Skin cancers and especially melanomas are constantly increasing in western countries with their incidence doubling every 12 years. Epidemiological reasons are quite clear: sun, pollution, ethnical migration and lifestyle.

However, the molecular mechanisms associated with this transformation are not yet fully elucidated, even though proteins belonging to the MAP-kinase, PI3K and β-catenin pathways were clearly shown to be involved. In order to better understand melanomagenesis, cellular heterogeneity and plasticity, and melanoma resistance we investigate the establishment and the renewal of the melanocyte lineage, as well as melanomagenesis.

Schematic representation of melanoma initiation and progression as a multistep process. Melanomagenesis involves various cellular mechanisms which are associated with oncogene expression / activation (in red NRAS, BRAF or/and β-catenin) or inactivation / downregulation of tumor suppressor (in blue, NF1, p16, PTEN or/and CDH1) proteins. RGP, radial growth phase; VGP, vertical growth phase; (see Conde-Perez and Larue, 2014)

It is becoming very clear that the MAP-kinase pathway induces melanocyte proliferation and senescence. Similarly, the lack of PTEN or p16, or the activation of β-catenin allows the bypass of senescence. However, the vast majority of the cells which are mutated for two of these types of proteins are not able to initiate a melanoma. This indicates that melanoma initiation is still not fully understood. Melanoma
initiation is followed by progression (involving most probably CDH1) and associated molecular heterogeneity (involving most probably MITF and BRN2).

In order to understand/improve prevention, early diagnosis, cellular transformation and therapy, we believe that it is crucial to know better the molecular and cellular mechanisms occurring during the normal and pathological development of this lineage and during melanoma initiation/progression in a cell autonomous and cell non-autonomous manner. Human genetics information associated with the production/study of murine melanoma models will allow for a better understanding of the molecular and cellular events occurring during oncogenesis.

In this respect, our general goal is to better understand the cellular and molecular mechanisms associated with the normal and pathological development of melanocytes. This general goal has five main aims:

1. **To better understand the b-catenin signaling during the establishment and renewal of the melanocyte lineage.**
2. **To better understand the cooperation between UV and Wnt/b-catenin signaling.**
3. **To induce cooperation of signaling pathways during melanomagenesis.**
4. **To evaluate the respective importance of MITF and BRN2 during melanoma initiation and progression.**
5. **To produce relevant melanoma models for humans.**

**Key publications**

Year of publication 2015

F Rambow, A Bechadergue, F Luciani, G Gros, M Domingues, J Bonaventure, G Meurice, J-C
Normal and Pathological Development of Melanocytes
UMR 3347/U1021 - Normal & Pathological Signaling: from the embryo to the innovative therapy of cancers

Marine, L Larue (2015 Dec 16)
Regulation of melanoma progression through the TCF4/miR-125b/NEDD9 cascade.
The Journal of investigative dermatology : DOI : 10.1016/j.jid.2016.02.803

New Functional Signatures for Understanding Melanoma Biology from Tumor Cell Lineage-Specific Analysis.
Cell reports : 840-53 : DOI : 10.1016/j.celrep.2015.09.037

A caveolin-dependent and PI3K/AKT-independent role of PTEN in β-catenin transcriptional activity.
Nature communications : 6 : 8093 : DOI : 10.1038/ncomms9093

Year of publication 2013

Beta-catenin inhibits melanocyte migration but induces melanoma metastasis.
Oncogene : 2230-8 : DOI : 10.1038/onc.2012.229

Year of publication 2012

Phosphorylation of BRN2 modulates its interaction with the Pax3 promoter to control melanocyte migration and proliferation.

Year of publication 2011

Salvatore Cortellino, Jinfei Xu, Mara Sannai, Robert Moore, Elena Caretti, Antonio Cigliano, Madeleine Le Coz, Karthik Devarajan, Andy Wessels, Dianne Soprano, Lara K Abramowitz, Marisa S Bartolomei, Florian Rambow, Maria Rosaria Bassi, Tiziana Bruno, Maurizio Fanciulli, Catherine Renner, Andres J Klein-Szanto, Yoshihiro Matsumoto, Dominique Kobi, Irwin Davidson, Christophe...
Alberti, Lionel Larue, Alfonso Bellacosa (2011 Feb 18)

**Thymine DNA glycosylase is essential for active DNA demethylation by linked deamination-base excision repair.**