Post doctoral position

31/03/2021

Post doctoral fellow or research engineer position available in Daniel Olive's lab for highly motivated candidates with a strong background in immuno-oncology and strong skills in bioinformatics.
Employer : CRCM - Inserm U1068
Duration: 12 months renewable
Location: Immunomonitoring department, Paoli Calmettes Institute, Marseille, France.

Summary

Background: Immune checkpoint inhibitors (ICI) response rate in non-small cell lung cancer (NSCLC) is around 30%. Patient's immune system influences response to ICI, but the biological bases of this response heterogeneity are poorly understood. Currently, immune parameters are emerging as candidate biomarkers of response to PD1-blockade strategies (Havel Nat Rev Cancer 2019). Effector and helper T cell activation and phenotype is associated with ICI responses (Kagamu Cancer Immunol Res 2020, Huang Nature 2017, Gide Cancer Cell 2019). Additional immune populations were shown to be critical to ICI efficacy, with higher response rates in patients with tumors enriched with cytotoxic cells ($CD8^+$ T cells, γδT cells, NK cells), helper T cells (CD4+ T cells) and depleted of MDSCs and Tregs (Kagamu Cancer Immunol Res 2020, Charengton Cell Reports 2017, Riaz Cell 2017, Sade-Feldman, Cell 2018, Modermott Nat Med 2018, Krieg Nature Med 2018). Importantly, induction of alternative immune checkpoints during treatment represents a potential mechanism of escape to ICI (Koyama Nat Com 2016; Kamphorst PNAS 2017; Kalbasi Nat Rev Immunol 2019).

To date, such studies are limited in NSCLC patients. Moreover, these studies often lack external validation cohorts, especially in a real-life setting. Likewise, most of these biomarkers underperform in terms of quality of prediction (lack of sensitivity and/or specificity), which is a major concern for clinical decision making. In addition, ICI-resistance may be multifactorial. Combination of markers, signatures or scores is therefore required to gather immune parameters, clinical parameters and tumor characteristics, to improve the quality of prediction.

Thereby, a full characterization of immune populations involved in primary and acquired resistance is necessary to develop sensitive, specific and robust immune signatures to predict clinical outcome in NSCLC patients treated with ICI. In this context, we propose a project of development and validation of an integrated immuno-clinical signature associated with clinical responses to ICI in NSCLC patients, using non-invasive liquid biopsies collected in a real-life setting. Additionally, understanding the biological mechanisms underlying primary and secondary resistance to treatment is an important prerequisite to improve the efficacy of ICI.

Objectives: The present project aims at 1/ identifying immune biomarkers and immune signatures associated with primary or secondary resistance to ICI in patients with NSCLC 2/ identifying mechanisms of resistance to ICI.

Methods: 70 patients with advanced NSCLC have been included in the Immunosup trial (NCT03595813). Peripheral blood samples have been collected at baseline and during treatment with anti-PD1 or anti-PDL1. Cytokines and soluble immune checkpoints will be analyzed using ELISA and Luminex. PBMC will be analyzed by mass cytometry (CyTOF Helios) using 3 validated panels of 40 mAb (T cells, NK cells, myeloid cells) and sc-RNA-seq (10X-genomics).

Expected Results: We will validate immune signatures previously identified in retrospective NSCLC cohorts in collaboration with Thierry Fest (Hematology Department, Inserm U1236, Rennes University Hospital, France) and Edward Garon (Oncology Department, David Geffen UCLA Medical School, UCLA, USA) in the frame of the Keynote-001 trial (Rochigneux et al, Word Conference on Lung Cancer 2019 Barcelona abstr#2292; Rochigneux et al ASCO 2020 abstr#294245). sc-RNAseq analyses will enable to understand the metabolic pathways and functions of the immune candidates associated with response to ICI.

Main activities

The candidate will interact with different teams leading the different workpackages of the project. The overall scientific coordination of this interdisciplinary project will be ensured by Pr. Daniel Olive. Mass cytometry analysis will be performed in Daniel Olive's lab (Paoli Calmettes Institute, Marseille, France). Philippe Rochigneux, a medical oncologist in Pr. Goncalves' department, and Anne-Sophie Chretien, an immunologist in Pr. Olive's department, will bridge the clinical aspects with the different workpackages. scRNAseq analyses will be performed in collaboration with Pierre Milpied (CIML, Marseille). Data analysis will be supervised by Samuel Granjeaud (bioinformatics department, CRCM, Marseille).

Successful candidates will have a strong background in immunology and a solid experience in the use of bioinformatics tools for high dimensional datasets analysis. Candidates with the following skills are especially encouraged to apply.

Technical skills

- mass cytometry
- sc-RNAseq

Data analysis

- opt-SNE, UMAP, phenograph, Citrus, CellCnn,
- Cell Ranger pipeline / SEURAT
- Stream, Wishbone, Monocle

Experience in programming (R and Python) is a plus.

Interested applicants should send their application by email to Pr. Daniel Olive (daniel.olive@inserm.fr) with the following documents

1) Cover letter indicating current and future research interests
2) Curriculum vitae
3) Brief summary of previous research experience
4) Names and contact information for 3 references