2017-07

IC-**3i** International PhD Program

PhD thesis project

2018 Call for application

Synchronizing Transport from the Plasma Membrane to the Endoplasmic Reticulum: New Assays, New Questions, New Applications

General information

Call	2018
Reference	2017-07-PEREZ
Keyword(s)	Intracellular transport, Life cell imaging, Trafficking, Golgi complex, Retrograde transport

Director(s) and team

Thesis director(s)	Franck Perez
Research team	Dynamics of Intra-Cellular Organization
Research department	UMR 144 - Subcellular Structure and Cellular Dynamics

Description of the PhD thesis project

Since more than a decade, the team is studying the dynamics and function of the Golgi complex and its role in regulating the anterograde secretory pathway. Mammalian cells are characterized by the co-existence of multiple pathways both in the anterograde direction, from the endoplasmic reticulum (ER) to the endosomal system and the plasma membrane, and in the retrograde one, back to the ER. Most of these pathways cross the Golgi complex which plays an essential role in sorting and processing cargos.

The laboratory has developed a novel system, the RUSH system, which enables the systematic analysis of the anterograde secretory routes. It allows to synchronize the transport of a large variety of cargos from the ER to downstream compartments. It is amenable to real time imaging, biochemical quantification and screening. It allows to analyze the impact of changes in cell physiology on cargo secretion and screen for perturbing siRNA or small molecules.

We will now tackle the question of the retrograde pathway and set-up a synchronized assay adaptable to diverse cargos. This will complement the existing assays (e.g. based on toxin transport) and allow us to get a more comprehensive picture and identify regulatory factors. This retrograde assay will be used to identify the underlying mechanisms using gene screening combined to novel proteomic approach that we have set-up to study the secretory pathway. We will then use both the anterograde and retrograde assays to challenge theoretical models of Golgi-dependent transport and in particular test whether opposite flows can cross the same Golgi complexes and what are the effect, predicted by the theory and observed, of Golgi organization, dynamics and function. Last but not least, we have shown that the RUSH assay allows to screen for small molecules able to specifically perturb the secretion of a chosen cargo. A similar approach will be followed to perturb the retrograde flow and to develop novel therapeutic approaches.

International, interdisciplinary & intersectoral aspects of the project

International:
We will collaborate with several international teams (e.g. D. Virshup in Singapore and J. Lippincott-Schwartz in the USA). The selected student will go to these labs to transfer our technologies and learn their systems.

Interdisciplinary:
We are currently filing patents to cover the use of the RUSH system for therapeutic applications. The retrograde RUSH will be essential to complete our portfolio, file additional patents and develop complementary therapeutics options.

Intersectoral:
Theoretical aspects will be analyzed with the team of P. Sens at Institut Curie. Predictions of their model, and in particular of the counterflow, both in terms of impact on transport speed and Golgi morphology, will be tested and refinement will rely on such positive loops between our teams.

Recent publications

1. Fourriere L, Divoux S, Roceri M, **Perez F**, Boncompain G.
Microtubule-independent secretion requires functional maturation of Golgi elements.
J Cell Sci. 2016 Sep 1;129(17):3238-50. doi: 10.1242/jcs.188870.

2. Kajiho H, Kajiho Y, Frittoli E, Confalonieri S, Bertalot G, Viale G, Di Fiore PP, Oldani A, Garre M, Beznoussenko GV, Palamidessi A, Vecchi M, Chavrier P, **Perez F**, Scita G.
RAB2A controls MT1-MMP endocytic and E-cadherin polarized Golgi trafficking to promote invasive breast cancer programs.
EMBO Rep. 2016 Jul;17(7):1061-80. doi: 10.15252/embr.201642032.

3. Moutel S, Bery N, Bernard V, Keller L, Lemesre E, de Marco A, Ligat L, Rain JC, Favre G, Olichon A, **Perez F**.
NaLi-H1: A universal synthetic library of humanized nanobodies providing highly functional antibodies and intrabodies.
Elife. 2016 Jul 19;5. pii: e16228. doi: 10.7554/eLife.16228.

4. Jimenez AJ, Maiuri P, Lafaurie-Janvore J, Divoux S, Piel M, **Perez F**.
ESCRT machinery is required for plasma membrane repair.
Science. 2014 Feb 28;343(6174):1247136. doi: 10.1126/science.1247136.

5. Boncompain G, Divoux S, Gareil N, de Forges H, Lescure A, Latreche L, Mercanti V, Jollivet F, Raposo G, **Perez F**.
Synchronization of secretory protein traffic in populations of cells.
Nat Methods. 2012 Mar 11;9(5):493-8. doi: 10.1038/nmeth.1928.

Expected profile of the candidate

Applicants should have a strong interest in cell biology and in the study of membrane trafficking. A strong capacity for independent and creative thinking as well as for team work is needed. The project relies on molecular biology, cell culture, microscopy and live cell imaging techniques and prior experience in these fields will be a plus.