2017-10

IC-**3i** International PhD Program

PhD thesis project

2018 Call for application

Identifying novel molecular regulators of human monocyte differentiation

General information

Call	2018
Reference	2017-10-SEGURA
Keyword(s)	Monocyte, Human transcriptional network, Single-cell RNA-seq, Bioinformatics

Director(s) and team

Thesis director(s)	Elodie Segura
Research team	Antigen Presentation in Dendritic Cells
Research department	U932 – Immunity and Cancer

Description of the PhD thesis project

The focus of the group is to better understand the biology of human antigen-presenting cells in health and pathology, in order to manipulate the properties of these cells for disease treatment, especially in cancer.

In particular, we are interested in monocytes, which are recruited by inflammtion and differentiate in tissues into monocyte-derived macrophages (mo-Mac) and monocyte-derived dendritic cells (mo-DC). Mo-Mac are known to suppress anti-tumor immune responses. Modulation of monocyte differentiation has therefore emerged as a promising strategy for therapeutic intervention. Using a novel model for human monocyte differentiation that we have developped, we recently showed that mo-Mac and mo-DC represent two separate lineages, controlled by distinct transcription factors (Goudot, Immunity 2017). However, the regulatory circuitries of monocyte differentiation remain to be characterized.

The objective of the PhD project is to identify novel molecular regulators governing monocyte fate commitment, and mo-DC versus mo-Mac differentiation. To address these questions, we will analyse the dynamics of monocyte differentiation using single-cell RNA-seq analysis and reconstruct developmental trajectories using bioinformatics tools. To complement this data, we will analyze chromatin accessibility and transcription factor footprints using ATAC-seq. To test the role of newly identified candidate regulators, we will either silence their expression in monocytes using shRNA or inhibit their activity using drugs, and analyze monocyte differentiation in our model. Finally, we will validate these findings using tumor ascites samples from cancer patients, that contain naturally-occurring human mo-DC and mo-Mac (Segura, Immunity 2013).

These results will provide novel insight into the molecular ontogeny of mo-DC and mo-Mac, and will be instrumental in the identification of potential molecular targets for the therapeutic manipulation of monocyte differentiation.

International, interdisciplinary & intersectoral aspects of the project

The project involves concepts, tools and methods from several disciplines (immunology, epigenetics, bio-informatics). In addition to being supervised by E.Segura (an immunology expert), the PhD student will be mentored by a bioinformatician to develop his/her skills in programming and data analysis. In this project, the PhD student will therefore be trained both in wet-lab techniques and in computational analysis.

The project will benefit from our established international collaborations with single-cell RNA-seq analysis experts (Nir Hacohen, Broad Institute).

Drugability of newly identified regulators will be evaluated by our industrial partners. Pre-clinical tumor models are available to carry out proof-of-concepts experiments.

Recent publications

1. Goudot C, Coillard A, Villani AC, Gueguen P, Cros A, Sarkizova S, Tang-Huau TL, Bohec M, Baulande S, Hacohen N, Amigorena S, **Segura E**.
Aryl hydrocarbon receptor controls monocyte differentiation into dendritic cells versus macrophages.
Immunity. 2017, 47: 582-596.

2. Durand M and **Segura E**.
The known unknowns of the human dendritic cell network. Front.
Immunol. 2015, 6:129

3. Guilliams M, Ginhoux F, Jakubzick C, Naik SH, Onai N, Schraml BU, **Segura E**, Tussiwand R, Yona S.
Dendritic cells, monocytes and macrophages: a unified nomenclature based on ontogeny.
Nat Rev Immunol. 2014, 14(8):571

4. **Segura E**, Amigorena S.
Inflammatory dendritic cells in mice and humans.
Trends Immunol. 2013, 34(9):440

5. **Segura E**, Touzot M, Bohineust A, Cappuccio A, Chiocchia G, Hosmalin A, Dalod M, Soumelis V, Amigorena A.
Human inflammatory dendritic cells induce Th17 differentiation.
Immunity. 2013, 38(2):336-48

Expected profile of the candidate

We are looking for an enthusiastic, intellectually curious and team-oriented individual. Applicants should be highly motivated to work in an interdisciplinary environment and to learn both wet-lab techniques and computational methods. Background in molecular biology, immunology, epigenetics or bioinformatics is recommended. Programming skills will be a plus, but not mandatory. Proficiency in English is compulsory.