Postdoctoral position available in the Radiobiology for Targeted and Personalized Radiotherapy Team

Research topic: Tumor-derived DNA plays an important role in the initiation of anti-tumor immune responses. Radiotherapy enhance the release of tumor DNA and consequently its ability to stimulate anti-tumor immunity. However, **the mechanisms that regulate tumor DNA immunostimulatory potential remain poorly understood**.
Targeted radionuclide therapy (TRT) use has been **increasing worldwide** after the approval by FDA of new radiopharmaceuticals in the last 10 years. However, these radiopharmaceuticals do not always fully meet expectations and the reasons of **such absence of curative effect are unknown.**

We have identified in preclinical studies that **TRT can kill cancer cells in an immunogenic manner, and transforms "cold" tumors into "hot" tumors** (infiltrated with immune cells) by triggering the **cGAS-STING pathway** through the accumulation of **cytosolic DNA**. DNases can evacuate DNA and restore homeostasis through various mechanisms. Tumor DNA can be degraded by extracellular DNases, such as the DNASE1L3, an endonuclease specifically produced by DC that digests the DNA released by dying cells and thus limits its ability to activate immune responses. However, to date the role of DNASE1L3 in radiotherapy and specifically in TRT efficacy is unknown. Tumor DNA can also be evacuated by extracellular vesicles (EVs). Over the past 30 years, EVs emerged as a major mechanism for cell-cell interactions and prominent regulators of the immune response. We already have demonstrated that EVs play a cytotoxic role upon TRT, and that EVs, which are likely loaded with tumor DNA, contribute to TRT efficacy by mediating an antitumor immune response *in vivo*.

The project, led by the Postdoctoral fellow, will aim to further delineate DNASE1L3 function in the activation of anti-tumor immunity in response to TRT and EVs vaccination.

Research environment: The Radiobiology for Targeted and Personalized Radiotherapy is a multidisciplinary team including 24 scientists and clinicians in the field of radiobiology, radiotherapy and nuclear medicine. Besides developing new radiopharmaceuticals for cancer imaging and therapy, Dr. Pouget Lab research is focused on radiobiology and on the role of targeted (radiative) and bystander effects of TRT in cancer. The team has access to all the radiation dedicated environment including shielded radiobiology labs and animal facilities, and the irradiation (SARRP, Xstrahl) equipment's. IRCM is well equipped with cutting-edge technologies and provides an exceptional environment for scientific interactions. This project will be conducted in collaboration with Dr. Vanja Sisirak (Immunoconcept team, Bordeaux), who have characterized DNASE1L3 in several contexts.

Recruitment procedure: Successful candidates will be highly motivated individuals with a PhD in cell biology, immunology, molecular biology or a related discipline, together with substantial experience in at least one of the following areas: • Cancer biology • Radiobiology • Extracellular vesicles • Animal handling/mouse genetics.

Key dates: Applications should be completed before the 5th of January 2024. Interviews will be planned as soon as the deadline is reached. The position is available from the 5th of February 2024.

To apply, please send an email explaining your background and interests, curriculum vitae, and contact information of three references to:

Julie Constanzo: Julie.constanzo@inserm.fr