Childhood cancers represent the second cause of death in children in developed countries. Most of these tumours develop from embryonal tissues and constitute, at the difference of adult tumours, accidents of development rather than of tissue renewal or aging. Other differences with adult cancers include the limited exposure of children to environmental mutagenic factors and the likely limited role of genetic instability. The link between oncogenesis and embryogenesis is highlighted by the frequent association of paediatric cancers with developmental abnormalities.

**Our objectives are to define the molecular lesions that characterize paediatric tumours.**

These molecular lesions constitute the starting point to achieve a better understanding of the specific processes that underlie paediatric tumour development as well as to elaborate new tools for diagnosis and prognosis and to propose new therapeutic options. In this process the construction of biochemical, cellular and animal models constitute critical steps. We are currently mainly working on three specific tumour types: Ewing’s sarcoma, malignant rhabdoid tumors and neuroblastoma.

Ewing’s sarcoma is characterized in almost all cases by gene fusion between EWS that encodes an RNA binding protein of unknown function and members of the ETS family of transcription factor. Our main focus now is to decipher EWS-FLI1 downstream pathways and in particular to identify genes that are direct targets of EWS-FLI1 and that may account for the oncogenic properties of this chimeric protein. In malignant rhabdoid tumor, which is one of the most aggressive paediatric cancers, we identified the allelic inactivation of SMARCB1 as being critical to the tumoral development. SMARCB1 encodes a member of the chromatin SWI/SNF remodeling complex and the loss of function of SMARCB1 is thought to impair the initiation of various differentiation
Figure 1: Knockdown of EWS-FLI1 expression allows Ewing cells to recover the phenotype of their mesenchymal cell progenitor.

programs. Importantly, alteration of subunits of the SWI/SNF complex is a frequent event in human cancers as shown by recent results from NGS studies. Neuroblastoma is a tumor derived from the sympathetic neural crest cells. It can occur in the context of PHOX2B or ALK mutation. Its aggressiveness can range from spontaneously regressing tumors to highly invasive and treatment resistant tumors. It is highly dependent upon the type of genetic alteration that characterizes tumor cells, being very low in case of numerical chromosome alterations only and high when segmental chromosome abnormalities are present. The recent finding that ALK can be mutated in both familial and sporadic cases opens new avenues to the understanding of neuroblastoma development.

Our project aims at:

• elucidating the nature of the progenitor cells which give rise to these cancers and the relationships between the normal and cancer stem cells with respect to the mechanisms of self-renewal and differentiation,

• understanding the individual susceptibility to develop these cancers. In neuroblastoma and rhadoid tumors strong predisposition is linked to the presence of germline ALK or SMARCB1 mutations, respectively.

No such strong predisposition has been observed in Ewing sarcoma. Yet, this tumor is mostly observed in populations of European descent and much rarer in populations of African or Asian descents suggesting that the occurrence of this tumor is at least partly determined by genetic susceptibility factors. Indeed, three loci were recently linked to the development of Ewing sarcoma. Further investigation of these loci is in progress and should enable to decipher the mechanisms underlying the genetic susceptibility; iii) developing relevant animal models of
these cancers. Genetically modified mouse models that recapitulate the human disease have been generated for neuroblastoma and rhabdoid tumors; iv) understanding the mechanisms of tumor progression through the analysis of clonal evolution of tumors taking advantage of next generation sequencing approaches; v) identifying some key fragilities of these cancers that could be at the basis of new therapeutic approaches.

**Key publications**

**Year of publication 2020**


*Transcriptional Programs Define Intratumoral Heterogeneity of Ewing Sarcoma at Single-Cell Resolution.*

*Cell reports*: 1767-1779.e6 : [DOI: 10.1016/j.celrep.2020.01.049]

**Year of publication 2019**

Simon Durand, Cécile Pierre-Eugène, Olivier Mirabeau, Caroline Louis-Brennetot, Valérie Combaret, Léo Colmet-Daage, Orphée Blanchard, Angela Bellini, Estelle Daudigeos-Dubus, Virginie Raynal, Gudrun Schleiermacher, Sylvain Baulande, Olivier Delattre, Isabelle Janoueix-Lerosey (2019 Aug 28)

*ALK mutation dynamics and clonal evolution in a neuroblastoma model exhibiting two ALK mutations.*

*Oncotarget*: 4937-4950 : [DOI: 10.18632/oncotarget.27119]

**Year of publication 2018**

Margaret A Tucker, Franck Tirode, Stephen J Chanock, Olivier Delattre (2018 Aug 11)

**Genome-wide association study identifies multiple new loci associated with Ewing sarcoma susceptibility.**

*Nature communications* : 3184 : [DOI : 10.1038/s41467-018-05537-2](https://doi.org/10.1038/s41467-018-05537-2)


**Transcriptomic definition of molecular subgroups of small round cell sarcomas**


**Activated ALK signals through the ERK-ETV5-RET pathway to drive neuroblastoma oncogenesis**

*Oncogene* : 37 : 1417, 1429 : [DOI : doi.org/10.1038/s41388-017-0039-5](https://doi.org/10.1038/s41388-017-0039-5)

Year of publication 2017

Céline Chauvin, Amaury Leruste, Arnault Tauziede-Espariat, Mamy Andrianteranagna, Didier Surdez, Aurianne Lescure, Zhi-Yan Han, Elodie Anthony, Wilfrid Richer, Sylvain Baulande, Mylène Bohec, Sakina Zaidi, Marie-Ming Aynaud, Laetitia Maillot, Julien Masliah-Planchnon, Stefano Cairo, Sergio Roman-Roman, Olivier Delattre, Elaine Del Nery, Franck Bourdeaut (2017 Nov 16)

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

*Cell reports* : 1737-1745 : [DOI : S2211-1247(17)31539-5](https://doi.org/S2211-1247(17)31539-5)