université PARIS-SACLAY
FACULTÉ DE PHARMACIE

Graduate School: Health and Drug Research
Master 2 Pharmaceutical Technology and Biopharmacy

Company/laboratory/public institution: Laboratory for Vascular Translational Science (LVTS U1148 INSERM)

Address: 46 rue Henri Huchard, 75018 PARIS

Supervision of trainee:

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Position: TSY: PharmPhD Chargé de Recherche Inserm

EL: PhD student

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Internship period: 20 January - 18 July 2025

Title of the project: Perfused 3D vascularized tumor model for drug screening applications

Three-dimensional culture models are used as a compromise between simplicity of use and physiological relevance, making them a reliable alternative to *in vivo* models while facing ethical and financial considerations. Interplays between the different cell types at stake, as well as interactions with the matrix are known to determine the fate of these constructs, with the recent dawn of mechanobiology[1,2]. This field of research takes a notable significance in cancer research, as mechanical constraints are known to modify cells migration, aggressiveness and chemoresistance. For these reasons, the integration of a dynamic compartment to any tridimensional tumoral model is vital[3,4]. In particular, few cancer models integrate a vascular compartment, and even fewer studies use perfused vascularization to push further our understanding of the angiogenesis near the tumor site[5]. This kind of models can be used to study cancer cell migration, development under flow, or exposure to drugs for example[6,7]. Therefore, they are of prime importance in our understanding of key cancer mechanisms.

This internship is part of an ongoing project which aims at developing a 3D vascularized dynamic cancer model for drug screening. In particular, the intern will first be in charge of the **perfusion of a vascularized cancer model** previously designed in the lab, in order to connect it to a microfluidic network. Using this dynamic culture platform, the intern will then **study the influence of anticancer drugs** on this vascularized tumor model. This is not restrictive, and the use of vasoconstrictive and vasodilative drugs can also be envisioned to challenge the response of this *in vitro* model.

The material used in this project is composed of two polysaccharides extensively studied in the lab[8–10], pullulan and dextran, forming a hydrogel that has been patterned to combine microwells that host cancer spheroids and a hollow channel for endothelial cell culture. This channel is lined with endothelial cells, mimicking a vessel, and adapted to microfluidic tubings[9,10]. The work will involve:

- Hydrogel synthesis and possible protocol optimizations.

- Cell culture with human umbilical vein endothelial cells (HUVECs) and cancer cells of various subtypes (Ewing sarcoma, breast, melanoma).

- Engineering of a microfluidic circuit *in vitro* and compatibility studies with tubing and needles (preliminary results have been obtained in a previous M2 project).

- Microscopy to assess the integrity of the vascularization, as well as biological characterizations of cancer cell viability.

The intern is expected to be interested in cell culture, in biomaterials, and in engineering and microfluidics. The intern is highly encouraged to take initiatives and to propose ideas. This internship will take place in our laboratory in Bichat Hospital, 18e, Paris, within a team and a lab constituted by more than 200 people, including researchers, clinicians, engineers, postdocs, PhD students, and interns. The team is specialized in biomaterials and hydrogel production for tissue engineeering, and therefore owns the equipment necessary to accomplish this project, including the process of fabrication and characterization of the materials, as well as 3D cell dynamic culture and biomolecular analysis. The lab is young and dynamic, and the student will benefit from many soft-skills and communication trainings such as journal club sessions, weekly team meetings, or a "3-min-M2" contest. We are also committed to facilitate student integration by sharing time together, such as meals and social activities.

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2. Kretschmer, M., Mamistvalov, R., Sprinzak, D., Vollmar, A. M. & Zahler, S. Matrix stiffness regulates Notch signaling activity in endothelial cells. *J Cell Sci* **136**, (2023).
3. Andrique, L. *et al.* A model of guided cell self-organization for rapid and spontaneous formation of functional vessels. *Sci Adv* **5**, 6562–6574 (2019).
4. Dellaquila, A., Le Bao, C., Letourneur, D. & Simon-Yarza, T. In Vitro Strategies to Vascularize 3D Physiologically Relevant Models. *Advanced Science* **8**, (2021).
5. Lopez-Vince, E., Wilhelm, C. & Simon-Yarza, T. Vascularized tumor models for the evaluation of drug delivery systems: a paradigm shift. *Drug Delivery and Translational Research 2024* 1–26 (2024) doi:10.1007/S13346-024-01580-3.
6. Saha, B. *et al.* OvCa-Chip microsystem recreates vascular endothelium-mediated platelet extravasation in ovarian cancer. *Blood Adv* **4**, 3329–3342 (2020).
7. Paek, J. *et al.* Microphysiological Engineering of Self-Assembled and Perfusable Microvascular Beds for the Production of Vascularized Three-Dimensional Human Microtissues. *ACS Nano* **13**, 7627–7643 (2019).
8. Simon-Yarza, T., Labour, M. N., Aid, R. & Letourneur, D. Channeled polysaccharide-based hydrogel reveals influence of curvature to guide endothelial cell arrangement in vessel-like structures. *Materials Science and Engineering C* **118**, (2021).
9. Le Bao, C. *et al.* Spatial-Controlled Coating of Pro-Angiogenic Proteins on 3D Porous Hydrogels Guides Endothelial Cell Behavior. *Int J Mol Sci* **23**, 14604 (2022).
10. Dellaquila, A. *et al.* Fibroblasts mediate endothelium response to angiogenic cues in a newly developed 3D stroma engineered model. *Biomaterials Advances* **154**, 213636 (2023).