MicroFluidic & 3D culture combination for a predictive in vitro screening of Nanomedicines

µF_3D_NANO

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Projet recherche 2020

The consortium

Leader

- Simona MURA
- Julien Nicolas
- Julie Mougin

- Nanoscale drug delivery systems
- 3D cell culture methodologies
- Preclinical evaluation

Light sheet fluorescence microscopy versus confocal microscopy: in quest of a suitable tool to assess drug and nanomedicine penetration into multicellular tumor spheroids. Lazzari G et al., ***European Journal of Pharmaceutics and Biopharmaceutics*** **2019**;142:195

Multicellular spheroid based on a triple co-culture: A novel 3D model to mimic pancreatic tumor complexity. Lazzari G et al., ***Acta biomaterialia*** **2018**;78:296

Design, functionalization strategies and biomedical applications of targeted biodegradable/biocompatible polymer-based nanocarriers for drug delivery. Nicolas J *et al.,* ***Chemical Society Reviews*** **2013**;42:1147.

Partner 1

- Anne Marie HAGHIRI
- Gilgueng HWANG
- Dominique DECANINI

- Nanostructuration of biocompatible materials
- Microfluidic platforms/organs on chip/flow control
- Nano and stereolitography

Microfluidic gas exchange devices and methods for making same. Haghiri-Gosnet AM DL, Lachaux J, Paris A, Hwang G. ***2018. EP18306405.4***.

On-chip Microfluidic Multimodal Swimmer toward 3D Navigatio. Barbot A *et al.,* ***Scientific Report*** **2016**; 6:19041

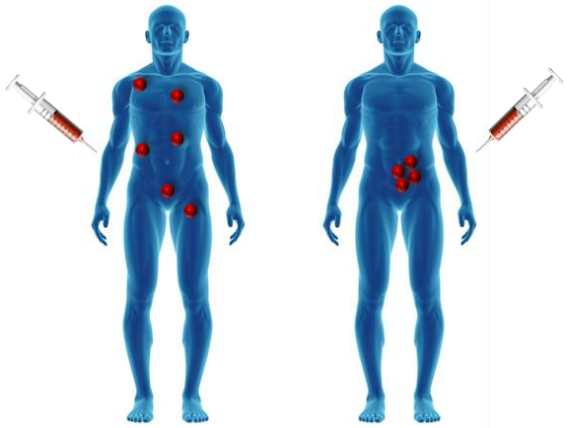
Improved electrochemical detection of a transthyretin synthetic peptide in the nanomolar range with a two-electrode system integrated in a glass/PDMS microchip. ***Lab on a chip*** **2014**; 14:2800

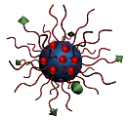
State of art

- Nanomedicines: advanced nanoscale system for therapeutic and imaging purposes

Traditional Chemotherapy

Free molecule

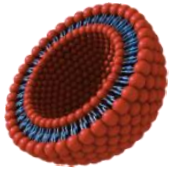




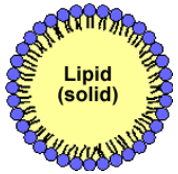
- Protection from degradation
- Increase intracellular penetration
- Cell/tissue targeting
- Overcome resistance
- Combine therapy and Imaging

NANOMEDICINES

Lipid

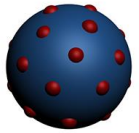


Liposomes



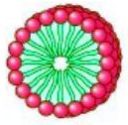
Solid Lipid NPs

Polymer

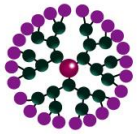


Nanoparticles

Micelles



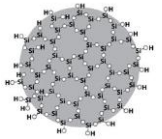
Dendrimers

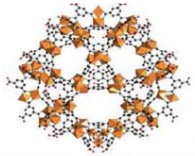


Organic-Inorganic

Gold NPs

Silica NPs





MOF NPs

Iron Oxyde NPs

Adapted from Wicki *et al.*, Journal of *Controlled Release* **2015**, 200: 138

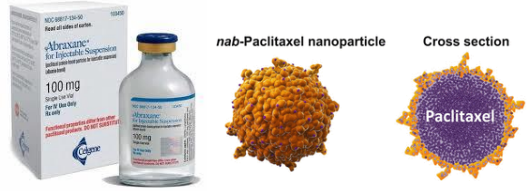
Nanomedicine in the marketplace

Doxil (1995)

- Metastatic breast cancer
- Kaposi's sarcoma in patients with AIDS
- Multiple myeloma

- Drug: doxorubicin

Abraxane (2005)



- Metastatic breast & pancreatic cancer
- Non-small cell lung cancer

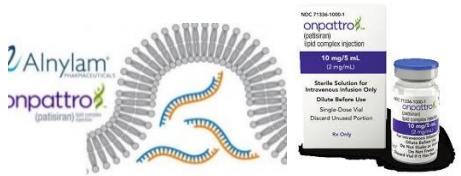
- Drug: Paclitaxel

VYXEOS (2017)

- Acute myeloid leukaemia

- Drug: daunorubicin & cytarabine

ONPATTRO (2018)



- Hereditary transthyretin amyloidosis

- Drug: siRNA

A.C. Anselmo, S. Mitragotri, *Bioengineering & Translational Medicine* **2019** e10143

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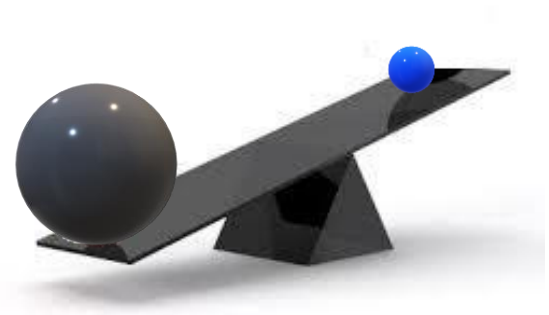
- Not straightforward clinical translation

Number of published articles

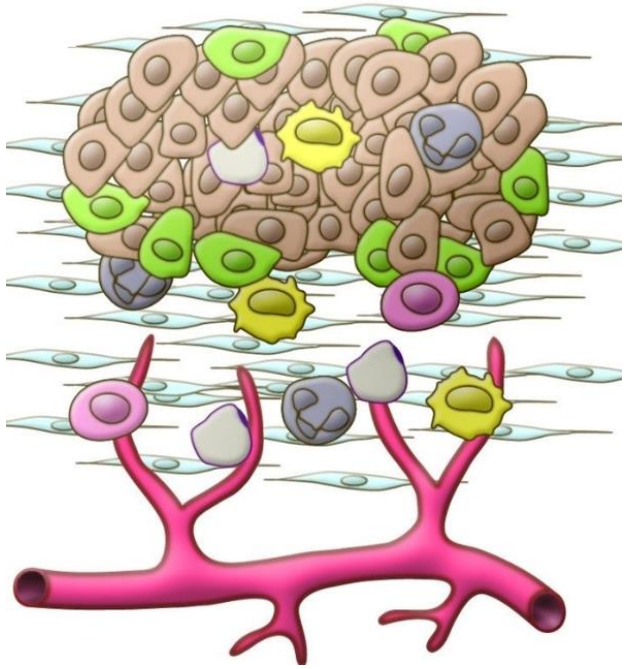
Nanomedicines in the market



A.C. Anselmo, S. Mitragotri, *Bioengineering & Translational Medicine* 2019 e10143

Need to reach the biological target

Transport through the microenvironnement



Extravasation

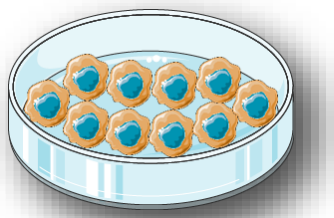
Efficient drug delivery to cancer cells requires crossing of multiple biological barriers

Need to have relevant predictive models

Tumor and microenvironment : multiple biological barriers

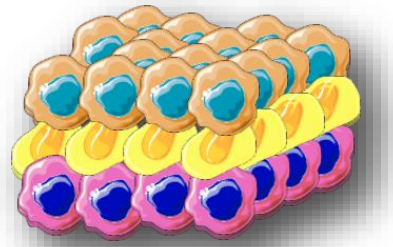
2D

- ⊕ Easy and convenient set-up
- ⊖ Highly reductionist
- ⊖ Flat cells, simple geometry
- ⊖ Lack of architecture
- ⊖ Less realistic drug response



3D

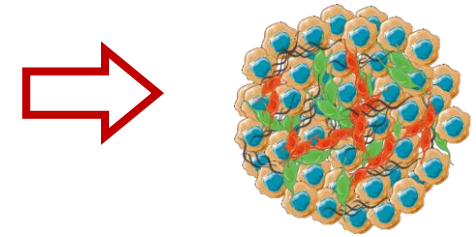
- ⊕ Gradients of oxygen, nutrients and waste
- ⊕ Tumor microenvironment
- ⊕ Cell-extracellular matrix interactions
- ⊕ Heterogeneous composition
- ⊖ Time consuming



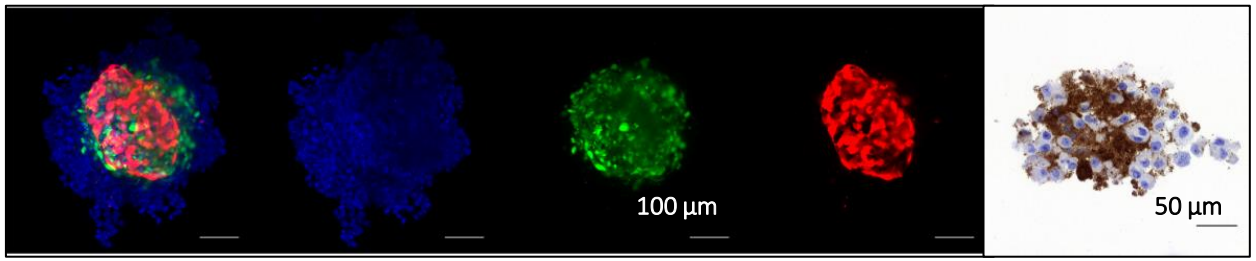
3D cell culture models

- **Heterotype tumor spheroids**

Pancreatic tumor
- Cancer cells
- Fibroblasts
- Endothelial cells

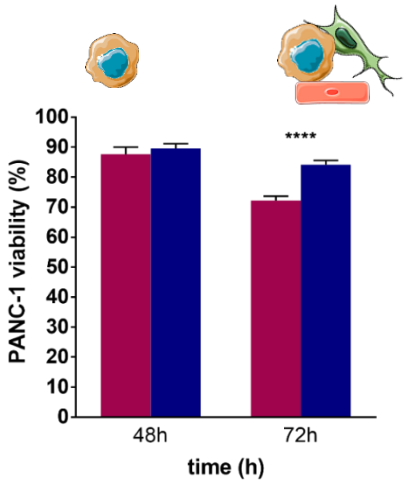


Nuclei | Fibroblasts | Endothelial cells | Fibronectin



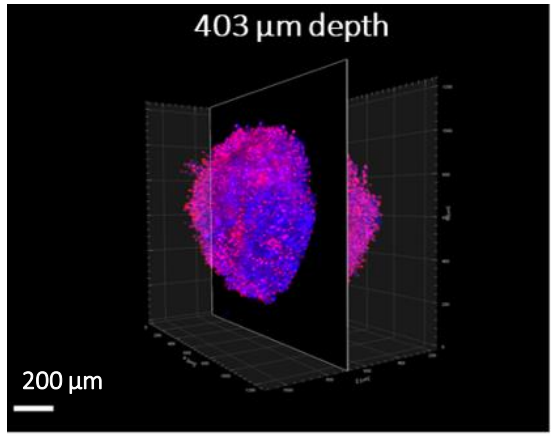
First pancreatic tumor model combining cancer cells and microenvironment components

Cytotoxicity

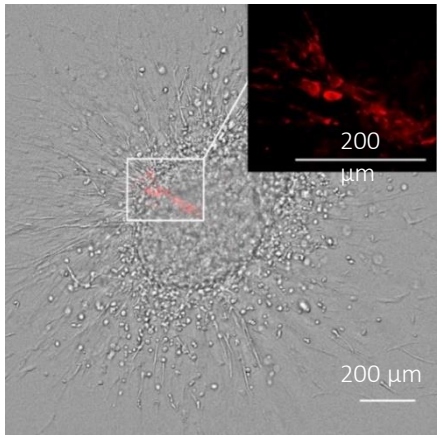


Tumor penetration

Doxorubicin
Nuclei



Angiogenesis



Lazzari G et al., *European Journal of Pharmaceutics and Biopharmaceutics* 2019;142:195; Lazzari G et al., *Acta biomaterialia* 2018;78:296

3D cell culture models

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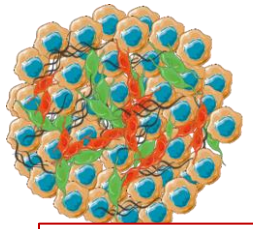
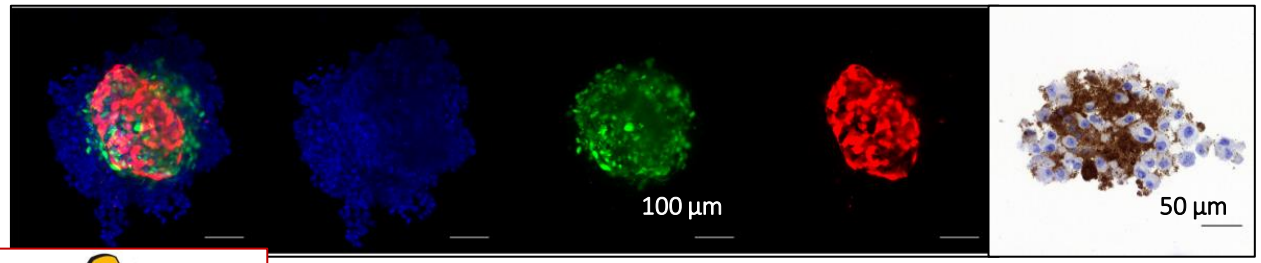
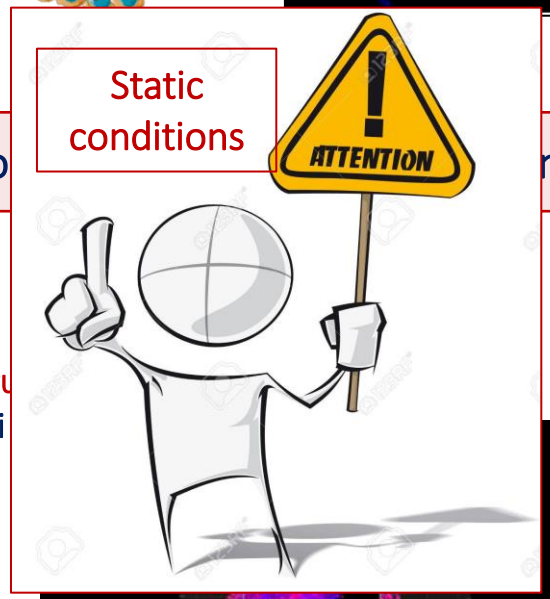


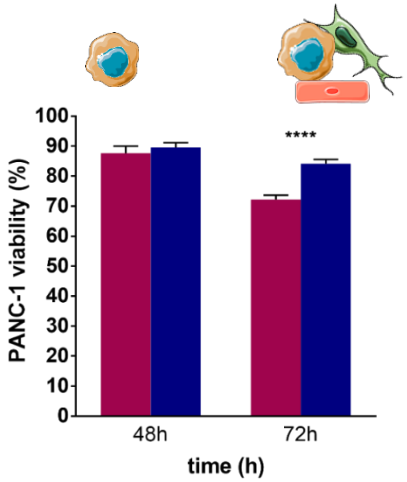
Nuclei Fibroblasts Endothelial cells Fibronectin



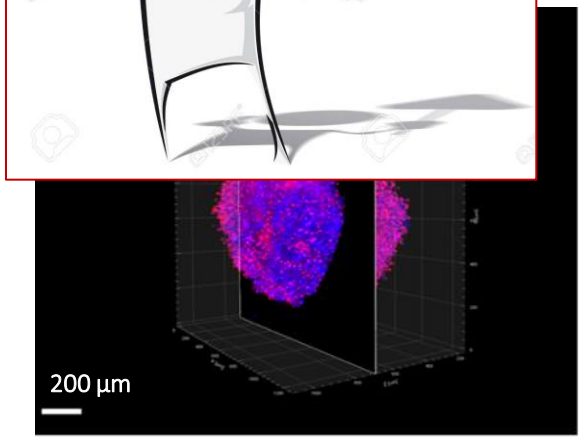
First pancreatic tumor mo nd microenvironment components



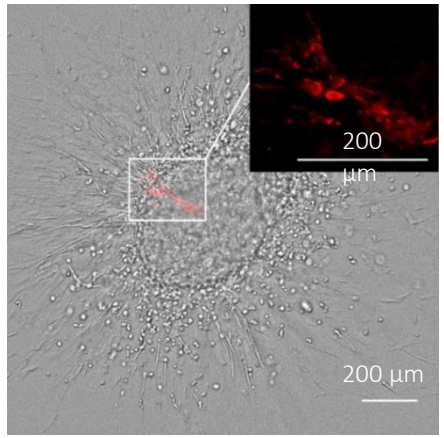
Cytotoxicity



Doxoru
Nuclei



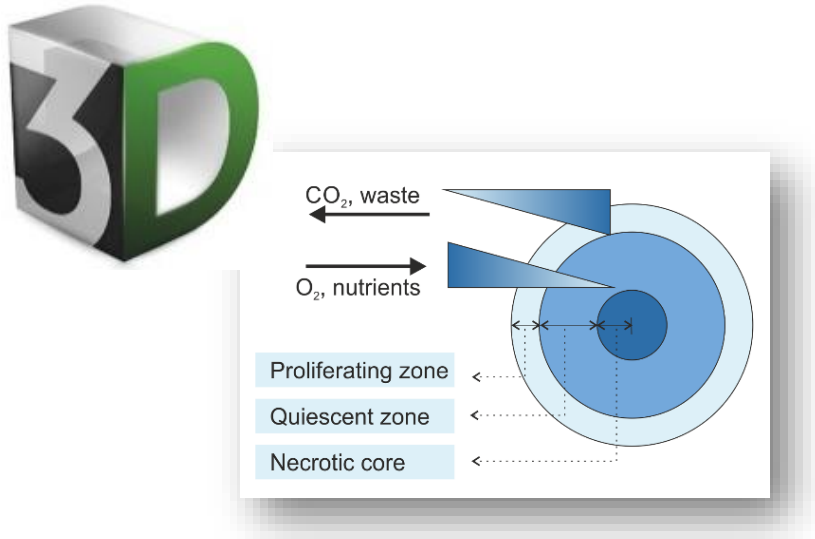
Angiogenesis

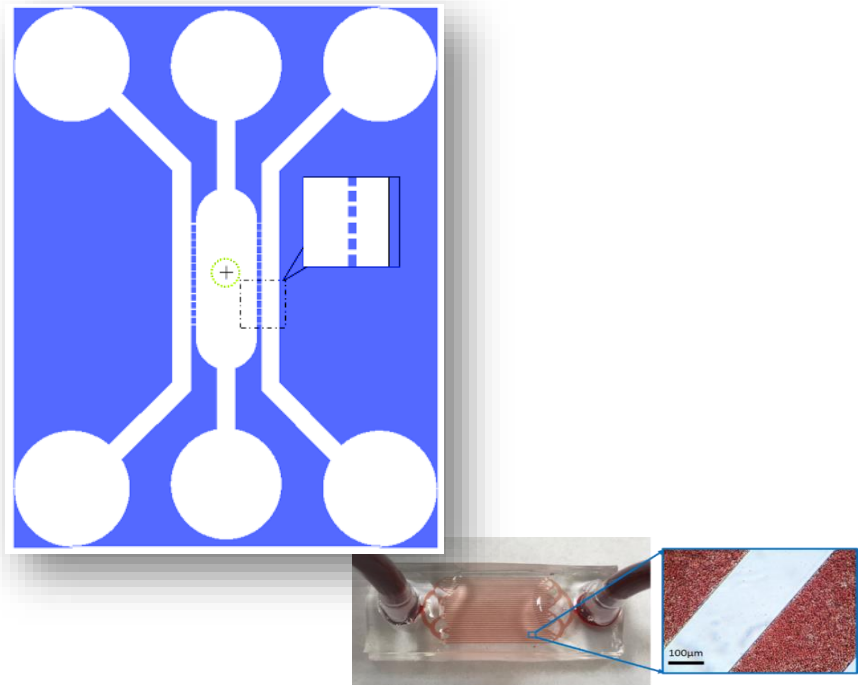


Lazzari G et al., *European Journal of Pharmaceutics and Biopharmaceutics* 2019;142:195; Lazzari G et al., *Acta biomaterialia* 2018;78:296

The project

µF_3D_Nano: combine biomimetic 3D culture methodologies and microfluidic technology





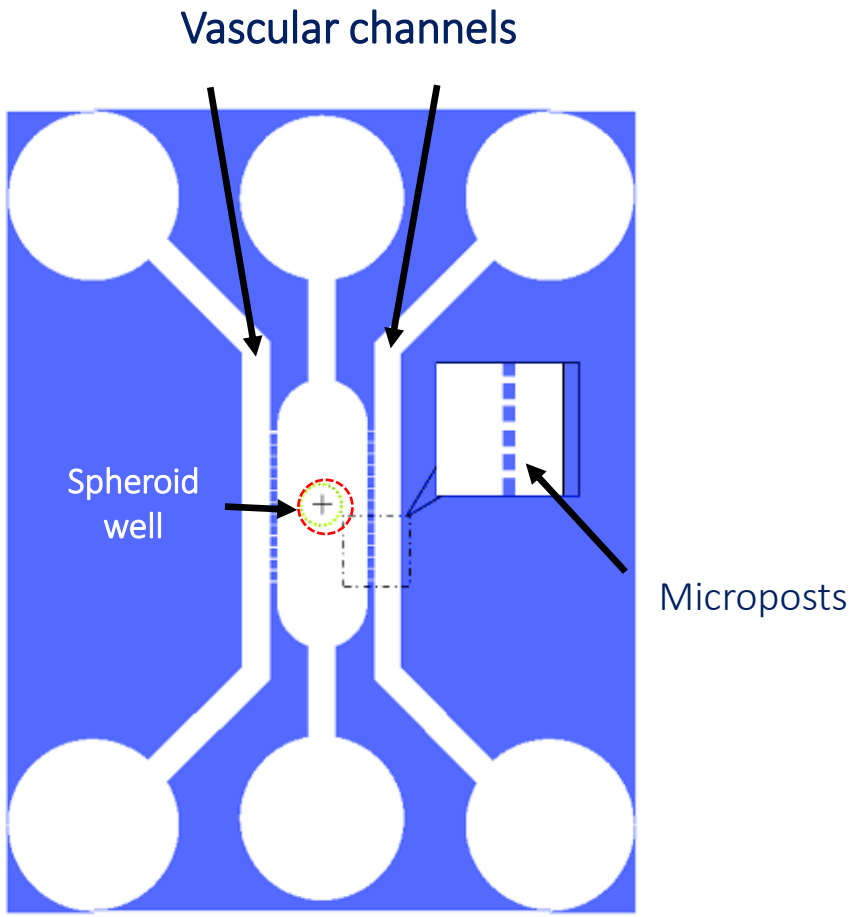
Develop efficient tools capable to mimic the in vivo physio-pathological conditions

Carry out a more predictive *in vitro* evaluation of nanomedicines

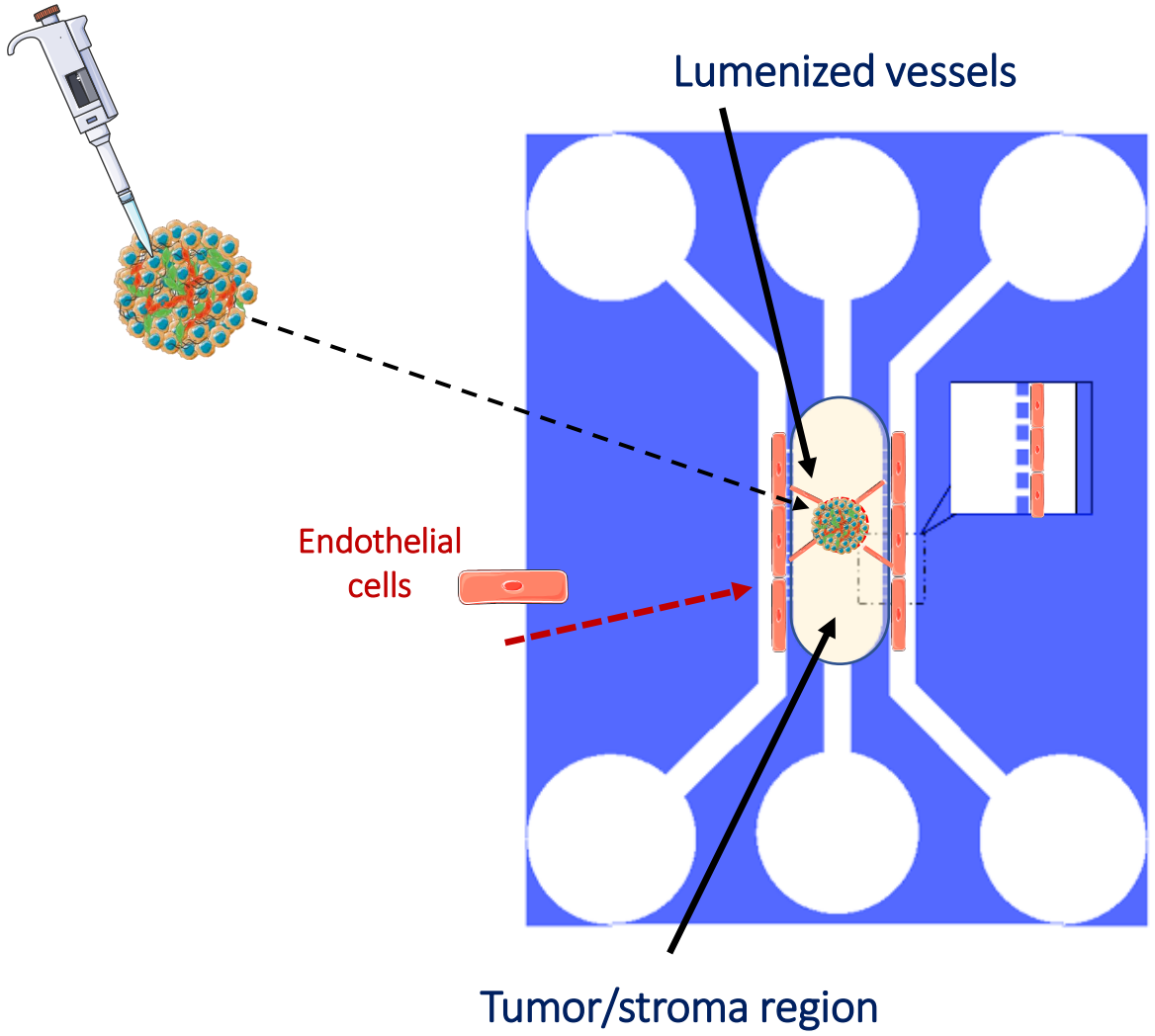
Correlate *in vivo* fate with nanomedicine physico-chemical properties

Haghiri-Gosnet AM DL, Lachaux J, Paris A, Hwang G. **2018. EP18306405.4**.

Task 1: Microfluidic device design, fabrication and optimization



Task 2: Cell culture in the microfluidic device



Task 3: Nanoparticle formulation & evaluation under flow: extravasation/tumor uptake

- Synthetic biodegradable polymers
- Size
- Shape
- Surface chemistry

- Monitoring of NP extravasation and accumulation
  - In situ
  - Following spheroid retrieval

Expected results

Provide an answer to the question:

"Which are the key features that would allow nanomedicines to successfully reach the tumor, deliver their cargo and exert the highest therapeutic activity thus finally leading to a clinical benefit?"

Drive the design of more efficient nanomedicines

- Reduction of in vivo studies (strong ethical impact)

Dr. Martina Ugrinic

November 2020 (12 months)

ETH zürich deMello group