Institut de Bioenginyeria de Catalunya

COLLABORATIVE IBEC INTERNATIONAL PhD PROGRAMME

Position

1. Project Title:
   Cancer on a chip device as a new approach for studying enzyme-powered nanomotors' mechanisms of action

2. Research project/ Research Group description

In the past decade, enzymatic-powered nanomotors (NMs) develop at the Smart Nanobiodevices group at IBEC have demonstrated significant efficacy as a treatment for bladder cancer in both in vitro and in vivo studies (1,2). However, gaps remain in the understanding of NMs' interactions with tumoral extracellular matrix, the mucus associated with tumors and the pH or oxygen gradients present in the tumor microenvironment (TME).

As a promising alternative, organ-on-a-chip (OoC) technology has emerged as an effective platform that enhances the complexity of traditional *in vitro* models while enabling real-time quantification of changes within the system. Despite its advantages, several critical challenges exist when working with OoC devices, including the lack of tubular channels, the absorption of drugs by polydimethylsiloxane (PDMS), and the optimization of cell seeding and distribution into the channels (3).

The Microsystems group led by Jaap den Toonder at ICMS has developed various OoC models that address these challenges, each offering distinct advantages and fabrication methods (4,5)

Lumina-Chip devices incorporate perfusable tubular micro-lumens connected to a central channel along their entire length through micro-gaps. These micro gaps (30 µM) are suitable for keeping hydrogel in the middle channel by providing enough surface tension without affecting the channel geometry, while still allowing for cellular migration and communication between the channel and the side lumens. This channel geometry promotes a more physiologically relevant environment, ensuring uniform wall shear stress under physiological flow conditions in the vessels. Furthermore, permeability analyses have indicated that the vessel wall of the Lumina Chip exhibits excellent barrier functionality. The optimization of Matrigel or gel-based channel filling and the seeding of various cell types have been refined, effectively preventing direct contact between the cells and PDMS, thereby enhancing cell attachment.

These devices allow for the evaluation of the therapeutic effectiveness of drugs loaded into the NMs, as well as the enhanced permeability and retention of NMs in tumors relative to normal tissues. Additionally,

these models provide the opportunity to gather more physiologically relevant data by examining changes in pH and oxygen levels.

References

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2 Simo, Serra-Casablancas et al. Urease-powered nanobots for radionuclide bladder cancer therapy. Nature Nanotechnology 2024 19 (4), 554-564
3. Use and application of organ-on-a-chip platforms in cancer research | Journal of Cell Communication and Signaling [Internet]. [cited 2024 Oct 7]. Available from: https://link.springer.com/article/10.1007/s12079-023-00790-7
4. Lumina-Chip - a tubular lumen-based microfluidic approach for enhanced physiological relevance in modeling cancer metastasis | Biological and Medicinal Chemistry | ChemRxiv | Cambridge Open Engage [Internet]. [cited 2024 Oct 7]. Available from: https://chemrxiv.org/engage/chemrxiv/article-details/65caa6e166c13817297f8c9
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3. Job position description

The student involved in this project will benefit from top-notch technologies like the development of novel drug delivery systems (nanobots) at IBEC and the fabrication of Organ on a chip devices (ICMS). The project will therefore have three different phases:

a) Synthesis and fabrication of enzyme-powered nanoparticles. Optimization of motion capabilities, drug-loading and release profiles. The student will learn wet-chemistry synthesis, enzyme catalysis, active matter phenomena and microscope video recording. The student will synthesize biodegradable and biocompatible nanoparticles functionalized with enzymes and loaded with therapeutic drugs. The next step will be to study of the motion in complex environments such Tumor microenvironments (TME). However, rhe inherent complexity of the TME limits the ability of conventional two-dimensional in vitro models to accurately replicate the behavior of nanomotors and the natural cellular responses to their interactions. Therefore, we will try to replicate 3D environments on chip. These will be carried out at the second phase of the project.

b) Fabrication of Cancer-on-chip devices. At the Jaap den Toonder's lab at ICMS, the student will learn how to fabricate microsystems to replicate TME. The student will learn the innovative design of Lamina-chip. Some modifications will be carried out to replicate different tumor scenarios. For example, the middle channel of the Lumina-chip can contain different types of hydrogels, such as collagen, as well as (cancer) cells or spheroids, while the tubular side channels can be lined with different cell types such as endothelial cells, representing blood or lymph vessels, or epithelial cells, representing healthy breast ducts. The precision, size, and circular geometry of these channels are achieved through femtosecond laser fabrication, allowing for a medium-throughput version of the device that includes nine Lumina Chips.

c) Study the penetration and distribution of Nanomotors into Cancer-on-chip devices. The Cancer-on-chip devices facilitate a variety of studies exploring the ability of nanomotors to traverse and modify types of tumor extracellular matrices, their selective migration toward cancer cells over healthy cells, and different methods of NM administration, such as intravenous or intratumoral injection.

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