Directeur d'unité
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1. Overview

The research conducted at the « Genome Integrity, RNA and Cancer » Unit explores multiple aspects of genome dynamics that integrate RNA biology in the context of genome maintenance and expression in normal and pathological situations, including cancer.

The Unit has a broad interest in understanding the molecular mechanisms underlying genome integrity and expression, from their basic functioning up to their pathological deregulation in human diseases such as cancer. By bringing together a unique complementarity of scientific and technical expertise, ranging from DNA replication, repair, and recombination, dynamics of gene expression, RNA biology, cancer immunology and cytoskeletal functions, one of our major goal will be to pursue our efforts to foster intra-Unit collaborations to help understanding at unprecedented levels the relationships between DNA metabolism, RNA metabolism and protein regulation by post-translational modifications. Beyond the complementary research expertise of the teams' Unit, an added value of the groups gathered at the Unit is the use of a wide range of available technologies/approaches (yeast genetics, biochemistry, mammalian cell-based assays, genetically-modifiable mouse models, tumorgrafts of human cells, genomics) and a diversity in biological models from unicellular eukaryotic organisms up to tumor cells and mice models that will also foster intra-Unit collaborations. In line with the scientific objectives detailed below, the Unit name « Genome integrity, RNA and Cancer" has been chosen to express (i) our long-

standing interest in the study of the DNA damage response, (ii) our commitment to add the "RNA dimension" in our understanding of genome integrity and, (iii) our willingness to translate our findings to the clinics, particularly in the context of cancer. For all these aspects, both basic and translational, our Unit benefits from the scientific and medical environment of Institut Curie. To strengthen our programs, accelerate scientific discovery and opportunities for clinical translation, we tend to always promote interaction and collaboration with other Units at the Institut Curie, the Curie translational department, the Curie technological platforms (CurieCoreTech) and with several departments at the Curie hospital. Overall, we envisage that our distinctive approach based on the integration of complementary research activities of our teams in the field of genome integrity and expression will lead to paradigm shifts and high profile research output as well as long-lasting benefits for human health.

2. Scientific objectives of the Unit

Living organisms are continuously exposed to DNA damage from endogenous (*i.e.* DNA replication, oxidative stress) or exogenous (*i.e.* irradiation, chemo-therapy) origins that impact genome integrity and expression. The DNA Damage Response is therefore critical to orchestrate a network of molecular pathways (DNA repair, gene expression, cell cycle control…) that ultimately impact cell fate decision. The main objective of the teams in our Unit is to understand the basic molecular and cellular mechanisms that underlie genome integrity including the study of DNA replication, recombination and reparation. In addition to the expertise of the teams (Sarah LAMBERT, Aura CARREIRA, Mounira AMOR-GUERET) constituting the Unit in this topic, we are in a position to describe genome integrity in unprecedented levels thanks to the complementary expertise of the teams of Carsten JANKE in cytoskeleton control of cell division and of the team of Stéphan VAGNER in RNA biology and gene expression. The Unit's teams work in a joint effort and coordinated manner on the following three common themes:

- **DNA replication stress from novel mechanisms to human disease.**
- **Mutual interactions between the DNA damage response and RNA metabolism.**
- **Chromosome segregation and tubulin functions**

3. Technological objectives

We intend to implement innovative technologies to simultaneously visualize, at the single cell level, up to 50 protein markers in tissue sections of interest using a novel *in situ* multiplexed imaging approach termed CODEX (CO-detection by InDEXing). This technology is new in Europe and our Unit is the first one in France to have bought the required equipment and to implement it. In addition, in a combined effort with the Orsay microscopy facility, we intend to implement in situ transcriptomics to enable analysis of cellular transcriptional states with spatial resolution, in tissue samples. This will allow us to interrogate specific pathways in tissue samples at the RNA level.

4. Translational objectives

Besides our basic research activities, several teams investigate translational aspects that can derive in new treatments for cancer (i.e. breast cancer, T-ALL, melanoma). The Unit continuously promotes the interactions with industrial partners and clinicians from the Curie hospital, but also from other hospitals in the Paris area (*i.e.* Gustave Roussy).

5. Teaching

The Unit has contributed to teaching and training at multiple levels. All group leaders and senior researchers are involved in hosting students and organizing Masters Courses. Together with the two Curie international courses (Curie training) organized by other Curie Units on "Non-coding genome" and "Epigenetics", the two Curie international courses organized by our Unit on "Genome instability and human diseases" and "Post-transcriptional gene expression" form an interesting series of courses on the general topic of "Genome Dynamics".

6. Summary of the recent work of our teams

Team "DNA recombination during replication for genome stability" (Sarah LAMBERT)

- The resection of nascent strands at dysfunctional forks is controlled by the NHEJ factor Ku (*J. Cell Sci.*, 2014; *Nat Com.*, 2017), the Chromatin remodeler Fft3^{SMARCAD1} (Life Sci Alliance 2019), and, if unscheduled, triggers pathological DNA structures in mitosis (*Mol. Cell*, 2017).
- Histone deposition at dysfunctionnal fork promotes replication restart (*PLoS Biology*, 2014; *PLoS Genetics* 2019).

Team "Genome instability and cancer predisposition" (Aura CARREIRA)

- BRCA2 presents a second DNA binding domain and acts as mediator in meiotic recombination (*Nat Com.,* 2016; *PNAS,* 2016).
- Some BRCA2 hypomorphic variants confer an increased moderate risk of breast cancer (*Cancer Res.,* 2017).

Team "Genetic instability and carcinogenesis" (Mounira AMOR-GUERET)

- CDA deficiency leads to genetic instability (*PLoS Genet.,*2015; *J Cell Sci.*, 2016; *Cell Cycle*, 2017; *Nat. Com.,* 2017).
- CDA deficiency is a novel and relevant predictive marker of susceptibility to antitumor drugs (*CCR,* 2017).

- BLM connects DNA damage to innate immune-sensing pathways (*J. Exp. Med.,* 2019).

Team “Controling microtubule dynamics and function with the tubulin code” (Carsten JANKE)

- Tubulin glycylation is essential for maintaining motile cilia, photoreceptors and primary cilia (*J Cell Biol,* 2013; *J Cell Sci,* 2017; *J Cell Biol*, 2017) and is involved in tumorigenesis (*EMBO J*, 2014).
- Deregulation of polyglutamylation causes neurodegeneration and reduced cargo transport in neurons (*EMBO J, 2018a,2018b*).

Team “RNA biology, signaling and cancer” (Stéphan VAGNER)

- DNA-damage response RNA-binding proteins. (DD-RBPs) control multiple aspects of the DNA damage response, from (post-)transcriptional gene expression to DNA repair (*TIBS* 2014; *Mol. Biol.*, 2016; *J. Mol. Biol.*, 2016).
- Targeting the eIF4F translation initiation complex relieves the resistance to anti-cancer therapies (*Nature*, 2014; *Cancer Res.*, 2016; , 2017, *Nature Med.* 2018, *Nat Com*., 2019).

Unit Publications

Publications clés

Année de publication : 2021

Gaetana Sessa, Belén Gómez-González, Sonia Silva, Carmen Pérez-Calero, Romane Beaurepere, Sonia Barroso, Sylvain Martineau, Charlotte Martin, Åsa Ehlén, Juan S Martínez, Bérangère Lombard, Damarys Loew, Stephan Vagner, Andrés Aguilera, Aura Carreira (2021 Feb 26)
BRCA2 promotes R-loop resolution by DDX5 helicase at DNA breaks to facilitate their repair by homologous recombination.
The EMBO journal : e106018 : DOI : 10.15252/embj.2020106018

Sudarshan Gadadhar, Gonzalo Alvarez Viar, Jan Niklas Hansen, An Gong, Aleksandr Kostarev, Côme Ialy-Radio, Sophie Leboucher, Marjorie Whitfield, Ahmed Ziyyat, Aminata Touré, Luis Alvarez, Gaia Pigino , Carsten Janke (2021 Jan 8)
Tubulin glycylation controls axonemal dynein activity, flagellar beat, and male fertility
ScienceScience : DOI : 10.1126/science.abd4914

Andrey Kleshnin, Léa Monet, Marina Plays, Hugo Vaysset, Claire Rougeulle, Stéphan Vagner (2021 Jan 6)
Amid darkness, light will prevail – a report on the 2020 annual SFC meeting on "Dark genome and Cancer"
Bulletin du cancer : DOI : S0007-4551(20)30510-5

Année de publication : 2020

Karol Kramarz, Kamila Schirmeisen, Virginie Boucherit, Anissia Ait Saada, Claire Lovo, Benoit Palancade, Catherine Freudenreich, Sarah A E Lambert (2020 Nov 7)
The nuclear pore primes recombination-dependent DNA synthesis at arrested forks by promoting SUMO removal.
Nature communications : 5643 : DOI : 10.1038/s41467-020-19516-z

Karol Kramarz, Anissia Ait Saada, Sarah A E Lambert (2020 Aug 26)
The Analysis of Recombination-Dependent Processing of Blocked Replication Forks by Bidimensional Gel Electrophoresis.
Methods in molecular biology (Clifton, N.J.) : 365-381 : DOI : 10.1007/978-1-0716-0644-5_25

(2020 Aug 26)
Identification and Analysis of Different Types of UFBs
Methods Mol Biol. : DOI : 10.1007/978-1-0716-0644-5_13