The dynamics of epigenetic remodeling and its precise involvement in tumor progression remains unknown, mainly due to the lack of cellular and animal models, and the plastic nature of epigenetic mechanisms. In the lab, we develop in vitro and in vivo models to monitor multiple epigenetic remodeling events at the single-cell level to reveal their timing of occurrence, address their stability over time, how they relate to the cellular phenotype.

Genes are not randomly distributed in the genome, and can be organized into domains of transcriptional co-regulation. A combination of epigenetic elements, among which chromatin modifications, chromatin conformation, long non-coding RNAs and nuclear localization, participate in organizing the genome into these domains and defining their respective transcriptional status. During development and cell differentiation, genes within these regions are coordinately regulated, such as in the HOX cluster.

Deregulation of these transcriptional domains occurs in cancer. Increasing evidence in the last years indeed suggest that the tumor epigenome undergoes long-range remodeling events, leading to the transcriptional deregulation of sets of neighboring genes. Alterations of the DNA methylation profile or the histone modifications landscape spread over several neighboring genes in tumor cells leading to the abnormal co-regulation of groups of genes, just like a gain or loss of DNA copy number. Large-scale genomic approaches have shown that these alterations target numerous genomic regions and accumulate in breast, prostate and bladder cancer cells. Long-range alterations can also extend to an entire chromosome: the inactive X-chromosome can be epigenetically deregulated and abnormally transcribed in breast tumors. Altogether, these findings imply that the tumor epigenome might be globally remodeled, through both activating and repressing mechanisms, thereby completely reshaping the expression program of the cell and potentially its identity.
If the timing and involvement of genetic events in tumorigenesis have been assessed in several models of tumor progression through the use of in vitro and in vivo systems, the dynamics of accumulation and the direct role of epigenetic aberrations have rarely been addressed, due in part to a lack of cellular and animal models.

In the lab we want to grasp the dynamics of epigenetic deregulation in tumor progression, by focusing on the long-rang epigenetic remodeling events (activating or repressing). Our aims are:

- to reveal the timing of occurrence of epigenetic alterations,
- address their stability over time,
- relate them to the cellular and clinical phenotype, especially resistance to treatment
- identify compounds with epigenetic remodeling potential

To do so, we are developing cellular tools to monitor epigenetic remodeling genome-wide in a variety of tumor cells, thanks to the targeted insertion of multiple reporters. Adding this innovative temporal component to the study of epigenetic alterations in cancer will refine their potential role in tumor progression and more accurately apprehend drug design. The team is focusing on the study of breast cancer, considering its high incidence (it is the most common cancer in women worldwide, 1.7 million new cases are diagnosed each year, representing 25% of all female cancers) and the frequent occurrence of epigenetic remodeling events in this tumor type. Thanks to collaborations with other groups at Institut Curie, we are working with a wide panel of models: breast cancer cell lines, patient-derived animal xenografts (PDX), tumor samples and mouse model of breast cancer.

The specificity of our team relies on how it works at the interface between translational and basic science. We have been selected as one of the four labelled SiRIC groups (Site de Recherche Intégrée contre le Cancer) of the Institut Curie precisely because we ask fundamental biological questions with direct clinical perspectives. We want to understand how and when long-range epigenetic alterations occur in breast cancer, and whether they are stably maintained in tumor progression, to elucidate whether they can be considered as reliable therapeutic targets. Moreover, we have a deep interest in performing drug screening to identify FDA-approved compounds that could have effect on the tumor epigenome.

Another key aspect in the group is to have in-house extensive expertise in both data mining and biology. We are developing intensive bioinformatics and statistics analyses to achieve proper understanding and modeling of our working models.

**The team is a SiRIC group (Site de Recherche Intégrée sur le Cancer) and is supported by the ATIP-Avenir program. We are looking for M2 students trained in biology and/or bioinformatics & statistics.**

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*Céline Vallot- épigénétique reportage*
Key publications

Year of publication 2016

Céline Vallot, Catherine Patrat, Amanda J Collier, Christophe Huret, Miguel Casanova, Tharvesh M Liyakat Ali, Matteo Tosolini, Nelly Frydman, Edith Heard, Peter J Rugg-Gunn, Claire Rougeulle (2016 Dec 20)

XACT Noncoding RNA Competes with XIST in the Control of X Chromosome Activity during Human Early Development.
*Cell stem cell* : 102-111 : [DOI: 10.1016/j.stem.2016.10.014]

Year of publication 2015

Céline Vallot, Jean-François Ouimette, Mélanie Makhlouf, Olivier Féraud, Julien Pontis, Julien Côme, Cécile Martinat, Annelise Bennaceur-Griscelli, Marc Lalande, Claire Rougeulle (2015 Apr 30)

Erosion of X Chromosome Inactivation in Human Pluripotent Cells Initiates with XACT Coating and Depends on a Specific Heterochromatin Landscape.
*Cell stem cell* : 533-46 : [DOI: 10.1016/j.stem.2015.03.016]

Year of publication 2013

Céline Vallot, Christophe Huret, Yann Lesecque, Alissa Resch, Nofissa Oudrhiri, Annelise Bennaceur-Griscelli, Laurent Duret, Claire Rougeulle (2013 Jan 22)

XACT, a long noncoding transcript coating the active X chromosome in human pluripotent cells.
*Nature genetics* : 239-41 : [DOI: 10.1038/ng.2530]

Year of publication 2010

Céline Vallot, Nicolas Stransky, Isabelle Bernard-Pierrot, Aurélie Hérault, Jessica Zucman-Rossi, Elodie Chapeaublanc, Dimitri Vordes, Agnès Laplanche, Simone Benhamou, Thierry Lebret, Jennifer Southgate, Yves Allory, François Radvanyi (2010 Dec 20)

A novel epigenetic phenotype associated with the most aggressive pathway of bladder tumor progression.
*Journal of the National Cancer Institute* : 47-60 : [DOI: 10.1093/jnci/djq470]