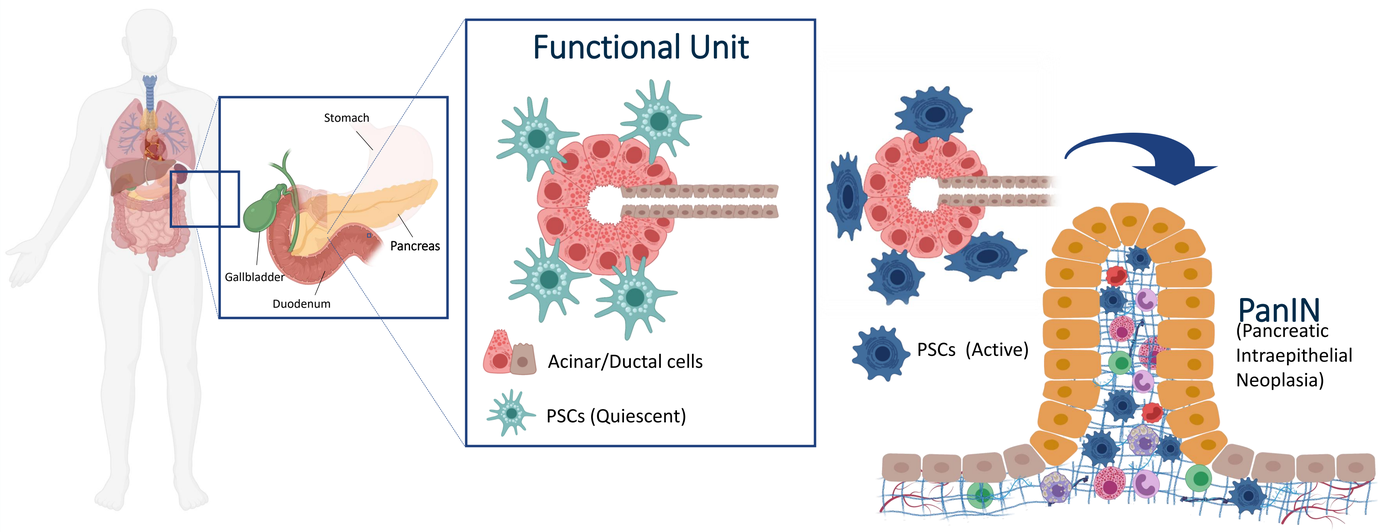
Towards PDAC-on-chip mimicking tumor-stroma interactions for drug testing

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INTRODUCTION

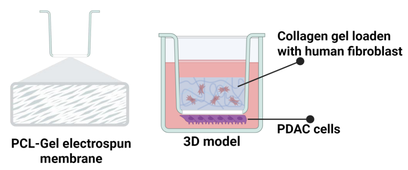


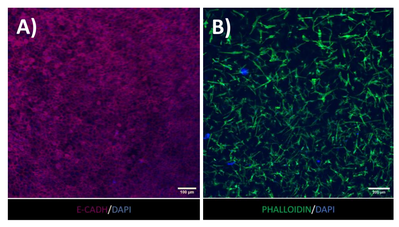
- Pancreatic Ductal Adenocarcinoma (**PDAC**) is the **most frequent** type of **exocrine pancreas tumor**[1,2].
- **PDAC progression** is strongly **influenced** by a **dense desmoplastic stroma**, mainly **driven** by **stromal cells** through **excessive extracellular matrix** (**ECM**) **deposition**, which impairs drug delivery and promotes tumor development[1,2].
- Nanoparticles (**NPs**) offer a promising approach to **improve drug loading**, **delivery**, **and selective accumulation within tumor tissues**[3].

Advanced 3D *in vitro* models that replicate PDAC microenvironment are essential tools to enable reliable drug screening and enhance the effective therapies.

Aim: to develop a biomimetic PDAC-on-chip model integrating tumor and stromal compartments for physiologically relevant drug testing and tumor-stroma interaction studies.

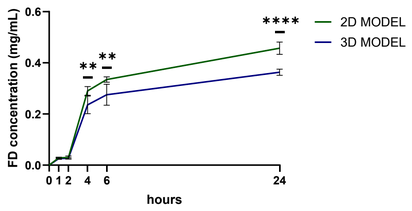
Transwell model





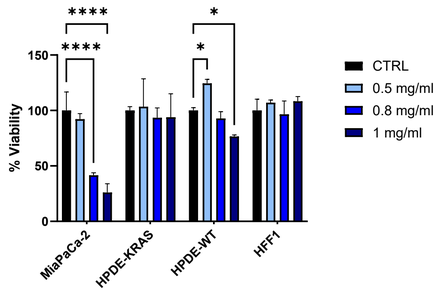
Immunostaining shows a physiological morphology and distribution of PDAC cells (**A**) and HFF1 (**B**) after 72h of maturation.

Permeability

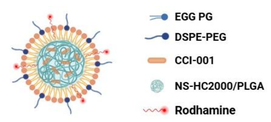


Fluorodextran (70 kDa) was administered apically, and permeability was measured basally over time. The **3D model showed lower permeability than the 2D setup** after 4 h, confirming the **stromal barrier effect**.

Free drug NPs cytotoxicity

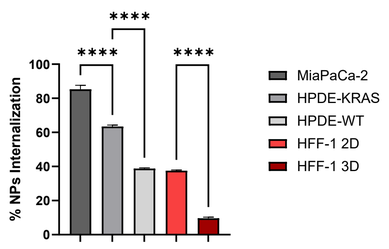


Preliminary **2D multiwell cytotoxicity** testing showed that **unloaded NPs were non-cytotoxic at 0.5 mg/mL after 48 h in all cell types** used in the model, supporting the use of this concentration for subsequent experiments.



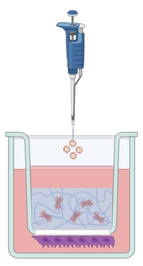
NPs, produced by nanoprecipitation, consist of a polymeric core for drug encapsulation and a lipid shell that improves stability.

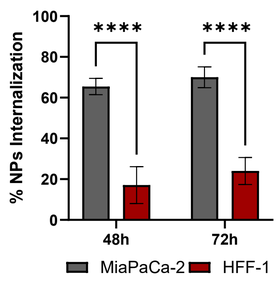
Free drug NPs uptake

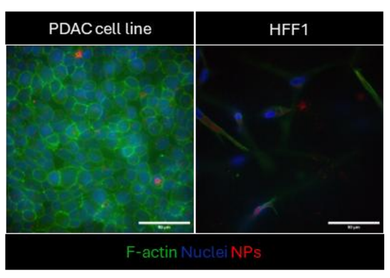


Preliminary **2D multiwell uptake testing** was performed on all cell lines. **NP uptake was higher in tumor cells than in non-tumor cells**, and lowest in HFF-1 fibroblasts embedded in collagen, highlighting the effect of the stromal component.



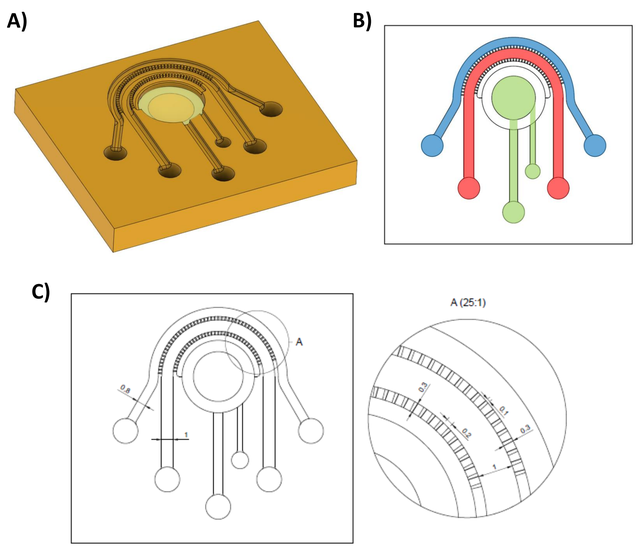






In the **Transwell model**, **NP distribution** was assessed **between the tumor and stromal compartments**. **NPs showed preferential uptake in PDAC cells** (MiaPaCa-2) than in HFF-1 fibroblasts.

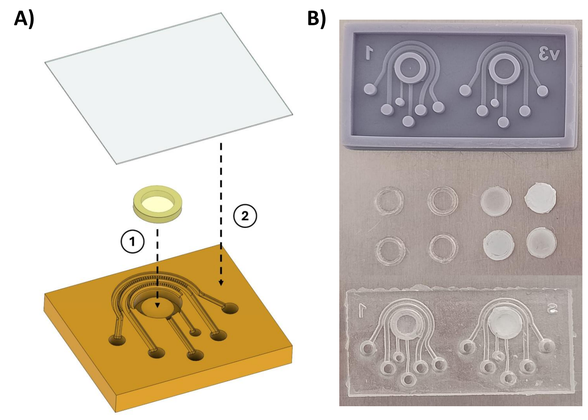
PDAC-on-chip model



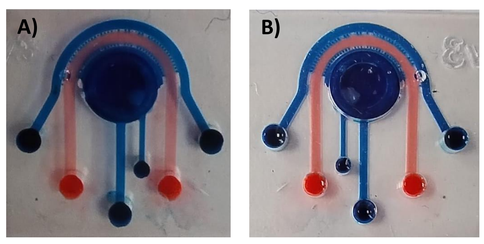
A) CAD model of the PDAC-on-chip showing the three compartments, micropillar arrays, and the central chamber hosting the PCL/Gel membrane holder.
B) **Top view** of the PDAC-on-chip layout highlighting the **medium channel** (**blue**), **stromal channel** (**red**), and **central chamber** for PDAC cell culture (**green**).
C) **Technical drawing** of the optimized **micropillar region**, with a magnified view of area A showing the **geometry** and **dimensions** used to confine the hydrogel while allowing molecular exchange.

Production & Assembly

PDAC-on-chip devices were fabricated by casting **polydimethylsiloxane** (**PDMS**) (10:1 PDMS/curing agent) into 3D-printed molds (Anycubic Photon Mono M7 Pro) and curing overnight 55 °C, followed by demolding.
A) **Assembly scheme**: (**1**) **insertion** of the electrospun **PCL/Gel membrane holder** into its housing; (**2**) **device sealing by plasma bonding**.
B) **Molds**, **holders with the electrospun PCL/Gel membrane**, and **PDMS PDAC-on-chip prototypes** with the holders inserted in position.



Device Validation



Preliminary device validation was performed using red-stained 5% w/v gelatin to mimic the stromal hydrogel and a blue aqueous solution to simulate medium perfusion. Bottom and top views (**A** and **B**, respectively) show effective **hydrogel confinement in the central channel** and **complete filling of the central chamber** and **outer channel**.

Scan the QR code to view two videos showing **hydrogel confinement** and **fluidic compartment filling** in the PDAC-on-chip.

CONCLUSION & FUTURE PERSPECTIVES

Preliminary Transwell results confirmed the **barrier effect of the stromal component**, with reduced permeability in the 3D model compared with the 2D setup. **Unloaded NPs at 0.5 mg/mL were non-cytotoxic after 48 h**, and **preferential NP uptake by PDAC cells** over stromal fibroblasts was observed both in preliminary 2D testing and in the Transwell model.
A biomimetic **PDAC-on-chip** device was developed **reproducing tumor-stroma crosstalk** in a physiologically relevant *in vitro* setting. The device design and fabrication workflow were optimized to improve mold printability and PDMS replication by refining both chip geometry and resin curing conditions. Preliminary validation confirmed **effective hydrogel confinement** within the stromal channel and **proper filling of the fluidic compartments**, supporting the reliability of the proposed architecture.
Future work will focus on **testing colchicine-loaded NPs** in the Transwell model, validating **PDAC-on-chip seeding**, and implementing **dynamic culture conditions** with tumor-stroma co-culture **within the microfluidic platform**.

ACKNOWLEDGMENT

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