

EuReCa International PhD Program

PhD thesis project

2023 Call for application

Investigating the role of Polycomb in epigenetic regulation and inheritance during mouse germline formation and embryogenesis: study of a new member of the PRC2 complex, EZHIP (Ezh2 Inhibitory Protein) using transgenic model

General information

Call	2023
Reference	2023-06-MARGUERON
Keyword(s)	Intergenerational epigenetic inheritance; Histone modifications; Polycomb; Mouse embryogenesis; Germline

Director(s) and team

Thesis director(s)	Raphaël Margueron
Research team	Mechanisms of Repression by Polycomb Proteins
Research department	U934/UMR3215 - Genetics and Developmental Biology

Description of the PhD thesis project

During ontogeny, chromatin modifiers contribute to the orchestration of spatiotemporal gene expression programs that underlie early development and organogenesis. The Polycomb repressive complex 2 (PRC2) is one of such central epigenetic remodelers. It is key for transmitting correct chromatin information from parent to offspring during the formation of the mouse germline. PRC2 methylates lysine 27 on histone H3 (H3K27me_{2/3}), a crucial step for the formation of closed chromatin structure refractory to transcription. PRC2 cofactors modulates its enzymatic activity, influencing the H3K27me₃ pattern. Among them, we recently characterized EZHIP as a negative regulator of PRC2 in gametes. Although Ezh1 KO animals are viable, mouse females display a reduce fertility phenotype.

We are currently investigating phenotypic and molecular changes upon maternal loss of EZHIP in oocyte, we have already gathered important results concerning its role in maintenance of gene imprinting in the progeny. Besides, preliminary evidences indicate that upon loss of maternal and paternal EZHIP, the progeny displays a variety of subtle phenotypes. Further investigation is needed to understand how PRC2-dependent transcriptional changes affect early post-natal life and adulthood.

This project will aim at deciphering the role of paternal EZHIP in the germline and upon its transmission at different stage of mouse life, using low input CUT&RUN and RNAseq technologies to assess chromatin and transcriptional changes.



International, interdisciplinary & intersectoral aspects of the project

International: the student will be mentored by Dr. Maria-Elena Torres-Padilla, Director of the Institute of Epigenetics and Stem cells at HelmHoltz Zentrum, Munchen Germany.

Intersectoral: A one-day immersion in a Start-up will be organized.

Interdisciplinary: the project relies both on biology and informatics. The student will follow specific training for bio-info.

Recent publications

1. Richart L, Picod-Chedotel ML, Wassef M, Macario M, Aflaki S, Salvador MA, Héry T, Dauphin A, Wicinski J, Chevrier V, Pastor S, Guittard G, Le Cam S, Kamhawi H, Castellano R, Guasch G, Charafe-Jauffret E, Heard E, **Margueron# R** and Ginestier# C. XIST loss impairs mammary stem cell differentiation and increases tumorigenicity through Mediator hyperactivation. *Cell*. 2022 Jun 9;185(12):2164-2183.e25. doi: 10.1016/j.cell.2022.04.034. Epub 2022 May 20. PMID: 35597241
2. Holoch D, Wassef M, Lövkvist C#, Zielinski D, Aflaki S, Lombard D, Héry T, Loew D, Howard M & **Margueron#**. A cis-acting mechanism mediates transcriptional memory at Polycomb target genes in mammals. *Nature Genetics*, 2021 Nov 15. doi: 10.1038/s41588-021-00964-2.
3. Ragazzini R, Pérez-Palacios R, Baymaz HI, Diop S, Ancelin K, Zielinski D, Michaud A, Givelet M, Borsos M, Aflaki S, Legoix P, Jansen PWTC, Servant N, Torres-Padilla ME, Bourc'his D, Fouchet P, Vermeulen M and **Margueron# R**. EZHIP constrains Polycomb Repressive Complex 2 activity in germ cells, *Nat Commun*. 2019, Aug 26; 10(1): 3858.
4. Wassef M, Luscan A, Aflaki S, Zielinski D., Jansen P, Baymaz I, Battistella A, Kersouani C, Servant N, Wallace MR, Romero P, Kosmider O, Just PA, Hivelin M, Jacques S, Vincent-Salomon A, Vermeulen M, Vidaud M, Pasmant E & **Margueron# R**. EZH1/2 function mostly within canonical PRC2 and exhibit proliferation-dependent redundancy that shapes mutational signatures in cancer, *PNAS*, 2019 Mar 26; 116(13): 6075-6080. doi: 10.1073/pnas.1814634116.
5. Campagne A, Lee MK, Zielinski D, Michaud A, Le Corre S, Dingli F, Chen H, Shahidian LZ, Vassilev I, Servant N, Loew D, Pasmant E, Postel-Vinay S, Wassef M, **Margueron# R**. BAP1 complex promotes transcription by opposing PRC1-mediated H2A ubiquitylation. *Nat Commun*. 2019 Jan 21; 10(1): 348. doi: 10.1038/s41467-018-08255-x.

Expected profile of the candidate

Applicants should have a strong interest for early development and epigenetic. They should have good communication skills, be self-motivated, adaptable and able to work in an innovative and challenging scientific environment. The project implies mouse genetics and bioinformatic.

