2016-13

IC-**3i** International PhD Program

PhD thesis project

2017 Call for application

Spatio-Temporal Replication Program of the Human Genome and its Impact on Genome Stability in Normal and Cancer Cells

General information

Call	2017
Reference	2016-13-CHEN
Keyword(s)	DNA Replication; Human; Genomics and Epigenomics; Bioinformatics; Genome Stability.

Director(s) and team

Thesis director(s)	Chunlong Chen
Research team	Replication Program and Genome Instability
Research department	Dynamics of Genetic Information

Description of the PhD thesis project

At each cell division of human cells, tens of thousands of replication origins need to be activated to ensure complete duplication of >3 billion base pairs of the genome. This program must adapt to cell differentiation and development, whose deregulation can challenge genome stability and leads to mutations, cancer and many other genetic diseases. However, despite intensive studies, the mechanisms that coordinate where and when replication initiates in the human genome remain poorly known.

Our team focuses on using high-throughput approaches and genome-wide data analyses to study the spatio-temporal replication program of the human genome and its impact on genome stability. Recently, in collaboration with experimental biologists, we have developed cutting edge genomics approaches to study the human replication program. These data provide new insight into the links between replication, gene transcription, epigenetic modification and 3D genome organization. However, the entire picture is far from clear and deserves further investigation.

In this project, we will combine high throughput single molecule sequencing, mathematical modeling and bioinformatics analysis to study the replication program of the human genome in various normal and cancer cell types and to study how its deregulation impacts on genome instability. We will develop new genome-wide approaches to analyze DNA replication at single molecule resolution to study the cell-to-cell heterogeneity of replication. Mathematical modeling and bioinformatics analysis will be performed to decipher the genetic and epigenetic determinants that govern origin activity in space and time. Finally, we will analyze how deregulation of these processes contributes to genome instability and human diseases.

This innovative pluridisciplinary project will establish novel techniques and provide important new data for the wider scientific communities working on DNA replication program and human health.

International, interdisciplinary & intersectoral aspects of the project

The PhD candidate will be mentored by Dr. CJ CHEN (Annoroad Gene Technology in Beijing, China, a high-tech company focusing on developing new diagnostic products and assisting research by high-throughput sequencing). The student will visit Annoroad at least twice (for 1-3 months each time) for training. The project is highly interdisciplinary in its nature. It involves the development and application of skills in biology, bioinformatics, biostatistics, as well as the analyzing, understanding and integrating of various types of genomic data. The candidate will be placed in a multidisciplinary environment. He/she will work in close collaboration with the bioinformatics/sequencing platform of Institut Curie and Annoroad and the worldwide experimental biologist experts.

Recent publications

1. Petryk N., Kahli M., d'Aubenton-Carafa Y., Jaszczsyzyn Y., Shen Y., Sylvain M., Thermes C., **CHEN C.**L.* and Hyrien O.* (*co-last authors)
Replication landscape of the human genome.
Nat Commun. 2016 Jan 11;7:10208. doi: 10.1038/ncomms10208.

2. Audit B., Baker A., **CHEN C.L**., Rappailles A., Guilbaud G., Julienne H., Arach G., d'Aubenton-Carafa Y., Hyrien O., Thermes C. and Arneodo A.
Multiscale analysis of genome-wide replication timing profiles using a wavelet-based signal-processing algorithm.
Nat Protoc. 2013 Jan;8(1):98-110. doi: 10.1038/nprot.2012.145.

3. **CHEN C.L.**, Duquenne L., Audit B., Guilbaud G., Rappailles A., Baker A., Huvet M., d'Aubenton-Carafa Y., Hyrien O., Arneodo A. and Thermes C.
Replication-associated mutational asymmetry in the human genome.
Mol Biol Evol. 2011 Aug;28(8):2327-37. doi: 10.1093/molbev/msr056.

4. Van Dijk E.L.*, **CHEN C.L***. (*co-first authors), d'Aubenton-Carafa Y., Gourvennec S., Kwapisz M., Roche V., Bertrand C., Silvain M., Legoix-Né P., Leoillet S., Nicolas A., Thermes C. and Morrillon A.
XUTs are a class of Xrn1-sensitive antisense regulatory non-coding RNA in yeast.
Nature. 2011 Jun 22;475(7354):114-7. doi: 10.1038/nature10118.

5. **CHEN C.L.,** Rappailles A., Duquenne L., Huvet M., Guilbaud G., Farinelli L, Audit B, d'Aubenton-Carafa Y., Arneodo A., Hyrien O. and Thermes C.
Impact of replication timing on non-CpG and CpG substitution rates in mammalian genomes. Genome Res. 2010 Apr;20(4):447-57. doi: 10.1101/gr.098947.109.

Expected profile of the candidate

We expect the candidate to have solid programming skills and a strong interest in genome biology. Experience with high-throughput sequencing and/or genomics data analysis is strongly recommended. Background in molecular and/or cell biology and knowledge of evolutionary biology is a plus. The candidate should be highly motivated, curious and enthusiastic to work in a collaborative team. Fluency in English (written and oral) is required.