DNA replication must adapt to changes in chromatin organization associated with 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 cutting-edge high-throughput genomic approaches and genome-wide data analyses to study the spatio-temporal replication program of the human genome and its impact on genome stability, in particular to address the following questions:

- What determines the replication program, i.e. the position, the time of firing and the efficiency of replication origins in the human genome?
- How this program is regulated and associated with gene transcription and chromatin organization?
- How deregulation of these programs challenges genome stability?
In collaboration with experimental biologists, we have developed a method (Repli-Seq) and generated one of the first high-resolution replication timing profiles of the human genome (Fig. 1). Studies of these profiles from different human cell types have allowed us to reveal that the genome is organized in megabase replication domains associated with higher order chromatin structural units. By evolutionary analyses, we have also established that replication is a major process driving genome mutational landscape in normal and cancer cells. We are now applying Repli-Seq technique to analyze the replication dynamics from cells upon replication stress to study how deregulation of the replication program challenges genome stability, in particular, common fragile site activity.

More recently, we have developed a new method to study the replication program based on the deep sequencing of Okazaki fragments (OK-Seq). This allows us to determine the fractions of rightward- (R) and leftward- (L) moving forks at each locus, and to construct the complete profiles of replication fork directionality (RFD = R-L) along the genome. A transition from rightward- to leftward-moving forks occurs when crossing a replication origin position, leading to an upward transition in the RFD profile (Fig. 1). The quality and novelty of the data, leads to new insights into the replication landscape of the human genome and to further unravel the links between replication, gene expression, epigenetic modification and 3D genome organization in normal and cancer cells.

Moreover, we are developing new genome-wide approaches to study replication program at single molecule/cell resolution, in order to further study the intrinsic (between alleles) and
extrinsic (cell to cell) variation in replication and to further investigate the relation between cell-to-cell heterogeneity of replication and the cell-to-cell heterogeneity in gene transcription and chromatin organization.

Our study on DNA replication will provide the important bases for further understanding its role during development and aging, and how its deregulation contributes to tumorigenesis and to human diseases.

**Key publications**

**Year of publication 2016**

Nataliya Petryk, Malik Kahli, Yves d’Aubenton-Carafa, Yan Jaszczyszyn, Yimin Shen, Maud Silvain, Claude Thermes, Chun-Long Chen, Olivier Hyrien (2016 Jan 12)

**Replication landscape of the human genome.**

*Nature communications* : 10208 : [DOI : 10.1038/ncomms10208]

**Year of publication 2011**

Marion Dubarry, Isabelle Loïdice, Chunlong L Chen, Claude Thermes, Angela Taddei (2011 Jul 5)

**Tight protein-DNA interactions favor gene silencing.**

*Genes & development*: 1365-70 : [DOI : 10.1101/gad.611011]

Chun-Long Chen, Lauranne Duquenne, Benjamin Audit, Guillaume Guilbaud, Aurélien Rappailles, Antoine Baker, Maxime Huvet, Yves d’Aubenton-Carafa, Olivier Hyrien, Alain Arneodo, Claude Thermes (2011 Mar 4)

**Replication-associated mutational asymmetry in the human genome.**


**Year of publication 2010**


**XUTs are a class of Xrn1-sensitive antisense regulatory non-coding RNA in yeast.**

*Nature* : 114-7 : [DOI : 10.1038/nature10118]

Chun-Long Chen, Aurélien Rappailles, Lauranne Duquenne, Maxime Huvet, Guillaume Guilbaud, Laurent Farinelli, Benjamin Audit, Yves d’Aubenton-Carafa, Alain Arneodo, Olivier Hyrien, Claude Thermes (2010 Jan 28)
Impact of replication timing on non-CpG and CpG substitution rates in mammalian genomes.

*Genome research*: 447-57; [DOI: 10.1101/gr.098947.109]