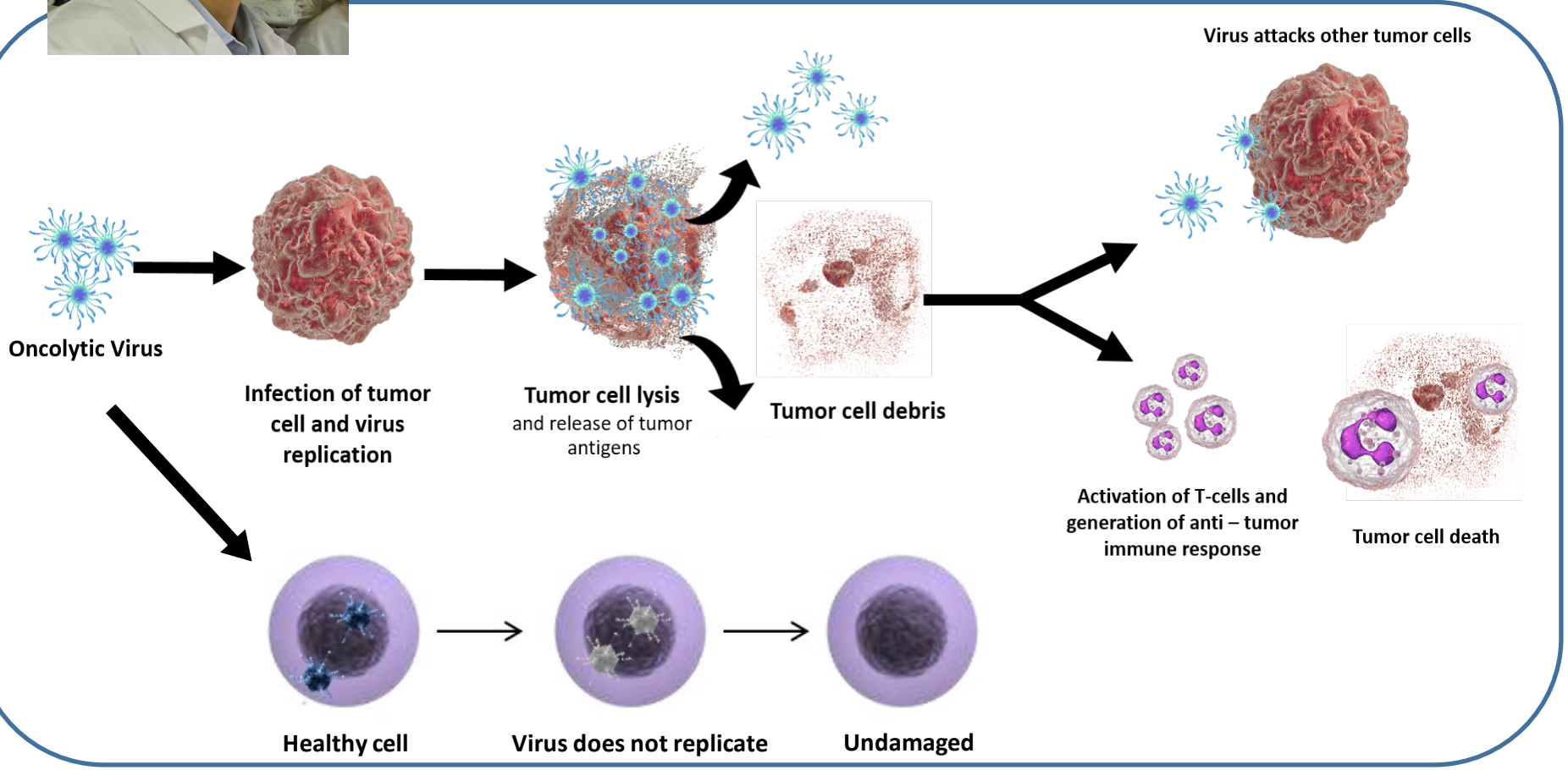


# Oncolytic virus on chip

**Maria Carla Parrini,** U830 Institut Curie

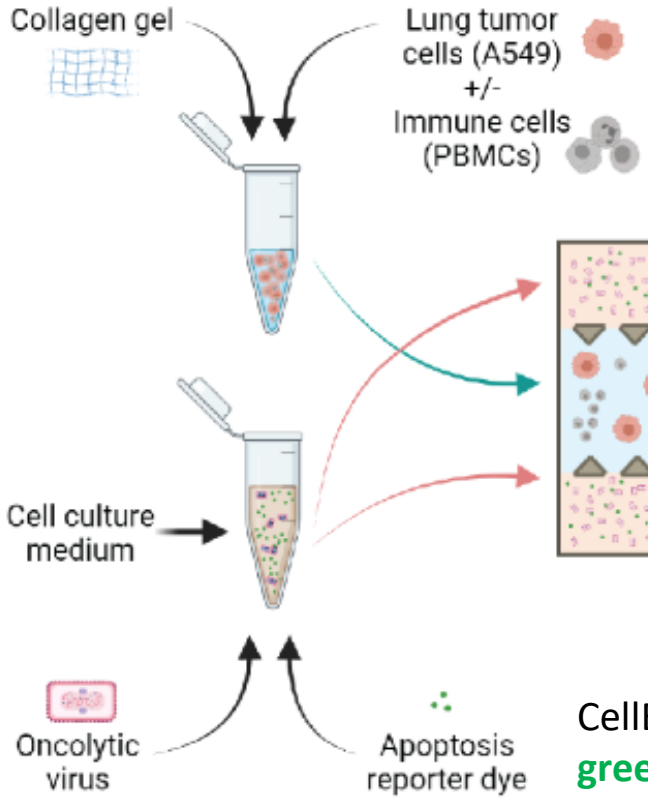
transgene

Collaboration with
Transgene company

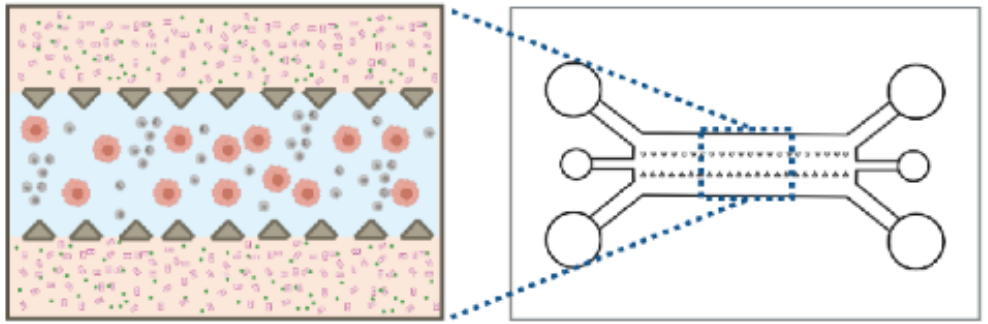


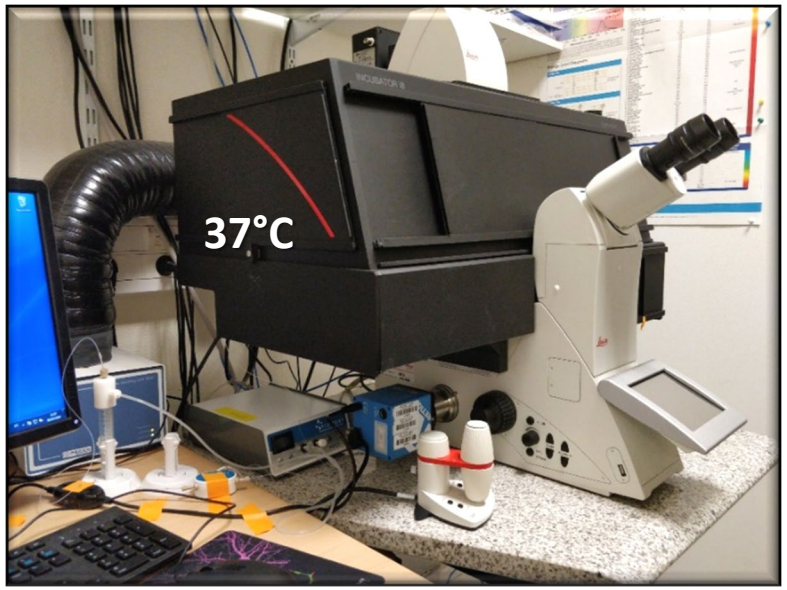

- Lytic
- Fast replication in host cell
- Can infect every cell
- Cause no symptoms in healthy individuals
- Enhanced replication in tumor cells

# Experimental design




Chip DAX-1 (AIM Biotech)






Live-cell imaging (3-5 days)

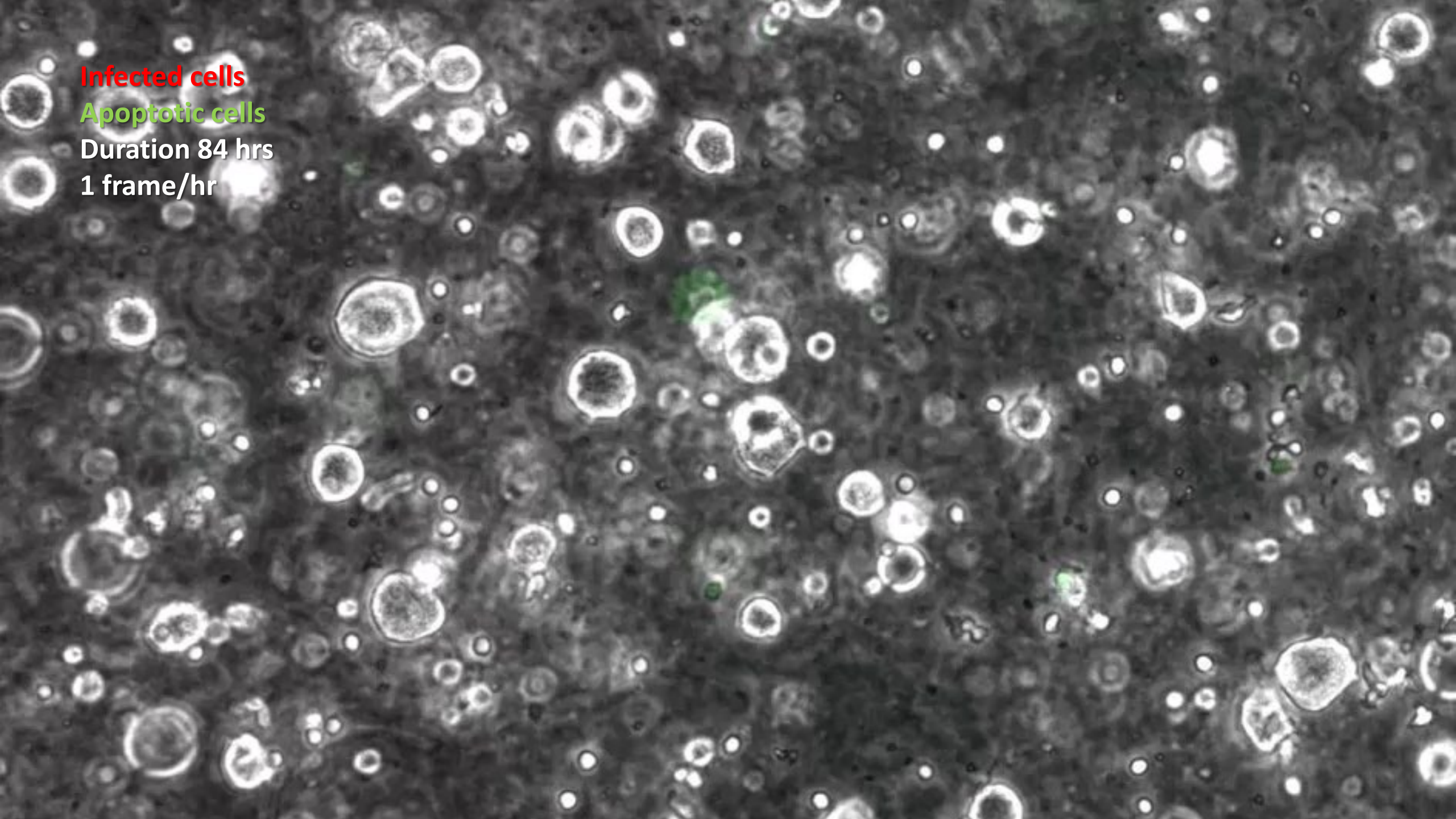
CellEvent caspase-3/7 **green** detection reagent (ThermoFischer)

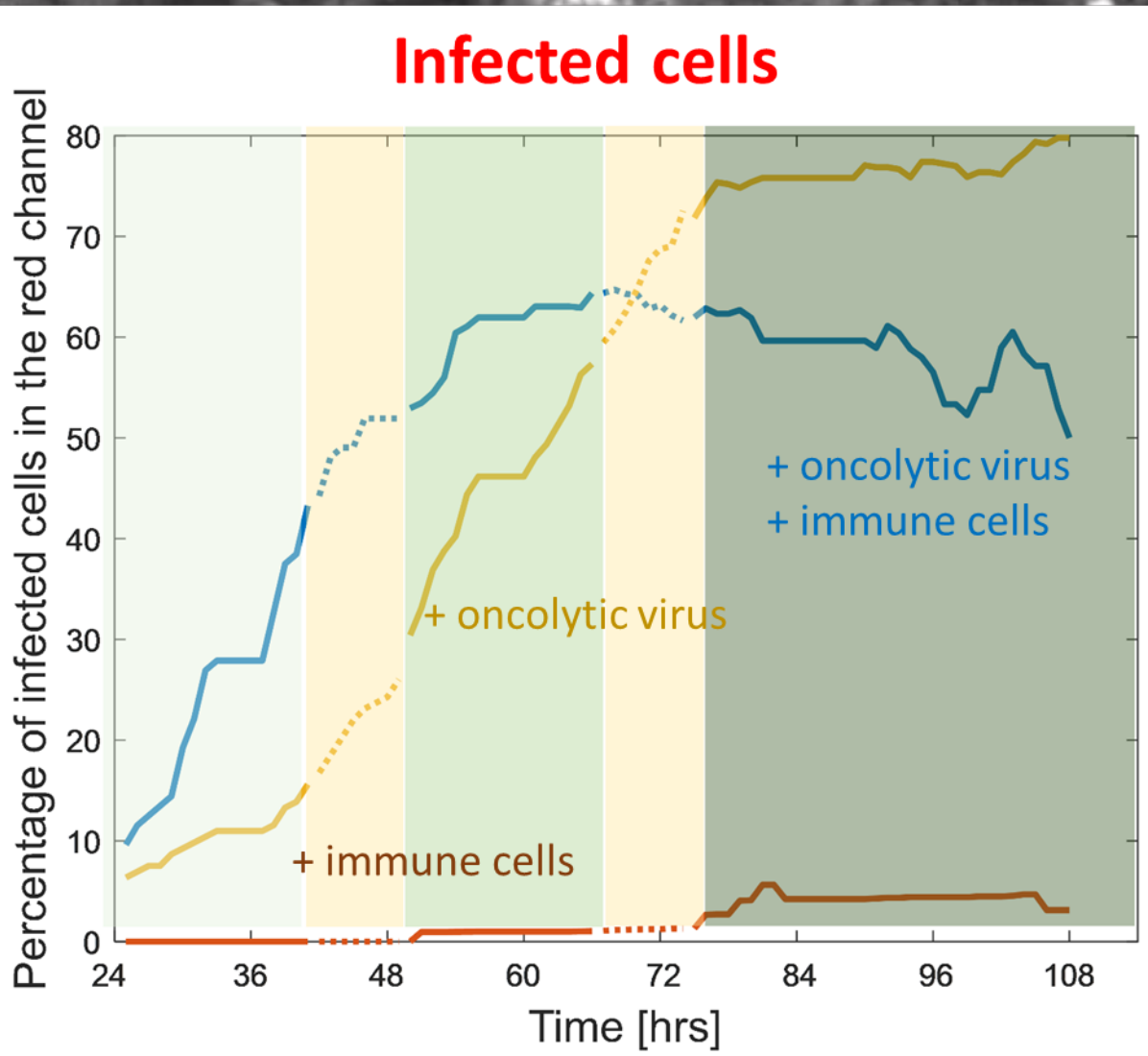
CopTG19104
Thymidine Kinase and Ribonucleotide Reductase deleted virus, expressing **mCherry**
MOI 0.1

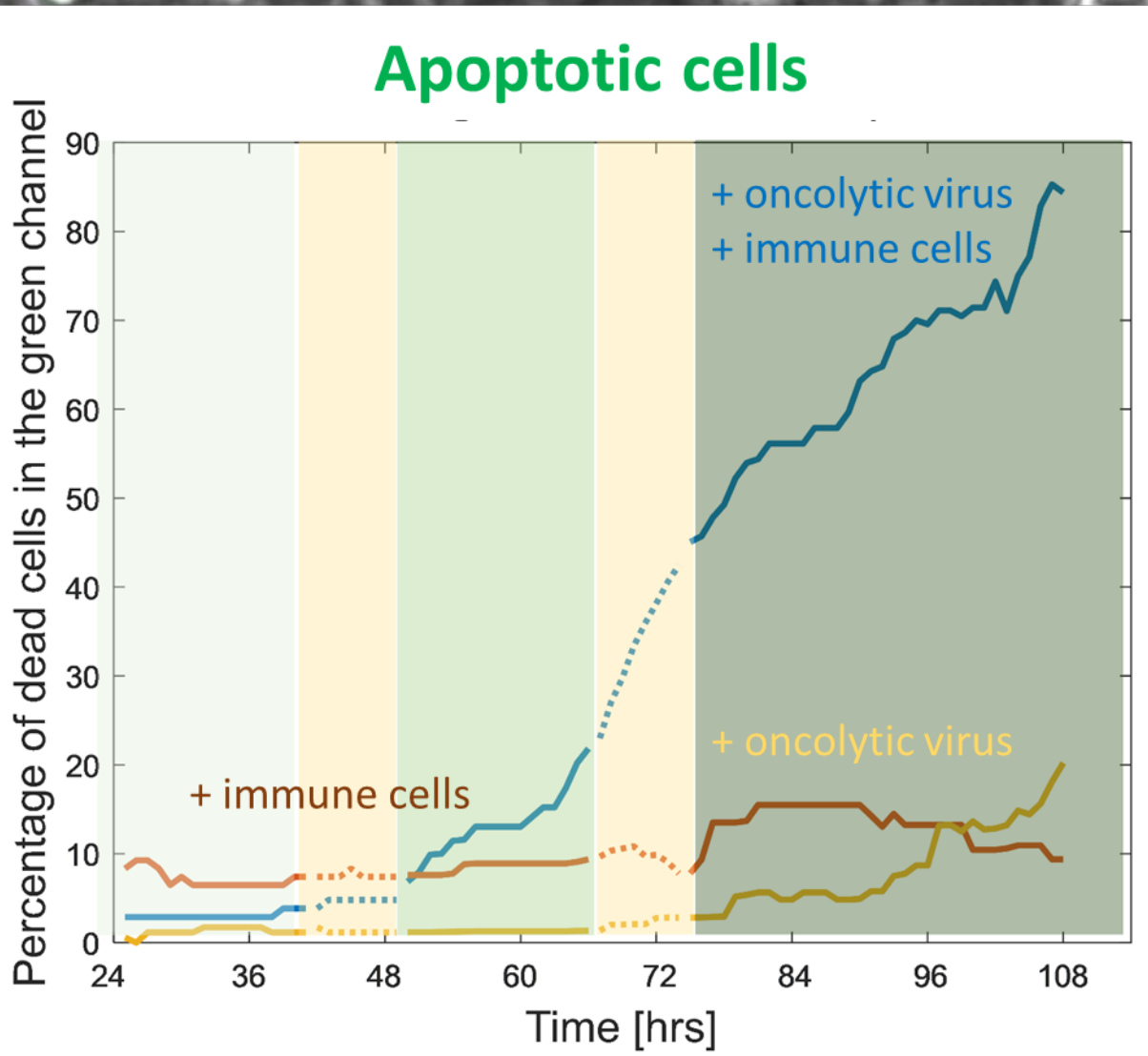
Biosensors and Bioelectronics 215 (2022) 114571

Direct imaging and automatic analysis in tumor-on-chip reveal cooperative antitumoral activity of immune cells and oncolytic vaccinia virus

Arianna Mencattini [a,b,1], Christine Lansche [c,1], Irina Veith [c], Philippe Erbs [d], Jean-Marc Balloul [d], Eric Quemeneur [d], Stéphanie Descroix [e], Fatima Mechta-Grigoriou [c], Gérard Zalcman [c,f], Cécile Zaupa [d,***,2], Maria Carla Parrini [c,**,2], Eugenio Martinelli [a,b,*,2]


Infected cells
Apoptotic cells
Duration 84 hrs
1 frame/hr




- Cooperative antitumoral activity of oncolytic

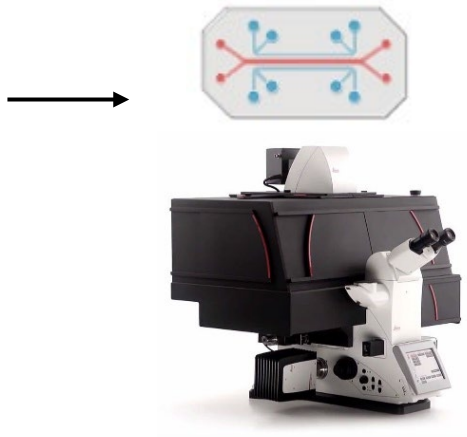
Hôpital Bichat Claude-Bernard AP-HP

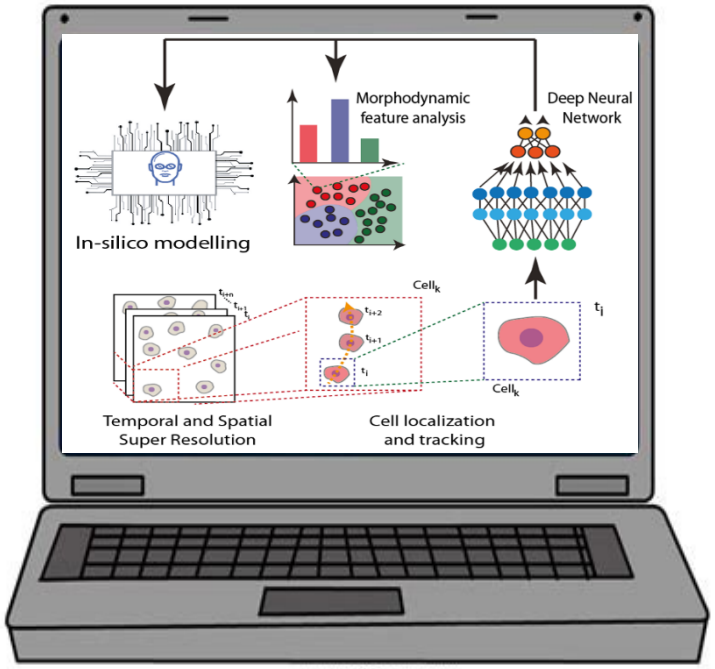
Collaboration with
Prof Gérard Zalcman

# Personalization of lung-tumor-on-chip platforms using patient-derived primary cells isolated from fresh tumor samples

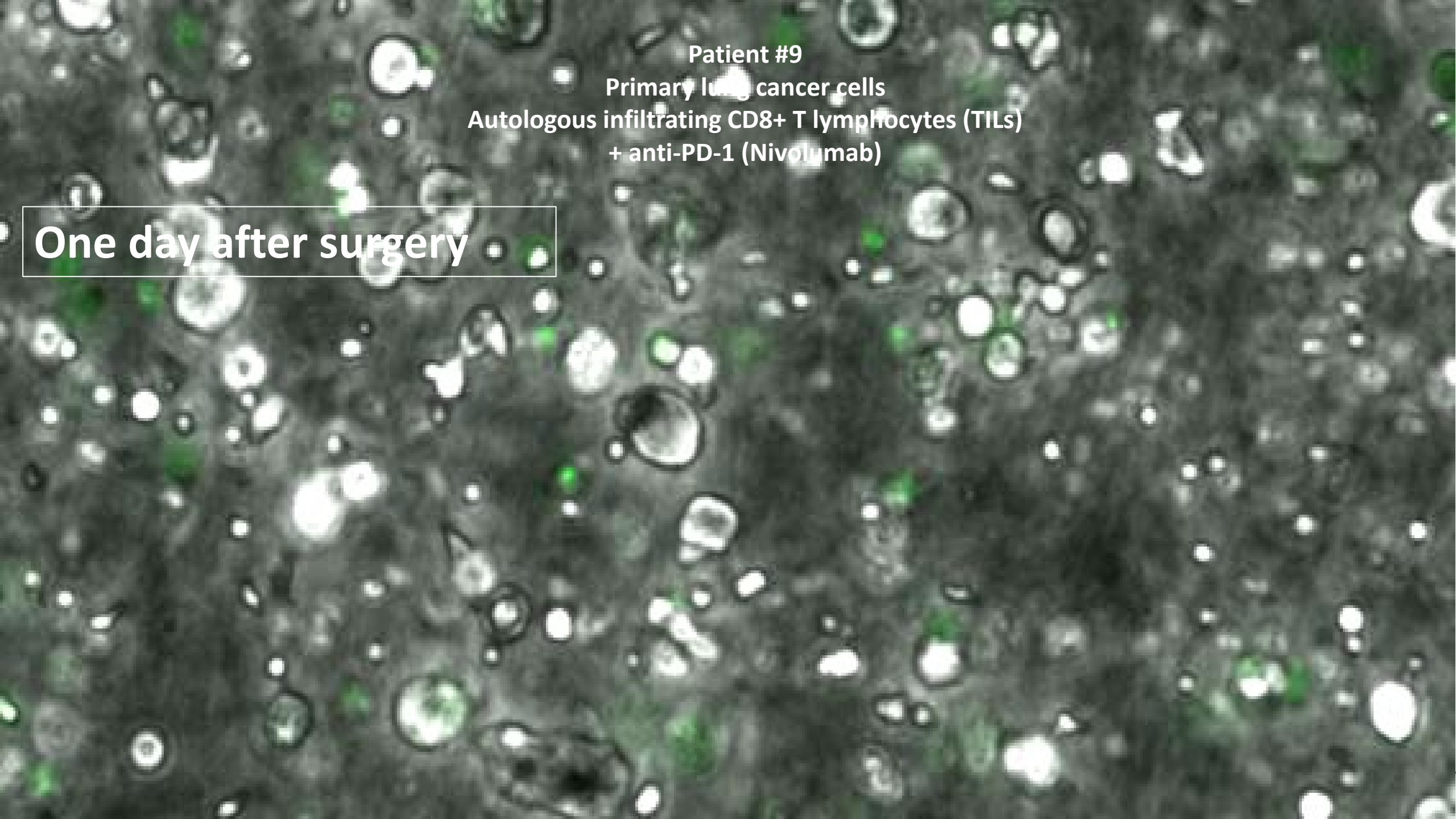
**Maria Carla Parrini**
U830 Institut Curie

From patient to chip






Veith et al, 2023, BioArXiV


Patient #9
Primary lung cancer cells
Autologous infiltrating CD8+ T lymphocytes (TILs)
+ anti-PD-1 (Nivolumab)
One day after surgery

# What could we further learn from the tumor on chip model ?

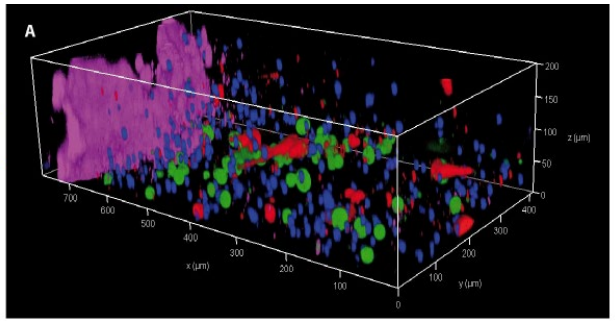
Claire Wilhelm

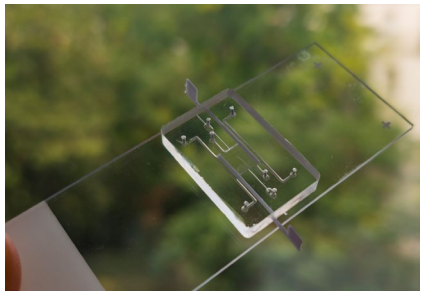
Gérard ZALCMAN

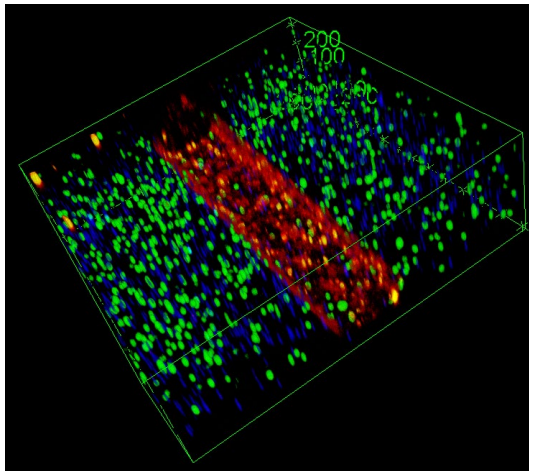
Maria Carla PARRINI

Fatima MECHTA-GRIGORIOU

Endothelium
Cancer cells
Immune cells
Fibroblasts

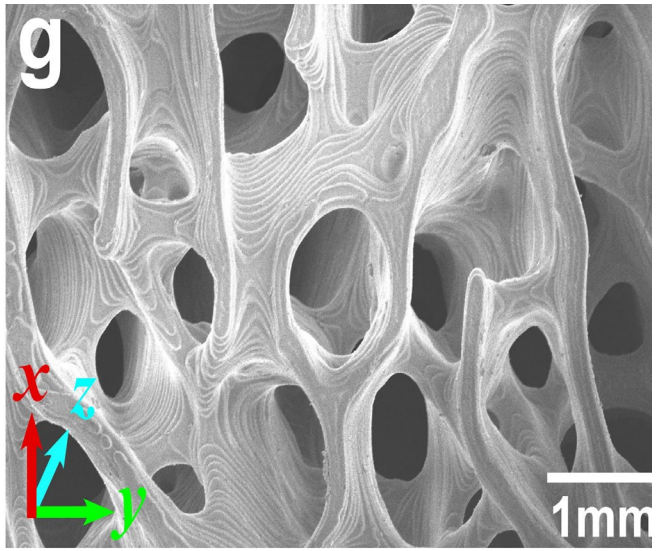


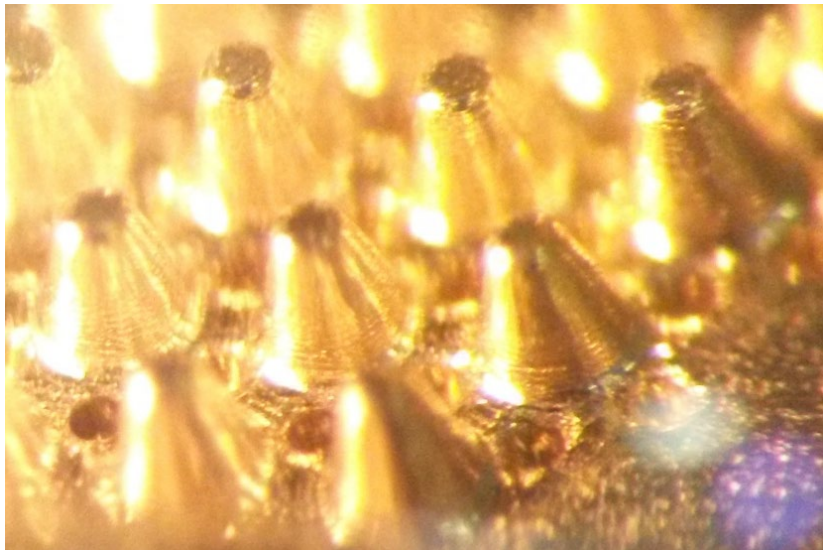





- Reconstitution of the response to immunotherapy in lung cancer on chip with patients samples
- How does hypoxia affect cell response to chemotherapy – understanding chemoresistance ?
- Hyperthermia/ Photothermia on chip to better understand the effect of combined therapies

# Based on 3D scaffold mimicking the organ geometry



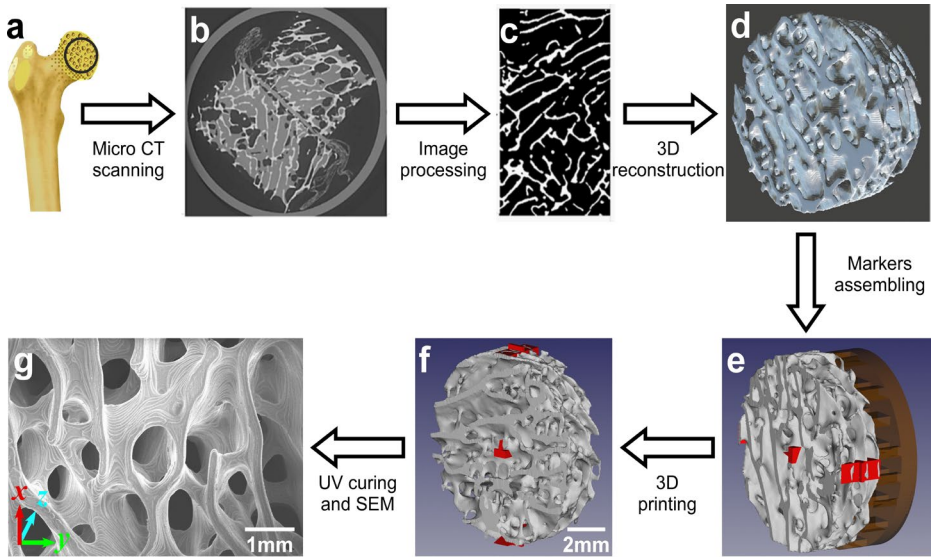



# Bone tumor metastasis

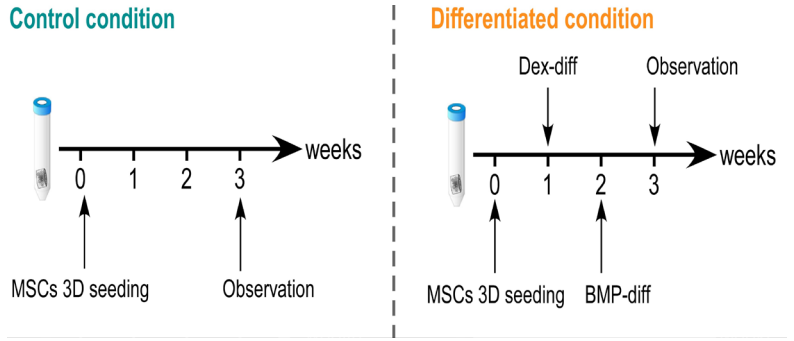
Jacques Camonis

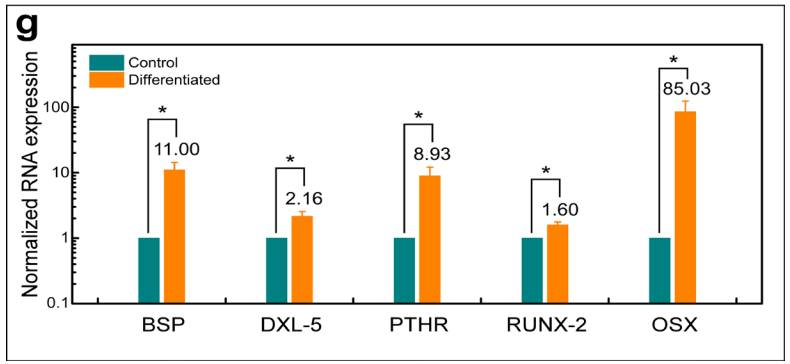
**Our Approach**

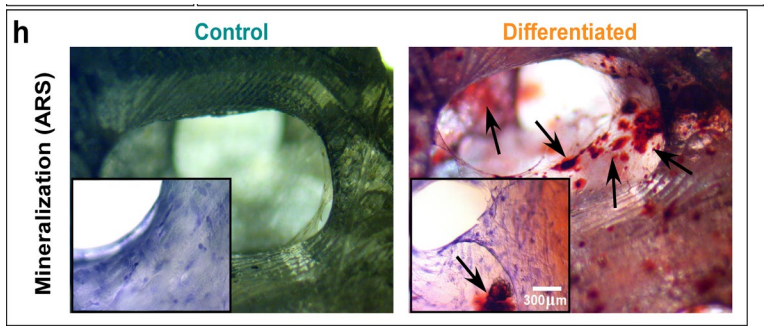
- 3D printing a bone 3D scaffold
- *In situ* mesenchymal stem cells (MSC) differentiation to model bone niche
- Patient derived xenograft (PDX) cells co-culture in the 3D scaffold



# 3D printed bone colonized with differentiated MSCs recapitulates bone features




Alizarin red S staining

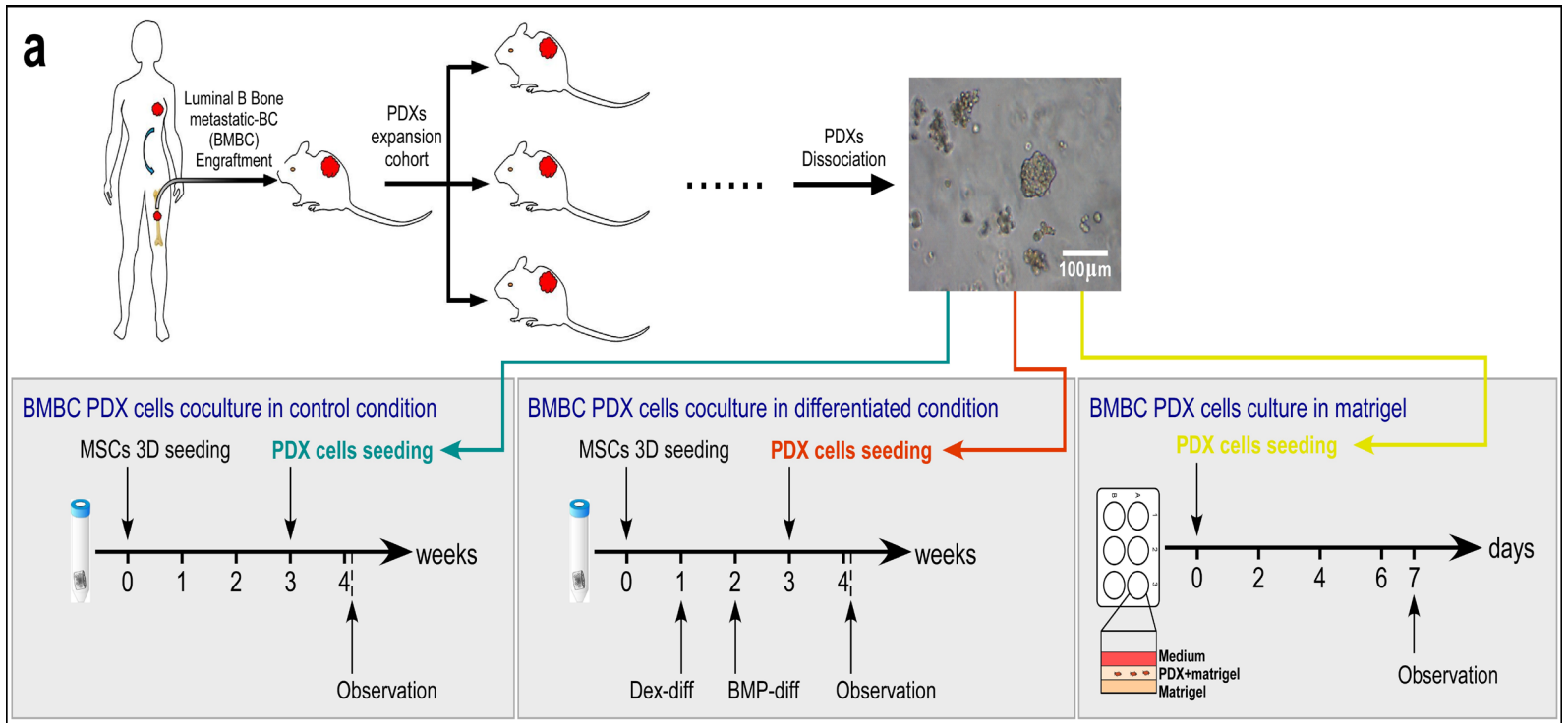
- **Osteocalcin secretion (hormone specific of bone tissue)**
- **Collagen I : ECM deposition**

- **Higher expression levels of genes involved in osteogenic lineage in differentiated conditions**

- **Calcium deposition in the bone scaffold in differentiated conditions**

Han et al, Biomaterials 2021

# Implementing Patient Derived Xenograft cells in the 3D model




Two types of PDX cells

- Triple Negative Breast Cancer prone to bone metastasis
- Bone Metastasis Breast Cancer

Comparison with

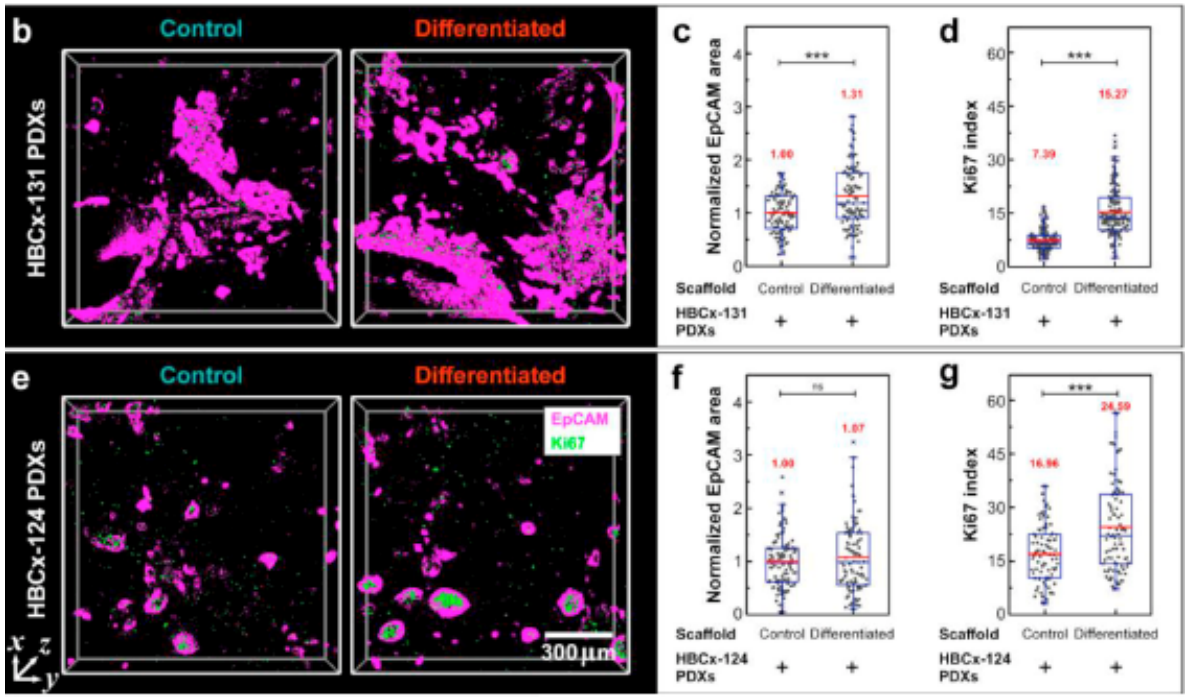
- 2D experiments MSC + PDX
- 3D experiments PDX in Matrigel



Montaudon et al . Nat Commun 2020 Aug 13;11(1):4053

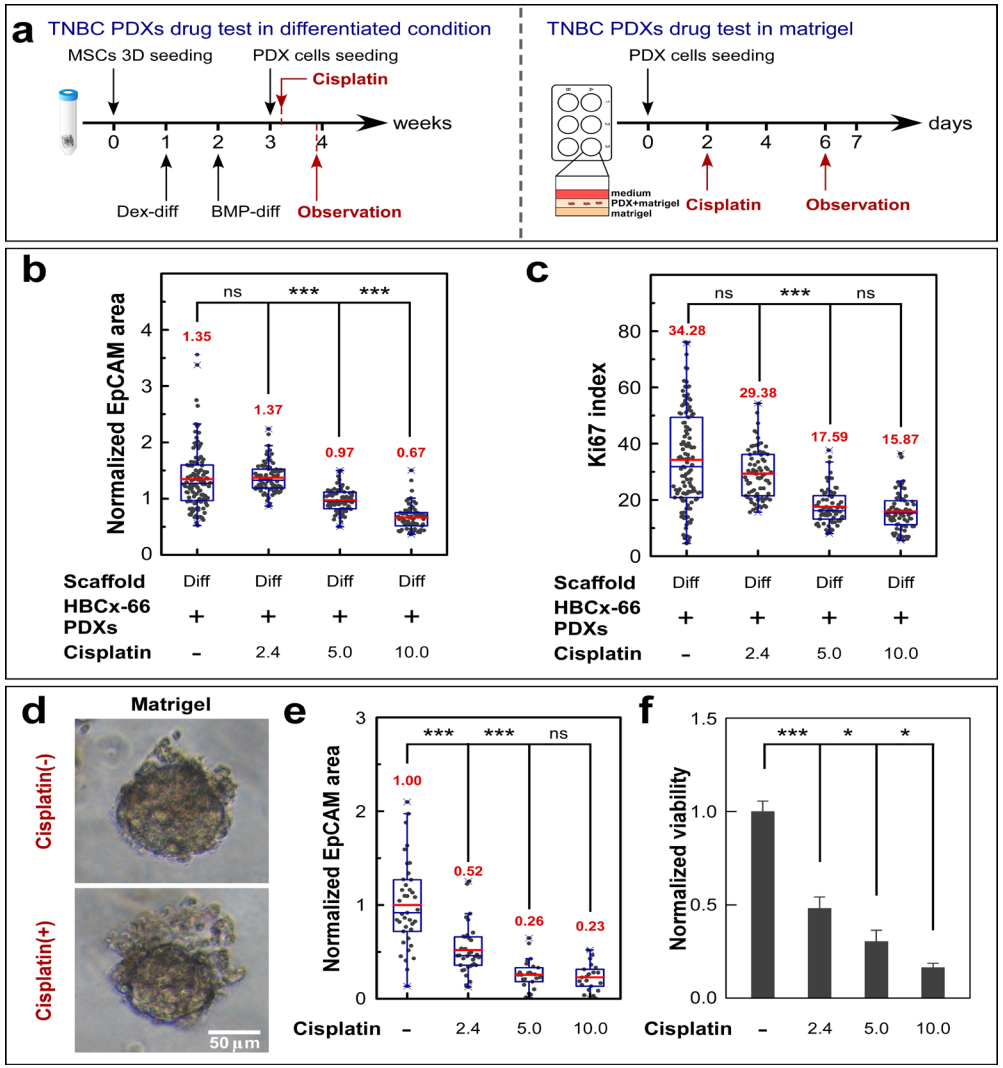
# Biomimetic bone niche maintains PDX cells colonization and proliferation as *in vivo*

Bone Metastasis Breast cancer PDX




- PDX cells performed better colonization, survival, and cycling proficiency in MSC osteogenic-differentiated when compared with culture in absence of MSC or with undifferentiated MSC
- Ki 67 Index same order of magnitude in vitro and in FFPE patients samples (11 patients- around 21%)
- PDX cells rarely survive in 2D dishes when co-cultured with differentiated MSC
- PDX cells survive in Matrigel but with very low proliferation level

# Investigating drug-response to cis-platin of TNBC cells in biomimetic bone niche




- **Cisplatin** : common chemotherapy for advanced TNBC
- In wells : **IC 50 2.4µM**

- **3D scaffold in differentiated conditions**

⩥ not significant decrease/cisplatin 2.4 µM

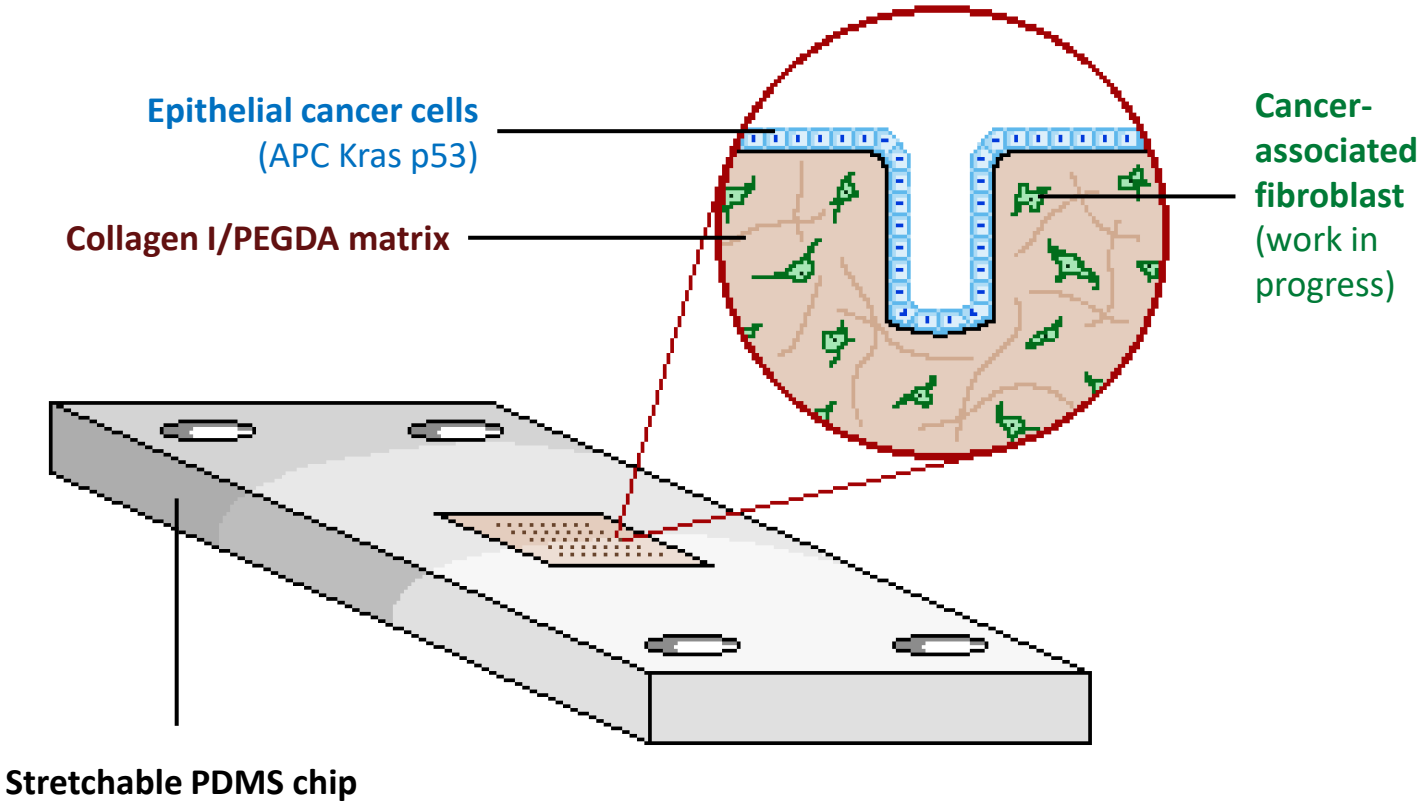
⩥ EpCAM-positive area decreased by 50% for cisplatin at 10 µM

- **Matrigel** : EpCAM area of PDX cells reduced to 50% at 2.4 µM of cisplatin

**As *in vivo* biomimetic bone models exhibited modulated drug sensitivity to cisplatin**

Han et al, Biomaterials 2021

# Colorectal Cancer on Chip - Influence of peristalsis on TME




Danijela Vignjevic

- 24h
- 0.1 Hz
- 8% strain

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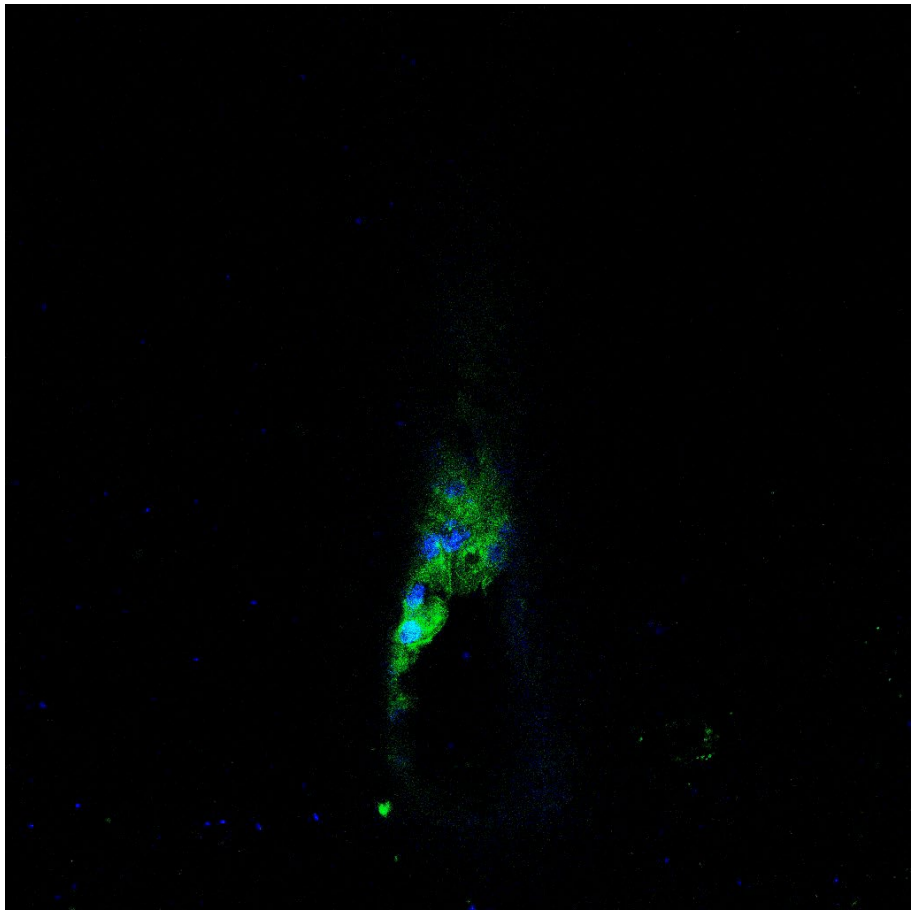
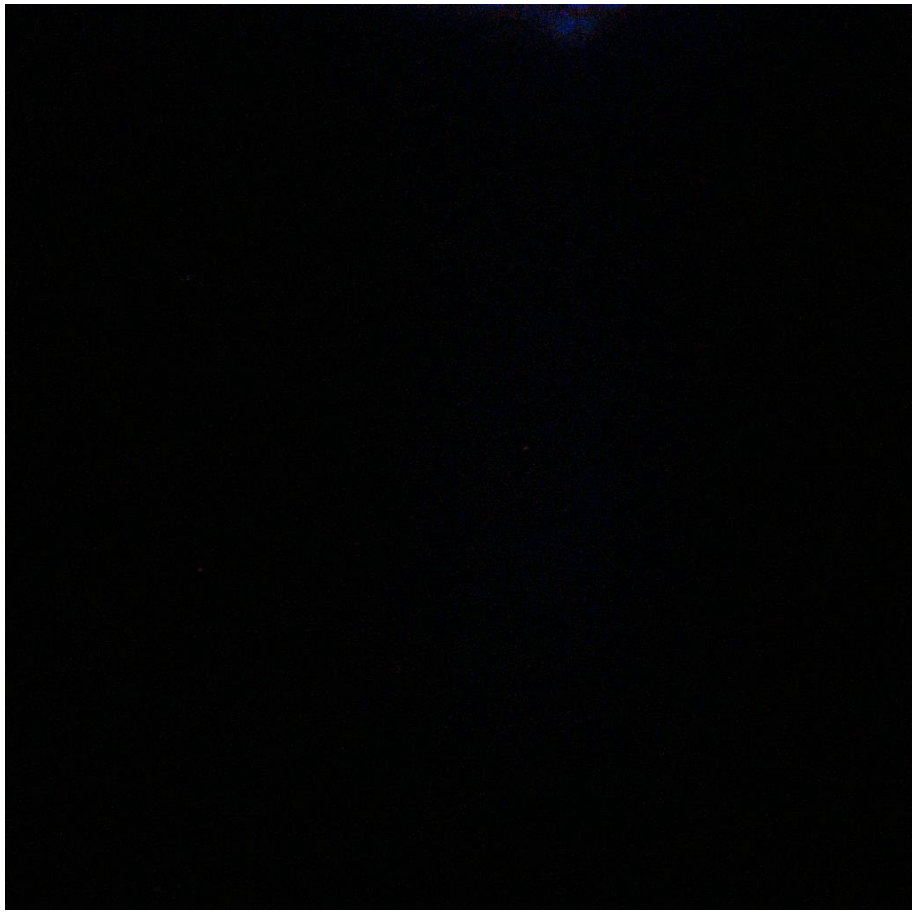


mTmG Mouse organoids



pVillin transgenic mouse model: NICD/p53-/-.

**Hoechst** (nuclei)

**Phalloidin** (F-actin)

**Ki-67** (proliferative cells)

# Tumors-on-chip and microphysiological models
# a new generation of *in vitro* models

- to study *ex vivo* immunocompetent tumor microenvironments
- to characterize ecosystem-level responses to anti-cancer drugs
- to dissect the roles of the cellular/physical components of the TME

## 👉 to achieve this it requires a wide interdisciplinary