EuReCa International PhD Program

PhD thesis project

2022 Call for application

Histone variant H3.3 and cellular programs during development and cancer

General information

Call	2022
Reference	2022-01-ALMOUZNI_SIMEONOV
Keyword(s)	Development and cancer; Histone variants and marks; Animal models, Single cell, Omics.

Director(s) and team

Thesis director(s)	Geneviève Almouzni & Iva Simeonova
Research team	Chromatin Dynamics
Research department	UMR3664 – Nuclear Dynamics

Description of the PhD thesis project

To shape the genome in 3 dimensions in the nucleus, DNA is organized into chromatin, of which the basic unit, the nucleosome core particle, comprises about 146 bp of DNA wrapped around histones. Importantly, histones exist as distinct variants with various post-translational modifications (PTM). In each cell type, their distinct genome distribution defines an epigenomic landscape. Strikingly, alterations in histone H3 variants have been reported in brain tumors in children and later in other types of cancers, and the interest in understanding their contribution to genome function is continuously increasing.

Our team is exploring the role of histone variants in genome organization and maintenance and their link to transcriptional regulation and lineage fate choices. We recently found that a unique amino acid (S31) in the histone variant H3.3 was absolutely essential to complete gastrulation in Xenopus embryos. Phosphorylation of this evolutionary conserved residue specific to the H3.3 variant also proved critical in transcriptional control during ES cell differentiation and macrophages activation. Thus, the use of specific histone variants for proper chromatin organization has emerged as essential for cell fate choices.

The PhD student will investigate histone H3.3 importance in cell fate changes, in the context of normal development and in pediatric glioblastoma. S/he will build on cellular and animal models established in the laboratory to follow cell fate by using cutting-edge transcriptomic approaches, combined with in silico analysis of public datasets. We hypothesize that unique H3.3S31 phosphorylation could promote transcription at key developmental loci and engage in/maintain specific cell fates. The regulation of H3.3 transcription by tissue-specific factors, and the H3.3S31 unique PTM cross-talk with neighboring residues could contribute to cell plasticity during normal physiology and would be high-jacked by tumor programs in cancers harboring H3.3 mutations.

International, interdisciplinary & intersectoral aspects of the project

The PhD student will acquire and develop a broad range of expertise in both bioinformatics and wet lab approaches ranging from basic biology to translational and medical implications. This will entail mastering the use of public datasets, use of cellular and in vivo models, and cutting-edge single cell transcriptomics (from sample preparation to analysis). The PhD student will benefit from mentoring and/or a secondment abroad via a collaborative network, to obtain additional training on early development embryos, single cell data and R&D applications.

Recent publications

1. CENP-A overexpression promotes distinct fates in human cells, depending on p53 status. Jeffery D, Gatto A, Podsypanina K, Renaud-Pageot C, Ponce Landete R, Bonneville L, Dumont M, Fachinetti D, **Almouzni G**. Commun Biol. 2021 Mar 26;4(1):417. doi: 10.1038/s42003-021-01941-5. PMID: 33772115

2. Two HIRA-dependent pathways mediate H3.3 de novo deposition and recycling during transcription. Torné J, Ray-Gallet D, Boyarchuk E, Garnier M, Le Baccon P, Coulon A, Orsi GA, **Almouzni G**. Nat Struct Mol Biol. 2020 Nov;27(11):1057-1068. doi: 10.1038/s41594-020-0492-7. PMID: 32895554

3. Histone variant H3.3 residue S31 is essential for Xenopus gastrulation regardless of the deposition pathway. Sitbon D, Boyarchuk E, Dingli F, Loew D, **Almouzni G**. Nat Commun. 2020 Mar 9;11(1):1256. doi: 10.1038/s41467-020-15084-4. PMID: 32152320

4. Dynamics of asymmetric and symmetric divisions of muscle stem cells in vivo and on artificial niches. Evano B, Khalilan S, Le Carrou G, **Almouzni G**, Tajbakhsh S. Cell Reports 2020 Mar 10;30(10):3195-3206.e7. doi: 10.1016/j.celrep.2020.01.097. PMID 32160529

5. Chromatin Plasticity: A versatile landscape that underlies cell fate and plasticity. Yadav T, Quivy JP, **Almouzni G**. Science 2018 Sep 28;361(6409):1332-1336. doi: 10.1126/science.aat8950. PMID: 30262494

Expected profile of the candidate

Applicants should have a strong desire to explore cell biological phenomena in an in vivo context, and should show solid capacity for independent and creative thinking. Background in molecular and cell biology, developmental biology, mouse genetics, and/or stem cell biology is strongly recommended. Background in immunology is a plus but not compulsory. The project highly relies on transcriptomic approaches. The applicant should have either experience in bioinformatics or a strong motivation to learn.