2016-09

IC-**3i** International PhD Program

# PhD thesis project

2017 Call for application

## From Genetic Predisposing Factors to Oncogenesis in Uveal Melanoma

## General information

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| **Call** | 2017 |
| **Reference** | 2016-09-STERN |
| **Keyword(s)** | Genetics, Oncogenesis, Uveal melanoma, Post-GWAS, gene regulation |

## Director(s) and team

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| **Thesis director(s)** | Marc-Henri Stern |
| **Research team** | Genomics & Biology of Hereditary Breast Cancers |
| **Research department** | U830 - Genetics & Biology of Cancers |

## Description of the PhD thesis project

Uveal melanoma (UM) is the most frequent ocular primary tumor in adults. If the disease metastasizes, generally to the liver, the prognosis is dismal. UM is very different from cutaneous melanoma. UM are genetically simple tumors with rare copy number alteration, mutually exclusive activating mutations of GNA11 or GNAQ genes, and mutually exclusive recurrent mutations targeting BAP1, SF3B1 and EIF1AX genes. Epidemiological studies have shown that UM affects mainly populations of European ancestry. However a role of pigmentation protecting against ultraviolet (UV) exposure was excluded by the absence of UV mutational signature in this disease. An alternative hypothesis is the prevalence of risk alleles in these populations of European ancestry. Thus, the team conducted a two-stage genome wide association study (GWAS) for UM in populations of European ancestry. Candidate susceptibility loci were identified, including the 5p region associated with the strongest odd ratio. Furthermore, 5p polymorphisms are associated with differential expression of genes in the vicinity.

This project aims to identify genetics factors predisposing to UM and characterize the biologic and oncologic pathways influenced by these factors. We propose to decipher the influence of these polymorphisms on 5p genes environment by studying chromatin marks, the binding of key transcription factors, and gene expression. We will then validate the causative role of the candidate variant on transcription factor binding and gene expression, by genome editing (CRISPR/cas9 method) in UM cell lines. We will subsequently analyse the influence of down and up regulation of the identified genes on malignant transformation, using cellular models of UM oncogenesis. In fine, the project will provide UM genetic susceptibility factors and their role in pathogenesis.

## International, interdisciplinary & intersectoral aspects of the project

International
The team is closely related to international experts (biologists and clinicians) in uveal melanoma and attend several committees, in addition to being leader of a work package in a H2020 European project (UM CURE).
The PhD student will be mentored by Dr Stephen Chanock (NCI-NIH, Bethesda, MD USA) who is a world expert in genetics of cancer.

Intersectoral
The team has a record in biomarker discoveries with two patents pending, and an exclusive licensing with a world leader in the field, Myriad Genetics.

Interdisciplinary
The specificity of our research team is to combine medical expertise, fundamental biology, genetics and mathematics/bioinformatics to achieve a comprehensive view on the scientific questions.

## Recent publications

1. Schoumacher M, Le Corre S, Houy A, Mulugeta E, **Stern MH**, Roman-Roman S, Margueron R. Uveal melanoma cells are resistant to EZH2 inhibition regardless of BAP1 status.
Nat Med. 2016 Jun 7;22(6):577-8. doi: 10.1038/nm.4098.

2. Popova T, Manié E, Boeva V, Battistella A, Goundiam O, Smith NK, Mueller CR, Raynal V, Mariani O, Sastre-Garau X, **Stern MH**.
Ovarian cancers harboring inactivating mutations in CDK12 display a distinct genomic instability pattern characterized by large tandem duplications.
Cancer Res. 2016 Apr 1;76(7):1882-91. doi: 10.1158/0008-5472.CAN-15-2128.

3. 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.

4. Furney SJ, Pedersen M, Gentien D, Dumont AG, Rapinat A, Desjardins L, Turajlic S, Piperno-Neumann S, de la Grange P, Roman-Roman S, **Stern MH***, Marais R*.
SF3B1 mutations are associated with alternative splicing in uveal melanoma.
Cancer Discov. 2013 Oct;3(10):1122-9. doi: 10.1158/2159-8290.CD-13-0330.

5. Popova T, Hebert L, Jacquemin V, Gad S, Caux-Moncoutier V, Dubois d'Enghien C, Richaudeau B, Renaudin X, Sellers J, Nicolas A, Sastre-Garau X, Desjardins L, Gyapay G, Raynal V, Sinilnikova OM, Andrieu N, Manié E, de Pauw A, Gesta P, Bonadona V, Maugard CM, Penet C, Avril MF, Barillot E, Cabaret O, Delattre O, Richard S, Caron O, Benfodda M, Hu HH, Soufir N, Bressac-de Paillerets B, Stoppa-Lyonnet D, **Stern MH**.
Germline BAP1 mutations predispose to renal cell carcinomas.
Am J Hum Genet. 2013 Jun 6;92(6):974-80. doi: 10.1016/j.ajhg.2013.04.012.

## Expected profile of the candidate

Applicants should have a strong scientific curiosity to explore the link between genetics and human oncogenesis, and should show solid capacity for independent and creative thinking. Background in cell biology, molecular biology and genetics is strongly recommended. Background in bioinformatics will be a plus. Good capacities to work in a team is required.