The general objectives of the research team are:

- to further characterize biomarkers in solid tumors, particularly neuroblastoma and malignant rhabdoid tumours, by detailed characterization of genetic and epigenetic alterations, and their development in tumor evolution
- to further study the underlying mechanisms leading to the observed alterations
- to use the identification of biomarkers as a marker of disease monitoring during treatment and follow-up
- to develop new therapeutic approaches based on the characterization of biomarkers, within the framework of structured clinical or clinico-biological trials, following establishment of *in vivo* models
Current Research projects:

1. **Models of clonal evolution in neuroblastoma:**
   identification of the emergence of ALK mutations and identification of the MAPK/RAS pathway in neuroblastoma progression.

At the time of relapse, neuroblastoma very often present a higher clinical aggressivity. Genetic studies of tumour samples obtained at diagnosis and relapse indicate that at the time of relapse, new genetic alterations can be observed. We have recently established that ALK mutations, thought to play a major role in neuroblastoma oncogenesis, can emerge at the time of relapse. In some instances, an ALK-mutated subclone at diagnosis can evolve into a major clone at relapse. Indeed, at diagnosis, ALK mutations can be observed at a subclonal level in as many cases as at a clonal level. Whole genome sequencing studies have furthermore identified the RAS/MAP pathway as a major player in neuroblastoma progression, within a large collaborative study. Further studies based on circulating tumor DNA within a clinical protocol NGSkids, recruiting patients since Oct 2014, will enable further insights into the molecular mechanisms of tumor progression and help to move towards new therapeutic strategies. Furthermore, the study of tumor spatial
and temporal heterogeneity in tumor samples and the study of patient derived xenografts will further contribute to the understanding of molecular events involved in tumor progression.

2. **Mouse Smarcb1-deficient models recapitulate subtypes of human rhabdoid tumors.**

Rhabdoid tumours are highly aggressive tumours of infancy and, despite intensive treatment, the outcome remains very poor. We have now established the first faithful mice model of cerebral rhabdoid tumours. This model has pointed out the unexpected diversity of rhabdoid tumours, in mice as in humans. This model also enables future experimental therapeutics in normal physiological conditions. High throughput screenings of drugs and molecules inhibiting genes are currently performed to orientate future therapeutics in human.

**Key publications**

**Year of publication 2019**


**Study of chromatin remodeling genes implicates SMARCA4 as a putative player in oncogenesis in neuroblastoma.**


**Year of publication 2017**

Mathieu Chicard, Leo Colmet-Daage, Nathalie Clement, Adrien Danzon, Mylène Bohec, Virginie Bernard, Sylvain Baulande, Angela Bellini, Paul Deveau, Gaëlle Pierron, Eve Lapouble, Isabelle Janoueix-Lerosey, Michel Peuchmaur, Nadège Corradini, Anne Sophie Defachelles, Dominique Valteau-Couanet, Jean Michon, Valérie Combaret, Olivier Delattre, Gudrun Schleiermacher (2017
Whole-Exome Sequencing of Cell-Free DNA Reveals Temporo-spatial Heterogeneity and Identifies Treatment-Resistant Clones in Neuroblastoma.

Clinical cancer research: 939-949 : DOI : 10.1158/1078-0432.CCR-17-1586

High-Throughput Drug Screening Identifies Pazopanib and Clofilium Tosylate as Promising Treatments for Malignant Rhabdoid Tumors.

Cell reports : 1737-1745 : DOI : 10.1016/j.celrep.2017.11.049

The occurrence of intracranial rhabdoid tumours in mice depends on temporal control of Smarcb1 inactivation.

Nature communications : 10421 : DOI : 10.1038/ncomms10421