2016-07

IC-**3i** International PhD Program

PhD thesis project

2017 Call for application

Functional and Therapeutical Implications of BAP1 Inactivation in Cancers

General information

Call	2017
Reference	2016-07-MARGUERON
Keyword(s)	chromatin, transcription, cancer, ubiquitination, polycomb.

Director(s) and team

Thesis director(s)	Raphaël Margueron
Research team	Maintenance of Transcriptional Repression by Polycomb Proteins
Research department	U934 / UMR 3215 - Genetics & Developmental Biology

Description of the PhD thesis project

BAP1 is a tumor suppressor found inactivated in a variety of cancers including uveal melanomas where its loss correlates with a highly metastatic behavior. At the functional level BAP1 is a nuclear deubiquitinase, which regulates the ubiquitination of various proteins including histone H2A. Its ortholog in Drosophila is part of a complex described as a component of the Polycomb machinery and therefore proposed to be involved in transcriptional repression.

Our ongoing study revealed a distinct role for BAP1 in mammals, whether its function relies on its chromatin modifying activity remains elusive.

The PhD student will investigate how BAP1 regulates transcription and in particular determine whether this effect is mediated by the regulation of histone H2A ubiquitination or involves other substrates. He/She will then determine how this result could explain the contribution of BAP1 deletion to uveal melanomas progression. In parallel, the student will take advantage of genetic screens to identify genes and pathways that become essential when BAP1 is mutated. The ultimate goal is to identify potential therapeutic strategy to treat BAP1-deficient malignancies.

International, interdisciplinary & intersectoral aspects of the project

Considering the broad range of skills covered by the PhD project, the student will benefit from mentoring by an international advisor for the more fundamental part and by an advisor with a strong background in translational research. The PhD project involves both wet-lab and computing.

Recent publications

1. Schoumacher M, Le Corre S, Houy A, Mulugeta E, Stern M-H, Roman-Roman S, **Margueron R**.
Uveal melanoma cells are resistant to EZH2 inhibition regardless of BAP1 status.
Nat Med. 2016 Jun 7;22(6):577-8. doi: 10.1038/nm.4098.

2. Wassef M, Michaud A, **Margueron R**.
Association between EZH2 expression, silencing of tumor suppressors and disease outcome in solid tumors.
Cell Cycle. 2016 Sep;15(17):2256-62. doi: 10.1080/15384101.2016.1208872.

3. Wassef M, Rodilla V, Teissandier A, Zeitouni B, Gruel N, Sadacca B, Irondelle M, Charruel M, Ducos B, Michaud A, Caron M, Marangoni E, Chavrier P, Le Tourneau C, Kamal M, Pasmant E, Vidaud M, Servant N, Reyal F, Meseure D, Vincent-Salomon A, Fre S, **Margueron R**.
Impaired PRC2 activity promotes transcriptional instability and favors breast tumorigenesis.
Genes Dev. 2015 Dec 15;29(24):2547-62. doi: 10.1101/gad.269522.115.

4. Sanulli S, Justin N, Teissandier A, Ancelin K, Portoso M, Caron M, Michaud A, Lombard B, Da Rocha ST, Offer J, Loew D, Servant N, Wassef M, Burlina F, Gamblin SJ, Heard E, **Margueron R**.
Jarid2 methylation via the PRC2 complex regulates H3K27me3 deposition during cell differentiation.
Mol Cell. 2015 Mar 5;57(5):769-83. doi: 10.1016/j.molcel.2014.12.020.

5. da Rocha ST, Boeva V, Escamilla-Del-Arenal M, Ancelin K, Granier C, Matias NR, Sanulli S, Chow J, Schulz E, Picard C, Kaneko S, Helin K, Reinberg D, Stewart AF, Wutz A, **Margueron R**, Heard E.
Jarid2 Is Implicated in the Initial Xist-Induced Targeting of PRC2 to the Inactive X Chromosome.
Mol Cell. 2014 Jan 23;53(2):301-16. doi: 10.1016/j.molcel.2014.01.002.

Expected profile of the candidate

Applicants should have a strong interest to explore the mechanisms of transcriptional regulation and their involvement in cancer. Background in chromatin biology and cancer research is strongly recommended. Previous experience with genome editing/genetic screen would be a plus. The project relies heavily on bioinformatics, the applicant should either have some training or be willing to acquire this expertise.