2018-04

IC-**3i** International PhD Program

PhD thesis project

2018 Call for application

Imaging at the single molecule level of nuclear organization and genome stability in quiescent cells

General information

Call	2018-2019
Reference	2018-04-TADDEI_MINE-HATTAB
Keyword(s)	Nuclear organization, Genome stability, quiescence, Photo Activable Localization Microscopy (PALM), Single particle tracking (SPT)

Director(s) and team

Thesis director(s)	Judith Miné-Hattab and Angela Taddei
Research team	Compartmentalization and Dynamics of Nuclear Functions
Research department	UMR3664 – Nuclear Dynamics

Description of the PhD thesis project

The eukaryotic genome is packaged into large-scale chromatin structures that occupy distinct domains in the nucleus. This DNA organization is a key contributor to genome functions. Our aim is to understand what determines the spatial and temporal behaviour of chromatin and how this affects two essential functions of the genome: gene expression and the maintenance of genome integrity. To understand these fundamental processes, we use budding yeast as a model system that allows genetics, molecular biology and advanced live microscopy approaches to be combined.

Here, we propose to investigate the dynamics organization of chromatin in quiescence, in response to DNA damage, and to study how DNA repair proceeds in this specific context. Indeed, quiescence has been so far understudied although cells spend most of their time in this state that is characterized by a reversible cell cycle arrest and is often associated with increased stress resistance and longevity.

Our team has recently shown that chromatin of quiescent cells undergoes a major spatial re-organization: however, how these changes affect DNA repair is unknown.
In the first part, we will characterize chromatin organization and dynamics using super resolution microscopy in quiescent cells. We will directly measure chromatin motion, compaction and histones stability at the single molecule level. We will investigate the role of several factors such as cohesion/condensing in chromatin compaction during quiescence. Since DNA dynamics is profoundly altered upon DNA damage in cycling cells, in the second part, we will address how DNA repair proceeds in the highly compacted chromatin meshwork of quiescent cells. For that, we will use super resolution microscopy as well as classical genetic assays.

Overall, the project will combine genetics, advanced microscopy and modelling to investigate chromatin organization in quiescence and address how genome stability is maintained in this context.

International, interdisciplinary & intersectoral aspects of the project

The project aims to answer fundamental biological questions using several approaches: cell biology, genetics, super resolution and modeling. Our laboratory has a strong expertise in cell biology, genetics, quiescence and more recently in super resolution microscopy. We installed a PALM set-up and developed home-made softwares for image analysis specifically adapted to our questions. We are in contact with several companies to develop new settings. We have a fruitful collaboration with the Dahan/Coppey team (Institut Curie), who are experts in super resolution imaging and we have active collaboration with physicist to compare our experimental results with simulation of chromatin dynamics and organization based on polymer physics.

Recent publications

1. Clément et al. Nature Communication 2018

2. Miné-Hattab et al., MBoC 2017

3. Hocher et al. 2018. Expanding heterochromatin reveals discrete subtelomeric domains delimited by chromatin landscape transitions. Genome Research published ahead of print; doi:10.1101/gr.236554.118

4. Batté et al, 2017. Nuclear organization and chromatin status modulate homologous recombination efficiency and outcome. EMBO J., 36, 2609-2625 *Equivalent contribution

5. Guidi et al. 2015. Spatial reorganisation of telomeres in long-lived quiescent cells. Genome Biol., 16, 206.

Expected profile of the candidate

Applicants should have a strong inter-disciplinary profile combining biology and experimental physics. Background in molecular biology, microscopy, advanced image analysis (programming), are mandatory. Knowledge or strong interest in DNA repair processes is required. The candidate should show solid motivation to learn different techniques ranging from genetics, cell biology, gene editing to super-resolution microscopy and image analysis. The candidate should be organized and able to develop his autonomy and creative thinking.