

INOVOTION/HCL PhD Project

Company name: INOVOTION SAS

City and postal code: La Tronche (France), 38700

Name of partner academic laboratory: CICLY ER3738; Lyon (Hospices Civils de Lyon; Hôpital Lyon-Sud)

Research topic: Isolation and amplification of Circulating Tumor Cells (CTCs) for their use as therapeutic tools.

Project description

During tumor development, certain cancer cells can escape from solid tumors and enter the bloodstream. These cells are known as Circulating Tumor Cells (CTCs).

The identification, isolation and characterization of CTCs is the focus of much research today, as they represent a non-invasive source of tumor material. CTCs thus offer exciting prospects for many clinical applications such as early cancer diagnosis, monitoring residual disease for early detection of relapse, or monitoring response to a treatment to detect resistance and adjust treatment accordingly. In hematology, CTCs have long been used, particularly in myeloproliferative syndromes, to monitor residual disease and define hematologic and molecular responses.

The goal of this research program is to develop a routine method to isolate CTCs from a blood sample (liquid biopsy), accurately count them, and grow them *in vitro* as tumoroids and then graft them *in ovo*. CTCs reflect the characteristics of the original tumor and provide rapid access to monitoring cancer progression and response to treatment. However, CTCs are extremely rare, which poses two major challenges. First, it is difficult to isolate them from the large number of blood cells, and none of the published or commercialized sorting systems can obtain sufficiently pure samples (many residual white blood cells remain).

In addition, the amplification of patient-derived CTCs requires new approaches, which are currently being developed by our consortium. The project, funded by PCSI-2022, has three main parts: (i) separation of CTCs, (ii) their counting and (iii) their amplification in tumoroids and *in ovo*. Sorting will be done in two steps, one for size separation (hydrodynamics) and one for separation by immunomagnetic depletion of white blood cells, for which the consortium has already developed a working prototype. Discrimination of CTCs from residual leukocytes will be achieved by counting using a lensless, portable optical device developed by the Institute des Nanotechnologies de Lyon (INL), the MagPure Chip, designed for routine use by medical biologists.

The aim of this PhD project is to optimize and validate 3D cell culture conditions for CTC mimic lines. After the cells of interest have been sorted, they will be grafted *in ovo* (onto chicken embryos). This model provides a nutrient-rich environment for rapid, physiological expansion of tumor cells. We will optimize grafting parameters (pre-amplification of CTCs, graft location) to improve the rate of positive grafts and amplification. Prospects include cancer monitoring and the development of personalized treatments.

Hosting Structures

INOVOTION

Inovotion is a biotechnology company (Contract Research Organization) implementing a unique *in vivo* evaluation approach for cancer drug discovery. Our cutting-edge patented technology, based on novel chicken egg assays, enables early analysis of drug candidates before the classical preclinical stage. By rapidly eliminating low-value molecules, we accelerate the drug discovery process and significantly reduce its cost. In our model, we can assess the efficacy and toxicity of potential cancer treatments and validate their targets.

Based on a proprietary technology originally invented in 2009, INOVOTION was founded in 2015 and has now completed over 450 studies. Our clients are public laboratories (universities and medical centers), biotech and pharmaceutical companies worldwide.

Our main missions are

- Participate in the search for the best candidates for cancer treatment
- Early detection of *in vivo* toxic effects of anticancer candidates
- Improve the productivity of preclinical and discovery processes by maximizing the optimization phase of candidate compounds
- Accelerate the overall drug discovery process to address unmet medical needs in oncology.

HCL (Hospices Civils de Lyon; CICLY ER3738 Laboratory, Hôpital Lyon-Sud)

The position is located at the Hospices Civils de Lyon (Lyon) and at Inovotion (Grenoble). The HCL are experts in molecular biology and will apply for CIFRE funding. Léa Payen and Sébastien Couraud are the principal investigators of the CIRCAN/CYCLI program (3 technicians, 1 researcher, 1 postdoc, 1 PU-PH thesis supervisor to be filled), which is sponsored and implemented at the Hospices Civils de Lyon and aims to improve the quality of life of patients. The team is working on assessing the *in vivo* chemosensitivity of CTCs to anticancer drugs, in an *in ovo* model (SENCIRTEG program - Inovotion collaboration since 2016) and *in vitro*, in an *in vitro* model (SENCIRTEG program - Inovotion collaboration since 2016) and *in vitro*, in a new microfluidic system model (LUTON program). Pr S. Couraud, Deputy Chief of the Pneumology and Thoracic Oncology Unit, coordinates several observational studies and L. Payen coordinates several observational and interventional studies on NSCLC aimed at better selecting patients according to their mutation status and vital prognosis. L. Payen oversees molecular profiling of ctDNA and CTCs in cancer.

Thesis Description

The aim of the thesis is to optimize and validate the conditions for isolation and 3D culture followed by *in ovo* transplantation of patient CTCs in order to obtain *in ovo* tumors with the physiological and genetic characteristics of those observed in patients.

This work will be carried out in collaboration with:

- The Lyon Institute of Nanotechnology (INL), which is developing a device for sorting/isolating CTCs from patient blood using microfluidic techniques.
- HCL, which will provide patient samples (prospective clinical trial) and carry out the isolation and 3D culture of CTCs.
- INOVOTION, which will master the transplantation model and the tumor cell treatments on the embryonated egg model.
- Analyses will be performed at both Inovotion and HCL.

Major Tasks

- Validate the use of the CTC sorting device developed by INL for routine use in the project.
- Optimize the *in vitro* (3D) culture conditions, to place CTCs in the best physiological conditions for *in ovo* transplantation.
- Optimize the *in ovo* transplantat conditions.
- Evaluate treatment response of in ovo-transplanted tumors.
- Analyze, interpret, and synthesize results.
- Write activity reports and scientific articles (publications) on the results and progress of the project.
- Oral and poster presentations on the project at internal meetings and scientific conferences.

Required Qualifications

Master's degree (Bac+5) in Biology/Cancerology

Knowledge and Skills

- Solid background in molecular biology, cell biology and biochemistry.
- Experience in oncology (approaches, methods, biomarkers, etc.).
- Experience in mammalian cell culture and aseptic techniques.
- Strong analytical and problem-solving skills
- Initiative to identify innovative approaches and new methodologies through literature searches and/or participation in discussions.
- Excellent written and verbal communication skills
- Experience with mammalian cell culture and aseptic techniques.
- Able to take initiatives for identifying innovative approaches and new methodologies through literature review and/or participation in discussions.
- Able to work independently and as a member of a cross-functional team.

Other Skills

Excellent Microsoft Office skills, particularly PowerPoint, Word and Excel. Excellent computer skills: ability to learn new systems quickly and navigate easily on the Internet and internal intranet sites.

Location: Mainly in Lyon (Lyon Sud Hospital), with regular travel to La Tronche (Grenoble).

Doctoral school: CANBIOS (Lyon)

Recruitment date: as soon as possible (taking into account the time needed for the ANRT to validate the Cifre).

Contract: Cifre (3 years)

Salary: €2,100 gross per month (ANRT salary scale)

Email address to send applications to: jobs@inovotion.com

INOVOTION

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References related to the project

including 3 completed theses, one postdoctoral internship in progress on the microfluidics part

- Descamps L, Garcia J, Barthelemy D, Laurenceau E, Payen L, Le Roy D, Deman AL. MagPure chip: an immunomagnetic-based microfluidic device for high purification of circulating tumor cells from liquid biopsies. *Lab Chip*. 2022 Oct 25;22(21):4151-4166. doi: 10.1039/d2lc00443g. PMID: 36148526.
- Descamps L, Audry MC, Howard J, Mekkaoui S, Albin C, Barthelemy D, Payen L, Garcia J, Laurenceau E, Le Roy D, Deman AL. Self-Assembled Permanent Micro-Magnets in a Polymer-Based Microfluidic Device for Magnetic Cell Sorting. *Cells*. 2021 Jul 9;10(7):1734. doi: 10.3390/cells10071734. PMID: 34359904; PMCID: PMC8307954.
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- Garcia J, Barthelemy D, Geiguer F, Ballandier J, Li KW, Aurel JP, Le Breton F, Rodriguez-Lafrasse C, Manship B, Couraud S, Payen L. Semi-automatic PD-L1 Characterization and Enumeration of Circulating Tumor Cells from Non-small Cell Lung Cancer Patients by Immunofluorescence. *J Vis Exp*. 2019 Aug 14;(150). doi: 10.3791/59873. PMID: 31475991.
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- Achkar IW, Kader S, Dib SS, Junejo K, Al-Bader SB, Hayat S, Bhagwat AM, Rousset X, Wang Y, Viallet J, Suhre K, Halama A. Metabolic Signatures of Tumor Responses to Doxorubicin Elucidated by Metabolic Profiling in Ovo. *Metabolites*. 2020 Jun 28;10(7):268. doi: 10.3390/metabo10070268. PMID: 32605263; PMCID: PMC7408021.
- Wang Y, Rousset X, Prunier C, Garcia P, Dosda E, Leplus E, Viallet J. PD-1/PD-L1 Checkpoint Inhibitors Are Active in the Chicken Embryo Model and Show Antitumor Efficacy In Ovo. *Cancers (Basel)*. 2022 Jun 23;14(13):3095. doi: 10.3390/cancers14133095. PMID: 35804865; PMCID: PMC9264844.