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

Parcours : **Biologie et Développement Cellulaires 'BDC'**
http://www.master2bdc.fr/
Fiche de Projet de Stage de M2, 2024-2025

Unité INSERM ou CNRS ou Université : Institut Cochin, Inserm U1016, CNRS UMR8104, Université Paris Cité **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 : 22 rue Méchain, 75014 Paris Email : jerome.delon@inserm.fr Tél : 01 40 51 66 40

Titre du projet : Impact de mutations génétiques de la RHO GTPase CDC42 identifiées chez des patients atteints d'hyper-inflammation

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.

Using whole-exome sequencing, we and others previously identified patients with missense **mutations** affecting the small GTPase **CDC42** that 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 techniques, including biochemistry, molecular and cell biology, flow cytometry and imaging. We will investigate the mutational landscape of the RHO pathways in a large and unique cohort of patients. In particular, we will determine to what extent new pathogenic mutations we have recently identified in the *CDC42* gene, alter the subcellular localization of the corresponding protein. We will identify whether changes in the activation state of CDC42 are induced. We will study the biochemical and cellular defects associated with the mutations to determine the impact of the mutations on CDC42 function. We will particularly focus our studies to understand how cytoskeletal elements (actin filaments and microtubules) can impact several inflammatory signaling pathways such as NF-κB, Pyrin and NLRP3 inflammasomes, and STING/type I IFNs.

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

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

- Iannuzzo A, Mertz P, Delafontaine S, Tacine R…, Georgin-Lavialle S, Meyts I and Delon J. C-terminal CDC42 variants in autoinflammatory patients trigger actin defects and NF-κB hyperactivation. *Submitted* (see in bioRxiv).
- Iannuzzo A…, Delon J. Autoinflammatory patients with Golgi-trapped CDC42 exhibit intracellular trafficking defects leading to STING hyperactivation. *Nature Communications* (under review, see in bioRxiv).
- Delafontaine S, Iannuzzo A…, Delon J and Meyts I. (2024) Heterozygous mutations in the C-terminal domain of COPA underlie a complex autoinflammatory syndrome. *Journal of Clinical Investigation*. 134(4):e163604.
- El Masri R and Delon J. (2021) RHO GTPases: from new partners to complex immune syndromes. *Nature Reviews Immunology*. (8):499-513.
- Bekhouche B…, Delon J. (2020) A toxic palmitoylation of Cdc42 enhances NF-κB signaling and drives a severe autoinflammatory syndrome. *Journal of Allergy and Clinical Immunology*. S0091-6749(20)30426-7.