2019-11-20

EuReCa International PhD Program

PhD thesis project

2020 Call for application

Targeting cancer-associated fibroblasts to increase T cell infiltration and tumor cell killing in non-small cell lung cancer

General information

Call	2020
Reference	2020-07-SALMON
Keyword(s)	Immunotherapy, Lung cancer, Cancer-associated Fibroblasts, Cell migration, Screen

Director(s) and team

Thesis director(s)	Hélène Salmon
Research team	Stroma & Immunity
Research department	U932 - Immunity and Cancer

Description of the PhD thesis project

Our laboratory combines experimental and computational approaches to study the stroma-immune crosstalk, and aims to decipher the contribution of stromal cells, especially cancer-associated fibroblasts (CAF), to regulating immune responses against cancer. The preferential T cell retention in the peritumoral stroma observed in a large fraction of lung tumors limits the success of immunotherapies; dissecting the mechanisms regulating T cell exclusion is therefore crucial to improve T cell-based therapies.

While most recent therapeutic strategies have focused on immune cells, CAFs have been underappreciated in cancer immunology. We previously reported that matrix fibers in human NSCLC stroma form a dense physical barrier around tumor nests, restricting lymphocyte: tumor cell contact. Here, the central hypothesis is that CAF are key regulators of T cell migration, and that targeting CAF molecules may enhance T cell infiltration in the tumor and synergize with immunotherapy to induce tumor regression.

The main objectives are:

1. to characterize the CAF compartment in lung tumor lesions and unravel their role in regulating T cell infiltration into the tumor mass,
2. identify key CAF molecules involved, and
3. assess the potential of targeting CAF molecules to promote T cell recruitment and induce tumor regression.

Preliminary data of CAF mapping from poorly and highly T cell-infiltrated lung mouse tumors revealed candidate genes associated with lymphocyte infiltration. We will cross-reference these signatures with single-cell RNAseq data we obtained from human lung tumors to identify CAF-specific genes potentially mediating T cell exclusion. We will test their effects on T cell dynamics and tumor lysis using CRISPR to knockout the candidate genes in a novel tumor/CAF spheroid system we recently developed. Finally, we will assess in vivo in mice the therapeutic potential of treatments combining fibroblast-drug targets and checkpoint blockade.

International, interdisciplinary & intersectoral aspects of the project

Inter-disciplinarity: our research project crosses the domains of biology, informatics, and pre-clinical research. It combines both basic research, aiming to decipher mechanisms of the fibroblast-immune cell crosstalk in tumor lesions, and translational research, with the testing of CAF targets.

Intersectoral exposure: our lab has strong collaborations with biotech companies (i.e. Shannon Turley from Genentech; Takeda) for expertise, funding, and access to reagents and clinical trial data.

International dimension: international co-mentors, USA: Ephraim Kenigsberg (Mount Sinai School of Medicine) for computational analysis; Shannon Turley (Genentech) for stromal cell biology/cancer immunotherapy. The thesis will involve conference meetings and a visit to Mount Sinai, New York.

Recent publications

1. **Salmon H**., Remark R., Gnjatic S., Merad M. Host tissue determinants of tumour immunity. 2019. Nature Reviews Cancer, 19(4):215-227.

2. **Salmon H**., Idoyaga J., Rahman A., Leboeuf M., Remark R., Jordan S., Casanova-Acebes M., Agudo J., Khudoynazarova M., Rivera C., Hogstad B., Hashimoto D., Gnjatic S., Bhardwaj N., Palucka A.K., Brown B., Brody J., Ginhoux F., Merad M. Expansion and Activation of CD103+ Dendritic Cell Progenitors at the Tumor Site Enhances Tumor Responses to Therapeutic PD-L1 and BRAF Inhibition. 2016. Immunity, 44(4):924-38.

3. Price J., Idoyaga J., **Salmon H**., Hogstad B., Bigarella C., Ghaffari S., Leboeuf M., Merad M. CDKN1A regulates Langerhans cell survival and promotes Treg cell generation upon exposure to ionizing irradiation. 2015. Nature Immunology, 16(10):1060-8.

4. Merad M., **Salmon H**. Cancer: a dendritic-cell brake on antitumor immunity. 2015. Nature, 523 (7560): 294-5. News and Views.

5. **Salmon H**., Franciszkiewicz K., Damotte D., Dieu-Nosjean MC., Validire P., Trautmann A., Mami-Chouaib F., Donnadieu E. Matrix architecture defines the preferential localization and migration of T cells into the stroma of human lung tumors. 2012. Journal of Clinical Investigation, 122(3):899-910.

Expected profile of the candidate

Applicants should hold a degree in Immunology/Cell Biology. Prior experience with mouse models/imaging/immunology assays is strongly recommended. Experience in molecular biology (cloning/gene editing; NGS techniques) would be an advantage. Candidates should show solid capacity for independent and creative thinking, and be willing to work in an interdisciplinary field in interaction with the computational analysts of the lab. This is a dynamic project that will offer opportunities to work on innovative techniques and concepts, and candidates should be eager to explore and learn.