2016-11

IC-**3i** International PhD Program

PhD thesis project

2017 Call for application

Involvement of Splice Factor Mutations in Oncogenesis

General information

Call	2017
Reference	2016-11-ALSAFADI&ROMAN-ROMAN
Keyword(s)	Splicing mutations, SF3B1, Uveal Melanoma, Therapeutic inhibitors

Director(s) and team

Thesis director(s)	Samar Alsafadi & Sergio Roman-Roman
Research team	Team Alsafadi; Uveal Melanoma Translational Group
Research department	Translational Research

Description of the PhD thesis project

Splice factor mutations are recurrently found in many cancers including hematological malignancies and uveal melanoma. SF3B1, SRSF2, ZRSR2 and U2AF35 are the most frequent spliceosome genes with mutually exclusive mutations in malignancies. Interestingly, each of these mutations is associated with a distinct splice pattern.

In order to determine the impact of recurrent splice factor mutations in oncogenesis, we hypothesize that oncogenic impact of these mutations is mediated by a set of genes shared by the different splice patterns.

We will explore the common transcripts or pathways affected by splice aberrations of the different splice factor mutations. We will investigate whether the splice aberration of the common genes impacts the total mRNA, and its consequences at protein level. Several splice inhibitors are under development for preclinical assessment. We will evaluate whether such inhibitors can restore the regular splice pattern arguing the clinical benefit of these splice modulators in tumors with splice factor mutations.

International, interdisciplinary & intersectoral aspects of the project

Our translational group benefits from close interactions with Novartis Institutes for BioMedical Research (Cambridge, USA) and is a part of the European consortium H2020 UM Cure. We also benefit from collaboration with ABIVAX, a pioneering biotech company that developed a generation of a chemical library of more than 1,000 small molecules targeting RNA splicing. In the framework of this collaboration, we interact with J. Tazi as mentor and consulting expert for evaluating the translational and industrial opportunities. Our group, composed of clinical research fellows and biologists, conducts a highly interdisciplinary research focusing on basic and translational research to develop novel therapeutic strategies for uveal melanoma.

Recent publications

1. **Alsafadi S**, Houy A, Battistella A, Popova T, Wassef M, Henry E, Tirode F, Constantinou A, Piperno-Neumann S, **Roman-Roman S**, Dutertre M, Stern MH.
Cancer-associated SF3B1 mutations affect alternative splicing by promoting alternative branchpoint usage.
Nat Commun. 2016 Feb 4;7:10615. doi: 10.1038/ncomms10615.

2. Carita G, Frisch-Dit-Leitz E, Dahmani A, Raymondie C, Cassoux N, Piperno-Neumann S, Némati F, Laurent C, De Koning L, Halilovic E, Jeay S, Wylie A, Emery C, **Roman-Roman S**, Schoumacher M, Decaudin. D.
Oncotarget. 2016 Jun 7;7(23):33542-56. doi: 10.18632/oncotarget.9552.

3. Amirouchene-Angelozzi N, Frisch-Dit-Leitz E, Carita G, Dahmani A, Raymondie C, Liot G, Gentien D, Némati F, Decaudin D, **Roman-Roman S**, Schoumacher M.
The mTOR inhibitor Everolimus synergizes with the PI3K inhibitor GDC0941 to enhance anti-tumor efficacy in uveal melanoma.
Oncotarget. 2016 Apr 26;7(17):23633-46. doi: 10.18632/oncotarget.8054

4. Amirouchene-Angelozzi N, Nemati F, Gentien D, Nicolas A, Dumont A, Carita G, Camonis J, Desjardins L, Cassoux N, Piperno-Neumann S, Mariani P, Sastre X, Decaudin D, **Roman-Roman S**.
Establishment of novel cell lines recapitulating the genetic landscape of uveal melanoma and preclinical validation of mTOR as a therapeutic target.
Mol Oncol. 2014 Dec;8(8):1508-20. doi: 10.1016/j.molonc.2014.06.004.

5. Quidville V*, **Alsafadi S***, Goubar A, Commo F, Scott V, Pioche-Durieu C, Girault I, Baconnais S, Le Cam E, Lazar V, Delaloge S, Saghatchian M, Pautier P, Morice P, Dessen P, Vagner S, André F. (* Joint first co-authors.)
Targeting the deregulated spliceosome core machinery in cancer cells triggers mTOR blockade and autophagy.
Cancer Res. 2013 Apr 1;73(7):2247-58. doi: 10.1158/0008-5472.CAN-12-2501

Expected profile of the candidate

We invite applications from highly motivated and outstanding students, mostly with a background in one of the following areas: cell biology, molecular biology, cancer biology and signaling pathways. Students with different background training, such as biochemistry, pharmaceutical sciences, medicine, as well as other life sciences are also welcome to apply. Applicants should have a strong desire to explore cell biological phenomena, and should show solid capacity for independent and creative thinking.