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, 2026-2027

Unité INSERM ou CNRS ou Université : Institut Cochin, Inserm U1016, CNRS UMR8104, Université Paris Cité **Intitulé Equipe : Dynamique des réponses immunes dépendantes du cytosquelette** **ED d'appartenance : BioSPC** **Responsables de l'Equipe : Jérôme Delon et Paolo Pierobon**	**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 : Deciphering the mechanisms responsible for inflammatory syndromes due to defects in the RHO GTPases pathways

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* and *ARPC1* genes, alter the subcellular localization of the corresponding proteins. We will identify whether changes in the activation states of these mutated proteins are induced. We will study the biochemical and cellular defects associated with the mutations to determine the impact of these variants on the functions of the RHO pathways. 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)

- El Masri R…, Vabres P, Delon J. (2025) A postzygotic *GNA13* variant upregulates the RHOA/ROCK pathway and alters melanocyte function in a mosaic skin hypopigmentation syndrome. *Nature Communications.* 16(1):1751.
- Iannuzzo A…, Delon J. (2024) Autoinflammatory patients with Golgi-trapped CDC42 exhibit intracellular trafficking defects leading to STING hyperactivation and ER stress. *Nature Communications.* 15(1):9940.
- 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.