A Research Engineer/Post-doc Position is available **at Institut Curie**, Paris,
in the laboratory " **Génétique et Biologie des Cancers**", Inserm U830.

Context

The laboratory "Genetics and Biology of Pediatric Tumors" directed by Olivier Delattre at Institut Curie develop several research programs to understand the biology and oncogenic transformation mechanisms of various pediatric tumors and identify new therapeutic strategies that could improve patients outcome. Institut Curie provides an excellent scientific environment for high quality research with state-of-the-art equipments as well as a constellation of seminars covering many resarch areas. The successful applicant will join the neuroblastoma team on a translational research project funded by INCa/DGOS and led by Isabelle Janoueix-Lerosey in collaboration with a group at Gustave Roussy and one at CEA.

Research project

Neuroblastoma is an embryonal cancer of the sympathetic nervous system that accounts for 8-10% of pediatric cancers. It represents an uttermost biological challenge for scientists and remains a disease with highly unmet medical needs for clinicians. The identification of ALK activating mutations has placed neuroblastoma among other ALKoma entities that may benefit from tumor-targeted therapies with tyrosine kinase inhibitors (TKIs) or monoclonal antibodies. The efficacy of new immunomodulatory antibodies, also called "immune checkpoint antibodies", has been demonstrated in several aggressive adult cancers. Interestingly, it has been shown that various TKIs have not only cell-autonomous effects but also impacts on the immune microenvironment, providing a rationale for the use of TKIs in combination with immunomodulatory antibodies.

The whole project aims at exploring the link between ALK induced oncogenic stress and immune suppression within the neuroblastoma microenvironment, and then at evaluating the synergistic combination between therapies blocking these two hallmarks of cancer. The successful candidate will define the impact of ALK-driven oncogenic stress on the tumor immune microenvironment in our neuroblastoma mouse models. The candidate will also evaluate the therapeutic potential of a monoclonal ALK antagonist antibody alone or in combination with ALK TKIs *in vitro* and *in vivo* using various models. In addition, we plan to further characterize the microenvironment of the mouse tumours by the analysis of mesenchymal cells, Schwann cells and tumor vasculature. We expect to discover new insights into the biology of ALK-driven neuroblastoma, and provide the rationale for both tumor-targeted and immune-targeted therapies that may benefit to neuroblastoma patients.

Requirement

The candidate will have obtained a PhD in a relevant discipline (cellular and molecular biology, oncology, immunology, …) with knowledge in cancer biology and tumor microenvironment. Experience in cellular biology, FACS analysis and mouse work is desirable.

How to apply

The position (18 months) is available from october, 16th, 2017. Applicants should send their detailed CV, a cover letter and contact information of at least two academic references to janoueix@curie.fr

Selected publications of the team:

Boeva V, Louis-Brennetot C, Peltier A, Durand S, Pierre-Eugène C, Raynal V, Etchevers HC, Thomas S, Lermine A, Daudigeos-Dubus E, Geoerger B, Orth MF, Grünewald TGP, Diaz E, Ducos B, Surdez D, Carcaboso AM, Medvedeva I, Deller T, Combaret V, Lapouble E, Pierron G, Grossetête-Lalami S, Baulande S, Schleiermacher G, Barillot E, Rohrer H, Delattre O, Janoueix-Lerosey I. Heterogeneity of neuroblastoma cell identity defined by transcriptional circuitries. **Nat Genet**. (2017) 49:1408-1413.

Cazes A, Lopez-Delisle L, Tsarovina K, Pierre-Eugène C, De Preter K, Peuchmaur M, Nicolas A, Provost C, Louis-Brennetot C, Daveau R, Kumps C, Cascone I, Schleiermacher G, Prignon A, Speleman F, Rohrer H, Delattre O, Janoueix-Lerosey I. Activated Alk triggers prolonged neurogenesis and Ret upregulation providing a therapeutic target in ALK-mutated neuroblastoma. **Oncotarget** (2014) 5*:* 2688-2702.

Cazes A, Louis-Brennetot C, Mazot P, Dingli F, Lombard B, Boeva V, Daveau R, Cappo J, Combaret V, Schleiermacher G, Jouannet S, Ferrand S, Pierron G, Barillot E, Loew D, Vigny M, Delattre O, Janoueix-Lerosey I. Characterization of rearrangements involving the ALK gene reveals a novel truncated form associated with tumor aggressiveness in neuroblastoma. **Cancer Res**. (2013) 73:195-204.

Mazot P, Cazes A, Boutterin MC, Figueiredo A, Raynal V, Combaret V, Hallberg B, Palmer RH, Delattre O, Janoueix-Lerosey I, Vigny M. The constitutive activity of the ALK mutated at positions F1174 or R1275 impairs receptor trafficking. **Oncogene** (2011) 30:2017-25.

Schleiermacher G, Janoueix-Lerosey I, Ribeiro A, Klijanienko J, Couturier J, Pierron G, Mosseri V, Valent A, Auger N, Plantaz D, Rubie H, Valteau-Couanet D, Bourdeaut F, Combaret V, Bergeron C, Michon J, and Delattre O. Accumulation of segmental alterations determines progression in neuroblastoma. **J Clin Oncol.** (2010) 28:3122-30

Janoueix-Lerosey I, Schleiermacher G, Michels E, Mosseri V, Ribeiro A, Lequin D, Vermeulen J, Couturier J, Peuchmaur M, Valent A, Plantaz D, Rubie H, Valteau-Couanet D, Thomas C, Combaret V, Rousseau R, Eggert A, Michon J, Speleman F and Delattre O. The overall genomic pattern is a predictor of outcome in neuroblastoma. **J Clin Oncol.** (2009) 27:1026-33.

Janoueix-Lerosey I, Lequin D, Brugières L, Ribeiro A, de Pontual L, Combaret V, Raynal V, Puisieux A, Schleiermacher G, Pierron G, Valteau-Couanet D, Frebourg T, Michon J, Lyonnet S, Amiel J and Delattre O. Somatic and germline activating mutations of the ALK kinase receptor in neuroblastoma. **Nature**. (2008) 455:967-970.