The INSERM/Institut Curie U830 conducts both basic and applied research in the field of cancer biology. Located on the Paris site of Institut Curie, it strongly benefits from the outstanding scientific environment of the Institut Curie research center and from the proximity of the cancer hospital. Indeed, most groups of the unit are closely connected to clinicians of the hospital and use patient specimens for their research activities.

Schematically there exist three main unifying themes of the unit:

- **Cancer genetics.**

  Multiple groups in the unit have contributed the characterization of inherited and somatic DNA variants to identify new predisposition syndromes, discover new tumor entities and investigate tumor evolution. The knowledge of these genetic abnormalities has also enabled development of genetically engineered animal models of neuroblastoma and malignant rhabdoid tumors. Current projects add new layers of information related to cancer susceptibility through genome wide association studies (GWAS) in Ewing sarcoma and uveal melanoma, to epigenetic characterization and investigations of protein-DNA interactions and to tumor heterogeneity taking advantage of single cell technologies. A particular interest has recently emerged on the targeting of unconventional neoantigens, as direct consequences of the tumor-specific genetic lesions in transcription, chromatin, and splicing factors, to design new immunotherapy approaches in collaboration with immunologists of the U932 unit. Finally, the unit remains very active in the clinical applications of its findings by developing new chemotherapeutics and tumor or circulating biomarkers.

- **Genetic instability and replicative stress.**
For the last decade, our unit has been deeply involved in characterizing the genetic abnormalities associated with BRCA1/2 mutations and the associated defect in homologous recombination (HR)-mediated DNA repair in breast and ovarian tumors. More recently, the role of these proteins in the response to replicative stress has become evident. We are directly addressing this issue with a focus on the study of the new alternative end joining repair pathway, including its interaction with the Fanconi Anemia (FA)/BRCA pathway and its role in limiting genetic instability and replicative stress and as such in promoting tumor survival. Identifying new targetable vulnerabilities in HR-deficient tumors represents a major axis of our unit.

- **Heterogeneity and plasticity of tumor cells and the microenvironment (TME).**

The final research theme in the unit concerns interactions between tumors and the microenvironment and how they impact resistance to treatment. We perform single cell characterization of clinical samples as well as leverage pre-clinical systems to dissect the molecular mechanisms behind these interactions including mouse models and tumor-on-chip technologies. Cancer types under investigation include diverse solid tumors in both adults (including breast, ovarian, and lung) and children (primarily neuroblastoma, sarcoma and rhabdoid tumor) and characterize both the immune and stromal compartments of the microenvironment. These studies are performed in close collaboration with both immunologists and clinicians of the institute. Particular expertise includes the role of cancer associated fibroblasts (CAFs) and their contributions to both immunosuppression and metastasis, heterogeneity and plasticity of tumors cells in terms of metabolism and signaling pathways, and T cell recruitment, differentiation, and dysfunction.

**Key publications**

Year of publication 2021


* **A first-in-class Polymerase Theta Inhibitor selectively targets Homologous Recombination-Deficient Tumors.**
  *Nature Cancer*: 598-610 : [DOI: 10.1038/s43018-021-00203-xs](https://doi.org/10.1038/s43018-021-00203-xs)

Olivier Saulnier, Katia Guedri-Idjouadiene, Marie-Ming Aynaud, Alina Chakraborty, Jonathan Bruyr, Joséphine Pineau, Tina O’Grady, Olivier Mirabeau, Sandrine Grossetête, Bartimée Galvan,
ERG transcription factors have a splicing regulatory function involving RBFOX2 that is altered in the EWS-FLI1 oncogenic fusion.  
*Nucleic acids research*: DOI: [10.1093/nar/gkab305](https://doi.org/10.1093/nar/gkab305)

STAG2 mutations alter CTCF-anchored loop extrusion, reduce cis-regulatory interactions and EWSR1-FLI1 activity in Ewing sarcoma.  

Genetic alterations of SUGP1 mimic mutant-SF3B1 splice pattern in lung adenocarcinoma and other cancers.  
*Oncogene*: 85-96: DOI: [10.1038/s41388-020-01507-5](https://doi.org/10.1038/s41388-020-01507-5)

Trajectory and Uniqueness of Mutational Signatures in Yeast Mutators  
*Proceedings of the National Academy of Sciences*: 117 n° 40: 24947-24956: DOI: [10.1073/pnas.2011332117](https://doi.org/10.1073/pnas.2011332117)

A subset of activated fibroblasts is associated with distant relapse in early luminal breast cancer  