Four decades of cancer molecular biology research have led to the identification of many molecular determinants of this pathology, and showed that they are organized in pathways which in turn are tightly interconnected in a complex network of interactions which covers essential cell processes (proliferation, death, differentiation, DNA repair, immune response...). The existence of crosstalks, feedbacks and compensatory mechanisms invalidates simplistic reasoning and requires mathematical modeling to decipher how cell integrates signals to give rise to particular phenotypes, and to exploit this knowledge for rationalizing clinical treatments.

Another very important aspect of today’s biological and clinical cancer research lies in the high-throughput characterisation of tumours and their micro-environment, at the genome, transcriptome, proteome and epigenome levels (using microarrays and next-generation sequencing (NGS)), as well as phenotypic level (using high-throughput imaging techniques). These large-scale technologies generate huge volumes of data, making cancer research a big data science.

The volumes, completeness and resolution of the data generated by these technologies makes it possible today to integrate them with our knowledge of the signalling circuitry of the cell to build personalized models of tumors which shed light on the functioning of the tumoral cell, how its fate is determined, and how to counteract deleterious phenotypes and propose personalized treatment, the so-called precision medicine approach. These goals have led us to propose new concepts and strategies falling within the field of computational systems biology of cancer.
The first step in the exploitation of high throughput molecular data consists in the extraction of a biological signal from measurements with a low experimental signal/noise ratio and conducted in parallel on thousands or millions of variables (genes, positions on the genome, etc.). This assumes that experimental artefacts be erased (data normalisation) and error rate controlled. We develop tools that achieve this goal in particular for NGS, taking into account the specificities of cancer when needed. Then the biological data must be converted into biological knowledge and e.g. any biological pathways involved in the disease identified. For this purpose, we also develop complexity reduction methods enabling the analysis of multi-dimensional data.

Understanding tumorigenesis and improving clinical strategies requires the detailed knowledge of the molecular interaction networks that control mechanisms of cell proliferation, death and differentiation. We are constructing an atlas of cell signaling of cancer, so far containing detailed map for cell cycle, DNA repair, EMT, programmed cell death and survival, and immune response. We also develop computational tools for the analysis of networks, for example for integrating mutational and expression profiles of tumors, or for finding optimal intervention points for a particular tumor in a therapeutic perspective.

We then study the tumoral systems in a dynamic manner, building mathematical models of their molecular networks and proposing prediction of the effect of perturbations like mutations or drug compound. Through this approach, we are able to demonstrate essential system properties (typically global phenotype). Recent applications include finding new therapeutic target candidates in triple negative breast cancer, identifying synthetic interactions in DNA repair machinery, deciphering the modes of action of microRNAs, predicting cell fate decision to die or survive upon cell death receptor engagement, understanding the mechanisms of tumor invasion, or proposing strategies for building relevant mouse models of metastasis.
Our mathematical models are then challenged with experimental data and iterative loops between modelling and experimentation allows model improvement and validation. In term of methodology, we use and develop innovative approaches based on literature analysis, complexity reduction, logical modelling, differential equation systems, robustness study, and multidimensional statistical analysis. We have developed a strong expertise in the abovementioned techniques, and put it in practice in many collaborative projects with biologists and clinicians, with a main focus on solid tumors (breast, bladder, uveal melanoma, colon, pediatric tumors...).

**Key publications**

**Year of publication 2018**


**Aberrant ERBB4-SRC Signaling as a Hallmark of Group 4 Medulloblastoma Revealed by Integrative Phosphoproteomic Profiling**


**Year of publication 2017**

Manuela Portoso, Roberta Ragazzini, Živa Brenčič, Arianna Moiani, Audrey Michaud, Ivaylo Vassilev, Michel Wassef, Nicolas Servant, Bruno Sargueil, Raphaël Margueron (2017 Feb 8)

**PRC2 is dispensable for HOTAIR-mediated transcriptional repression.**

*The EMBO journal* : [DOI : e201695335]


**Xist-dependent imprinted X inactivation and the early developmental consequences of its failure.**

*Nature structural & molecular biology* : [DOI : 10.1038/nsmb.3365]
Daniela Chmiest, Nanaocha Sharma, Natacha Zanin, Christine Viaris de Lesegno, Massiullah Shafaq-Zadah, Vonick Sibut, Florent Dingli, Philippe Hupé, Stephan Wilmes, Jacob Piehler, Damarys Loew, Ludger Johannes, Gideon Schreiber, Christophe Lamaze (2016 Dec 6) **Spatiotemporal control of interferon-induced JAK/STAT signalling and gene transcription by the retromer complex.** *Nature communications* : 13476 : DOI : 10.1038/ncomms13476
