Our team has a long-lasting expertise in the signaling field in cancer by working for several decades on two oncogenic families: the RAF Ser/Thr kinases (Peyssonnaux and Eychene, Biol Cell 2001) and the MAF transcription factors (Eychene et al., Nat Rev Cancer 2008). We have made major contributions by identifying and cloning a member of each of these two families (Benkhelifa et al., Oncogene 1998; Marx et al., EMBO 1988). We also deciphered their mechanisms of regulation including those by phosphorylation (Benkhelifa et al., Mol Cell Biol 2001; Hmitou et al., Mol Cell Biol 2007; Rocques et al., Mol Cell 2007; Herath et al., Blood Cancer J 2014).

Our studies have progressively led us to focus our interest on two types of cancers in which these families play a key role: MEDULLOBLASTOMA and MELANOMA.

Our current projects focus on deregulated signaling pathways and transcription factors involved in the initiation and progression of these two pathologies and their mechanisms of resistance to treatments.

Medulloblastoma (MB) is the most common malignant brain tumor of childhood arising in the
cerebellum. Although multimodal treatments have significantly increased the survival rate, 20-30% of patients remain incurable. Most of them belong to a poorly characterized MB subgroup, called group 3 (G3), which displays unexpected expression of a retina photoreceptor-specific differentiation program. This defines an aberrant retinal identity to this tumor unrelated to the cerebellum where it originates. We demonstrated that NRL, a MAF family member, established this aberrant identity and, importantly, is required for tumor maintenance by promoting proliferation and protecting medulloblastoma cells from apoptosis ([Garancher et al., Cancer Cell 2018](#)). This work extends the concept of lineage addiction in cancer by showing that an aberrant identity characterized by a lineage unrelated to the tissue of origin could represent a dependency.

We also showed that pharmacological agents targeting anti-apoptotic proteins display interesting therapeutic potential for group 3 MB.

We are currently working on deregulated signaling pathways and transcription factors in the poorly characterized G3 MB as well as on the mechanisms of resistance to radiotherapy.

**Melanoma**, one of the deadliest skin cancers, is mainly driven by deregulation of the RAS/RAF/MEK/ERK pathway due in about 50% of cases to mutations in the BRAF gene and in 15% in NRAS.

We have developed different genetic mouse models to evaluate the specific contributions of the different RAF kinases during normal and pathological melanocytic lineage development. We demonstrated that RAF/MAPK signaling is dispensable for early melanocyte lineage development but required for melanocyte stem cell self-maintenance ([Valluet et al., Cell reports 2012](#)), thereby providing the first in vivo demonstration that RAF proteins can be involved in stemness.
We also used these knockouts to investigate the role of both RAF kinases in NRAS<sup>Q61K</sup>-induced melanoma at each step of tumor progression, from initiation (benign nevi formation) to invasive melanoma (Dorard et al., Nat Commun. 2017). We showed that BRAF has a critical role in initiation of NRAS-driven melanoma that cannot be compensated by CRAF. In contrast, RAF proteins display compensatory functions in full-blown tumors and ARAF can sustain proliferation in the absence of BRAF and CRAF, highlighting an addiction to RAF signaling in NRAS-driven melanoma (Druillennec et al., Mol Cell Oncol. 2017).

Numerous nevi are observed upon activation of NRAS in the mouse melanocytic lineage. The presence of BRAF (BRAF KO) is required for their formation while that of the CRAF is not necessary (CRAF KO).

We are currently investigating the molecular mechanisms underlying the contribution of the three RAF kinases in melanoma progression and resistance to treatments.
Key publications

Year of publication 2019


An autocrine ActivinB mechanism drives TGFb/Activin signaling in Group3medulloblastoma

EMBO Molecular Medicine : 11 : e9830 : DOI : 10.15252/emmm.201809830

Year of publication 2018

Alexandra Garancher, Charles Y Lin, Morgane Morabito, Wilfrid Richer, Nathalie Rocques, Magalie Larcher, Laure Bihannic, Kyle Smith, Catherine Miquel, Sophie Leboucher, Nirmitha I Herath, Fanny Dupuy, Pascale Varlet, Christine Haberler, Christine Walczak, Nadine El Tayara, Andreas Volk, Stéphanie Puget, François Doz, Olivier Delattre, Sabine Druillennec, Olivier Ayrault, Robert J Wechsler-Reya, Alain Eychène, Franck Bourdeaut, Paul A Northcott, Celio Pouponnot (2018 Mar 14)

NRL and CRX Define Photoreceptor Identity and Reveal Subgroup-Specific Dependencies in Medulloblastoma.


Year of publication 2017

Coralie Dorard, Charlène Estrada, Céline Barbotin, Magalie Larcher, Alexandra Garancher, Jessy Leloup, Friedrich Beermann, Manuela Baccarini, Celio Pouponnot, Lionel Larue, Alain Eychène, Sabine Druillennec (2017 May 13)

RAF proteins exert both specific and compensatory functions during tumour progression of NRAS-driven melanoma.

Nature communications : 15262 : DOI : 10.1038/ncomms15262

Year of publication 2014

Catherine Dehainault, Alexandra Garancher, Laurent Castéra, Nathalie Cassoux, Isabelle Aerts, François Doz, Laurence Desjardins, Livia Lumbroso, Rocío Montes de Oca, Geneviève Almouzni, Dominique Stoppa-Lyonnet, Celio Pouponnot, Marion Gauthier-Villars, Claude Houdayer (2014 May 23)
The survival gene MED4 explains low penetrance retinoblastoma in patients with large RB1 deletion.  
*Human molecular genetics*: 5243-50 : DOI: 10.1093/hmg/ddu245  

N I Herath, N Rocques, A Garancher, A Eychène, C Pouponnot (2014 Jan 21)  
**GSK3-mediated MAF phosphorylation in multiple myeloma as a potential therapeutic target.**  
*Blood cancer journal*: e175 : DOI: 10.1038/bcj.2013.67  

Year of publication 2012  

Agathe Valluet, Sabine Druillennec, Céline Barbotin, Coralie Dorard, Anne H Monsoro-Burq, Magalie Larcher, Celio Pouponnot, Manuela Baccarini, Lionel Larue, Alain Eychène (2012 Oct 2)  
**B-Raf and C-Raf are required for melanocyte stem cell self-maintenance.**  
*Cell reports*: 774-80 : DOI: 10.1016/j.celrep.2012.08.020