2019-11-20

EuReCa International PhD Program

PhD thesis project

2020 Call for application

A synthetic platform for siRNA delivery

General information

Call	2020
Reference	2020-03-JOHANNES
Keyword(s)	Immunotherapy, therapeutic RNA delivery, endosomal escape, protein engineering, organic synthesis

Director(s) and team

Thesis director(s)	Ludger Johannes
Research team	Endocytic Trafficking & Intracellular Delivery
Research department	UMR3666/U1143 – Cellular and Chemical Biology

Description of the PhD thesis project

Cancer immunotherapy is a current focus in medical oncology. We have previously shown that the non-toxic and poorly immunogenic B-subunit of Shiga toxin (STxB) is an efficient natural vector for the delivery of cancer antigens to key regulatory cells of the immune system, the dendritic cells, leading to a therapeutic antitumor response.

The goal of the current program is to extend the scope of STxB as a dendritic cell targeting tool to the delivery of therapeutic siRNAs which are designed to block immunosuppressive mechanisms. For this, the major limiting step in siRNA delivery, i.e. endosomal escape to reach the cytosol, must be overcome. Of note, STxB has an intrinsic endosomal escape capability, and the current project aims at augmenting this characteristic to enable efficient siRNA delivery.

The PhD student will chemically modify STxB to achieve this goal, exploiting the fact that the host team within the Cellular and Chemical Biology unit at Institut Curie has recently established the full chemical synthesis and refolding of the STxB protein. Variants of STxB will be conjugated through click reactions to chosen chemical moieties. By working at the interface between organic chemistry and cell biology, we expect the PhD student to generate a patentable STxB delivery system that combines targeting specificity for dendritic cells with efficient translocation to the cytosol of siRNAs to interfere with the expression of immunosuppressive molecules. This should favor the development of a fully synthetic delivery platform technology with maximal crosspriming efficiency against cancer antigens.

The PhD student will profit from a striving international scientific environment at Institut Curie, with high end equipment in organic chemistry (500 MHz NMR, UPLC-MS…) and cell biology (55 light microscopy systems including lattice light sheet microscopy, electron microscopy…), regular seminars by world leading scientists, and cutting-edge training courses.

International, interdisciplinary & intersectoral aspects of the project

At the Institut Curie, the PhD student will be placed in an international environment with 385 students and 298 post-docs from 75 different countries. The PhD project furthermore involves international collaborations. It is expected to positively impact the ongoing efforts to develop the STxB technology for the clinical management of cancer by immunotherapy (6 patent families, 5 of which delivered in the US, Europe…).

The PhD student will be in direct interaction with an ongoing biotech company creation project. The PhD program is interdisciplinary by nature, linking chemistry, cell biology, and immunology. The focus can be modulated according to personal preferences. The PhD student will thereby be trained to become an independent thinker at the frontier between disciplines.

Recent publications

1. Forrester, A., S.J. Rathjen, M.D. Garcia Castillo, C. Bachert, A. Couhert, L. Tepshi, S. Pichard, J. Martinez, H.-F. Renard, C.A. Valades Cruz, F. Dingli, D. Loew, C. Lamaze, J.C. Cintrat, A.D. Linstedt, D. Gillet, J. Barbier, and **L. Johannes**. in press. Functional dissection of the retrograde Shiga toxin trafficking inhibitor Retro-2. Nat. Chem. Biol.

2. Watkins, E.B., J. Majewski, E.Y. Chi, H. Gao, J.C. Florent, and **L. Johannes**. 2019. Shiga toxin induces lipid compression: a mechanism for generating membrane curvature. Nano Lett. 19:7365-7369.

3. **Johannes, L**., and M. Lucchino. 2018. Current challenges in delivery and cytosolic translocation of therapeutic RNAs. Nucleic Acid Ther. 28:178-193.

4.Shafaq-Zadah, M., C.S. Gomes-Santos, S. Bardin, P. Maiuri, M. Maurin, J. Iranzo, A. Gautreau, C. Lamaze, P. Caswell, B. Goud, and **L. Johannes**. 2016. Persistent cell migration and adhesion rely on retrograde transport of beta1 integrin. Nat. Cell Biol. 18:54-64.

5. Renard, H.-F., M. Simunovic, J. Lemière, E. Boucrot, M.D. Garcia-Castillo, S. Arumugam, V. Chambon, C. Lamaze, C. Wunder, A.K. Kenworthy, A.A. Schmidt, H. McMahon, C. Sykes, P. Bassereau, and **L. Johannes**. 2015. Endophilin-A2 functions in membrane scission in clathrin-independent endocytosis. Nature. 517:493-496.

Expected profile of the candidate

Confirmed keen interest in chemical biology. Outstanding academic track record. Solid training in any disciplines that are pertinent for the project, i.e. organic synthesis, cell biology, and/or biochemistry. Corresponding profiles are all welcome as long as the candidate has a strong drive to receive complementary training on site. Availability for international travel for collaborations. Mastery of the English language. Desire to be a team player in a highly dynamic international environment.