2019-11-20

EuReCa International PhD Program

PhD thesis project

2020 Call for application

Unraveling the architecture of human centromeres and its impact in the (epi)genetic mechanisms of centromere speficiation, immune response and in maintaining chromosome integrity

General information

Call	2020
Reference	2020-02-FACHINETTI
Keyword(s)	Centromere, DNA topology, Immune response, Genome instability, Epigenetics

Director(s) and team

Thesis director(s)	Daniele Fachinetti
Research team	Molecular Mechanisms of Chromosome Dynamics
Research department	UMR 144 – Cell Biology & Cancer

Description of the PhD thesis project

The centromere is required for correct chromosome inheritance. Defects in centromere formation lead to numerical and structural chromosome alterations, the latter often present at centromeres. These alterations promote cellular senescence and inflammation, and are common features of cancer cells.

The Fachinetti lab is studying how centromeres are established, structured and maintained to understand how chromosome inheritance is achieved. Despite human centromere position is epigenetically regulated, centromeres have a unique DNA sequence, a series of highly repetitive arrays spanning several megabases bound by centromeric proteins. Centromere DNA consists of ~3% of total genome, but the biological function of these megabase domains is unknown. A current work from our laboratory demonstrates that centromeric DNA plays an important role in preserving centromere position.

Additionally, centromeric DNA was identified as the preferential nuclear association site for the innate immune sensor cGAS, suggesting that this binding is required to limit the response to nuclear self-DNA. How centromeric DNA promotes centromere identity and how/why cGAS binds to centromeres remain to be investigated. The complexity of its DNA sequence suggests that centromeres has a unique chromosomal structure that has to be tightly regulated to prevent the occurrence of chromosome alterations. Their structure could play a key role in centromere specification and act as a base for nuclear immuno signaling.

Combining interdisciplinary and intersectional approaches in an international context, this project aims to characterize the topological architecture of human centromeres and to explore the relationship between centromere DNA, centromere function, immune-response activation and, overall, maintenance of genome stability. This proposal will provide crucial insight in our

understanding of the general balance between genetic and epigenetic elements that regulate genome function.

International, interdisciplinary & intersectoral aspects of the project

The proposed project will cross the boundaries of different disciplines, shifting from the use of biological knowledge (molecular, cell biology and immunology), physics (from single-molecule methods to electron microscopy) to biochemistry (protein purification assays and protein/DNA interaction).

The project will be carried out at the Institut Curie in the Fachinetti team (Chromosome Dynamics team) with exchanges with the Manel group (Immunology team). The PhD candidate will also work with Lumicks (NL) to perform single-molecule measurements using the correlative optical tweezers-confocal microscopy and in Italy to perform electron microscopy on DNA molecules. These international collaborations will allow the candidate to achieve experience in biophysics and in the industrial sector.

Recent publications

1. Dumont, M.*, Gamba, R.*, Gestraud, P., Klaasen, S., Worrall, J.T., De Vries, S.G., Boudreau, V.,Salinas- Luypaert, C., Maddox, P.S., Lens, S.M.A., Kops, G.J.P.L., McClelland, S. E., Miga, K.H.; **Fachinetti, D**. (2019). Human chromosome-specific aneuploidy is driven by DNA-dependent centromeric features. EMBO Journal.

2. Gemble, S., Anthony, S., Carole, P., Dumont, M., Hervé, S., Meitinger, F, Oegema, K., Rodriguez, R., Almouzni, G., **Fachinetti D**.* & Basto, R*. (*Co-corresponding authors) (2019) Centromere dysfunction compromises mitotic spindle pole integrity. Current Biology, S0960-9822(19)30932-7.

3. Gentili, M., Lahaye, X., Nadalin, F., Nader, G., Lombardi, E.P., Herve, S., De Silva, N., Rookhuizen, D. C., Zueva, E., Goudot, C., Maurin, M., Bochnakian, A., Amigorena, S., Piel, M., **Fachinetti, D**., Londoño-Vallejo, A. and Manel, N. (2019). The N-terminal domain of cGAS determines preferential association with centromeric DNA and activation in the nucleus. Cell Reports, 26(9):2377-2393.

4. Barra,V., Logsdon, G.A., Scelfo, A., Hoffmann, S., Hervé, S., Aslanian, A., Nechemia-Arbely, Y., Cleveland, D.W., Black, B.E. and **Fachinetti, D**. (2019) Phosphorylation of CENP-A on serine 7 does not control centromere function. Nature Communications, 10(1):175.

5. Lahaye X, Gentili M, Silvin A, Conrad C, Picard L, Jouve M, Zueva E, Maurin M, Nadalin F, Knott GJ, Zhao B, Du F, Rio M, Amiel J, Fox AH, Li P, Etienne L, Bond CS, Colleaux L, Manel N. NONO Detects the Nuclear HIV Capsid to Promote cGAS-Mediated Innate Immune Activation. (2018) Cell, 4;175(2):488-501.e22.

Expected profile of the candidate

Applicants should have a strong interest in the fundamental mechanisms of chromosome dynamics and the desire to do multidisciplinary research in biology and biophysics. Background in molecular biology, biochemistry and knowledge of modeling-based approaches oriented to solve biological problem is strongly recommended. The project highly relies on single molecules microscopy and in vitro approaches, for which the applicant should have either experience or a strong motivation to learn. The applicants should show solid capacity for independent and creative thinking.