Master Biologie Moléculaire et Cellulaire 'BMC',
Université de Paris - *UFR Sciences du Vivant*

Parcours : **Biologie et Développement Cellulaires 'BDC'**
http://www.master2bdc.fr/
Fiche de Projet de Stage M2, Année 2020-2021

Unité INSERM ou CNRS ou Université : INSERM U1016, CNRS UMR 8104, Université de Paris **Intitulé Equipe :** Signalisation des cellules immunes et infection rétrovirale **ED d'appartenance :** BioSPC **Responsable de l'Equipe :** Clotilde Randriamampita	**Responsable du Stage :** Jérôme Delon **Contacts** Adresse : Institut Cochin, 22 rue Méchain, 75014 Paris Email : jerome.delon@inserm.fr Tel : 01 40 51 66 40

Titre du projet : Impact de mutations génétiques des RHO GTPases identifiées chez des patients sur la physiologie cellulaire

Résumé du Projet de Stage (en 300 mots maximum, mots clés en gras)

Small GTPases of the Rho family, their regulators and their effectors assemble molecular platforms at the surface of membranes that control multiple signaling pathways. These signaling platforms are involved in various physiological functions and processes in the cell, such as the regulation of the cytoskeleton, adhesion, migration or the cell cycle. Mirroring these major functions, their deregulations can be at the origin of human pathologies such as immune deficiencies and inflammatory syndromes. However, how molecular defects in Rho pathways result in clinical symptoms is extremely complex and has remained poorly understood.

In this project, we identified patients with missense mutations affecting the small GTPase CDC42, as well as $G\alpha_{13}$, a subunit of a heterotrimeric G protein that recruits a Rho exchange factor, all of which result in a spectrum of disabling skin diseases, often with inflammatory and immune symptoms. **These rare diseases provide a unique opportunity to unravel the inner workings of Rho GTPases molecular circuits from the molecule to the patient.** With this aim, we will use complementary expertise, including biochemistry, molecular and cell biology, and imaging. We will investigate the mutational landscape of the Rho pathways in a large and unique cohort of patients, identify the biochemical and cellular defects associated with the mutations, and determine the impact of the mutations on Rho GTPase functions and in chemokine signaling pathways regulated by Rho GTPases.

The project should thus impact fundamental and translational research in several ways.

Publications de l'équipe relatives au projet de stage (max 5)

- Bekhouche B, Tourville A, Ravichandran Y, Tacine R, Abrami L, Dussiot M, Khau-Dancasius A, Boccara O, Khirat M, Mangeney M, Dingli F, Loew D, Boëda B, Jordan P, Molina TJ, Bellon N, Fraitag S, Hadj-Rabia S, Blanche S, Puel A, Etienne-Manneville S, van der Goot FG, Cherfils J, Hermine O, Casanova JL, Bodemer C, Smahi A, Delon J. A toxic palmitoylation of Cdc42 enhances NF-κB signaling and drives a severe autoinflammatory syndrome. J. Allergy Clin. Immunol. 2020 Apr 10:S0091-6749(20)30426-7. doi: 10.1016/j.jaci.2020.03.020.
- Megrelis, L., El Ghoul, E., Moalli, F., Versapuech, M., Cassim, S., Ruef, N., Stein, J.V., Mangeney, M. and Delon J. (2018) Fam65b phosphorylation relieves tonic RhoA inhibition during T cell migration. Front. Immunol. 9:2001
- Froehlich, J., Versapuech, M., Megrelis, L., Largeteau, Q., Meunier, S., Tanchot, C., Bismuth, G., Delon, J., Mangeney, M. (2016). FAM65B controls the proliferation of transformed and primary T cells. Oncotarget. 7: 63215-63225.
- Megrelis L. and Delon J. Rapid and robust analysis of cellular and molecular polarization induced by chemokine signaling. *J Vis Exp* (94) (2014)
- Rougerie,P., Largeteau, Q., Megrelis, L., Carrette, F., Lejeune, T., Toffali, L., Rossi, B., Zeghouf, M., Cherfils, J., Constantin, G., Laudanna, C., Bismuth, G., Mangeney, M., Delon, J. Fam65b is a new transcriptional target of FOXO1 that regulates RhoA signaling for T lymphocyte migration. 2013; *J Immunol* 190(2):748-755.