OPENING FOR A PHD POSITION

(2020-2023)

IRCM INSERM U1194 Montpellier (France) in partnership with a biopharmaceutical company offers one PhD position in:

Targeted radionuclide therapy against cancer-associated fibroblasts: role of intercellular communications between CAFs, tumor and immune cells

The Institut de Recherche en Cancérologie de Montpellier (IRCM), a joint research unit of INSERM, the University of Montpellier, and the Institut du Cancer de Montpellier (ICM), brings together fundamental, translational, and clinical expertise in oncology. The "Radiobiology and Targeted Radiotherapy" team is led by Dr. Jean-Pierre Pouget. The team's projects focuses on the study of the biological effects of radiotherapy using conventional X-rays or radiolabeled biomolecules. This is a translational research team composed of 17 permanent members (including 6 clinicians), 4 postdoctoral fellows and 4 PhD students. In addition to fully equipped cell culture, chemistry/biochemistry spaces, the lab is equipped with shielded lab spaces dedicated to ligands radiolabeling, in vitro experiments as well as therapeutic and imaging experiments in animals. The team has a direct access to the IRCM small animal housing facility as well as 7 core facilities (including Flow Cytometry, Microscopy and Histology).

https://www.ircm.fr/index.php?pagendx=415

Project

Context

It is now admitted that cancer therapy cannot be only restricted to cancer cells but must also consider the tumor cells microenvironment (TME) as it can promote resistance of cancer cells to such therapies. Therefore, novel treatment strategies should combine anticancer and anti-stroma agents. The TME or stroma is a complex ecosystem consisting of an extracellular matrix scaffold populated by endothelial cells, immune cells, as well as activated fibroblasts, termed cancer-associated fibroblasts (CAFs). TME components enter into a dynamic crosstalk involved in multiple stages of cancer development including tumor initiation, progression, and metastasis. Fibroblasts are spindle-shaped, non-epithelial (cytokeratin$^-$, E-cadherin$^-$), non-endothelial (CD31$^-$) and non-immune (CD45$^-$) cells of a mesenchymal lineage origin (vimentin$^+$) in normal tissue where they are considered as quiescent cells with negligible metabolic and transcriptional activities. Conversely, resident fibroblast may become activated during processes such as wound healing, acute or chronic inflammation or tissue fibrosis but also in the context of cancer, considered as a "wound that never heals". Their activation is then dependent on growth factors released by the cancer cells and also by infiltrating immune cells. CAFs represent one of the most abundant stromal cell types of several carcinomas including pancreatic cancers where 60–70% of the tumor tissue is composed of a desmoplastic stroma characterized by extensive collagen deposition and activated CAFs. Morphology and spatial distribution are key determinants in order to identify fibroblasts in a resting or activated state. Different markers, which are lower or not expressed by their normal counterparts, can also be used to identify activated fibroblasts such as α-smooth muscle actin (α-SMA), fibroblast- specific protein-1 (FSP-1), fibroblast-activation protein (FAP), PDGF receptors (PDGFR) α or β, neuron-glial antigen-2 (NG2), periostin (POSTN), podoplanin (PDPN), tenascin-C (TNC).

Objectives

The aim of this PhD project is to investigate, in preclinical PDAC tumors models, the biological response of CAFs to targeted radionuclide therapy and to investigate the intercellular communications between CAFs, tumor and immune cells.

Methodology

Developing appropriate 2D and 3D in vitro models to mimic cancer-stroma features of PDAC will be one of the first objectives of the thesis. Murine/ human primary or immortalized CAFs will be considered together with human/murine tumor and immune cells. The expression of CAFs cell surface markers will be monitored. Relevant in vivo PDAC models will be next established in immunodeficient and immunocompetent mice. CAFs will be next targeted in vitro and in vivo using a radiolabeled biomolecule against a specific CAF's cell surface marker. In vitro, the biological response of CAFs will be assessed and intercellular communications between CAFs, tumor and immune cells will be investigated through secretome analysis. Therapeutic efficacy and side effects of TRT against CAFs, together with remodeling of the ECM and immunomodulation will be evaluted in vivo in immune competent PDAC mouse models.

Techniques: 2D and 3D co- cell cultures, targeted radionuclide therapy, molecular and cellular biology, Omics, animal experiments.

Key words: Cancer associated fibroblasts, secretome analysis, immune response, targeted radionuclide therapy, PDAC

Starting date: 01/10/2020

Funding: Allocation doctorale Région Occitanie and sponsorship from a Pharma. The candidate will benefit from the scientific support of SIRIC Montpellier Cancer and of Labex MabImprove.

Selection criteria:

We are looking for a motivated candidate with a strong biology background. Experience with cancer associated fibroblast culture and extraction would be highly appreciated. Animal handling experience would be also an advantage. Background in radiation biology is not a prerequisite. International student are welcome to apply.

If you are interested in this position, please send your application (most recent CV, motivation letter stating your previous research experience, name/phone/email of at least one reference) to: jean-pierre.pouget@inserm.fr and sophie.poty@inserm.fr

Deadline: 31/07/2020