Gudrun Schleiermacher
Chef d'équipe
gudrun.schleiermacher@curie.fr
Tel: +33 1 44 32 45 50

Franck Bourdeaut
Chef d'équipe
franck.bourdeaut@curie.fr
Tel: +33 1 44 32 45 50

The general objectives of the research team are:

- to further characterize biomarkers in solid tumors, particularly neuroblastoma and malignant rhabdoid tumours, by detailed characterizion 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

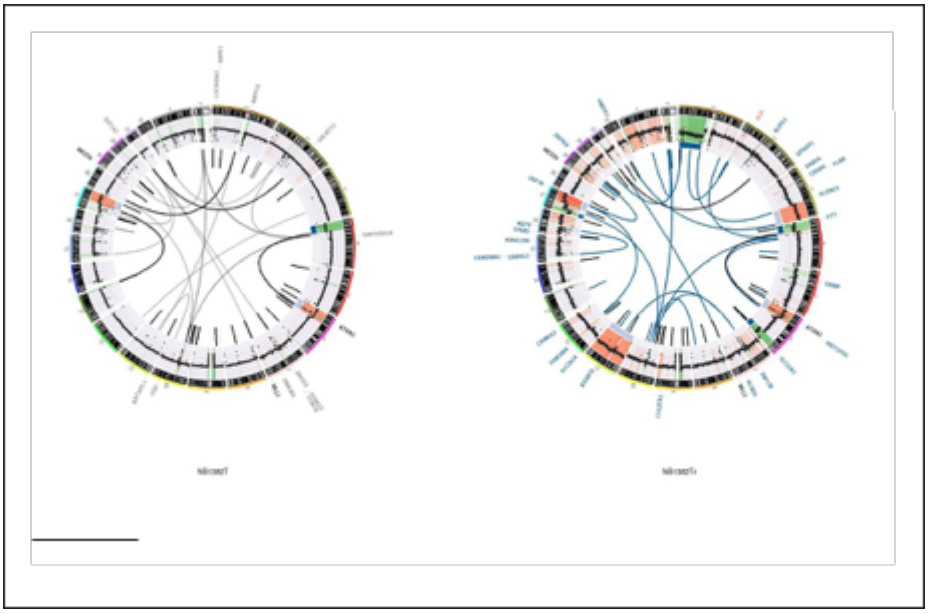

Figure 1: Circos plots of whole genome sequencing of a neuroblastoma studied at diagnosis and at relapse.

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 2018

Forget Antoine, Martignetti Loredana, Puget Stéphanie, Calzone Laurence, Brabetz Sebastian, Picard Daniel, Montagud Arnau, Liva Stéphane, Sta Alexandre, Dingli Florent, Arras Guillaume, Rivera Jaime, Loew Damarys, Besnard Aurore, Lacombe Joëlle, Pagès Mélanie, Varlet Pascale, Dufour Christelle, Yu Hua, L. Mercier Audrey, Indersie Emilie, Chivet Anaïs, Leboucher Sophie, Sieber Laura, Beccaria Kevin, Gombert Michael, D. Meyer Frauke, Qin Nan, Bartl Jasmin, Chavez Lukas, Okonechnikov Konstantin, Sharma Tanvi, Thatikonda Venu, Bourdeaut Franck, Pouponnot Celio, Ramaswamy Vijay, Korshunov Andrey, Borkhardt Arndt, Reifenberger Guido, Poullet Patrick, D. Taylor Michael, Kool Marcel, M. Pfister Stefan, Kawauchi Daisuke, Barillot Emmanuel, Remke Marc, Ayrault Olivier (2018 Sep 10)
Aberrant ERBB4-SRC Signaling as a Hallmark of Group 4 Medulloblastoma Revealed by Integrative Phosphoproteomic Profiling
Cancer Cell : 34 : 379-395 : DOI : 10.1016/j.ccell.2018.08.002

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 Dec 2)
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

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-Planchon, 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

Year of publication 2016

Zhi-Yan Han, Wilfrid Richer, Paul Fréneaux, Céline Chauvin, Carlo Lucchesi, Delphine Guillemot, Camille Grison, Delphine Lequin, Gaelle Pierron, Julien Masliah-Planchon, André Nicolas, Dominique Ranchère-Vince, Pascale Varlet, Stéphanie Puget, Isabelle Janoueix-Lerosey, Olivier Ayrault, Didier Surdez, Olivier Delattre, Franck Bourdeaut (2016 Jan 29)
The occurrence of intracranial rhabdoid tumours in mice depends on temporal control of Smarcb1 inactivation.
Nature communications : 10421 : DOI : 10.1038/ncomms10421