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

Parcours : **Biologie et Développement Cellulaires 'BDC'**
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Fiche de Projet de Stage de M2, 2025-2026

Unité INSERM ou CNRS ou Université : Institut Cochin, Inserm U1016, CNRS UMR8104, Université Paris Cité **Intitulé Equipe : Dynamics of the cytoskeleton-dependent responses of immune cells** **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 Tel : 01 40 51 66 40

Titre du projet : Deciphering the mechanisms responsible for pathologies 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 skin pigmentation defects, 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 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 expertise, including biochemistry, molecular and cell biology, and imaging techniques. 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 CDC42 function. We will particularly focus our studies to understand how the cytoskeleton can impact on the inflammatory microenvironment.

The project should thus impact 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. A postzygotic *GNA13* variant upregulates the RHOA/ROCK pathway and alters melanocyte function in a mosaic skin hypopigmentation syndrome. Nat Commun. 2025 Feb 18;16(1):1751. doi: 10.1038/s41467-025-56995-4. PMID: 39966435; PMCID: PMC11836271.
- Iannuzzo A,…, Delon J. Autoinflammatory patients with Golgi-trapped CDC42 exhibit intracellular trafficking defects leading to STING hyperactivation and ER stress. Nat Commun. 2024 Nov 16;15(1):9940. doi: 10.1038/s41467-024-54294-y. PMID: 39550374; PMCID: PMC11569173.
- Delafontaine S, Iannuzzo A,…, Delon J, Meyts I. Heterozygous mutations in the C-terminal domain of COPA underlie a complex autoinflammatory syndrome. J Clin Invest. 2024 Jan 4;134(4):e163604. doi: 10.1172/JCI163604. PMID: 38175705; PMCID: PMC10866661.
- El Masri R, Delon J. RHO GTPases: from new partners to complex immune syndromes. Nat Rev Immunol. 2021 Aug;21(8):499-513. doi: 10.1038/s41577-021-00500-7. Epub 2021 Feb 5. PMID: 33547421.
- Bekhouche B, Tourville A,…, 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 Nov;146(5):1201-1204.e8. doi: 10.1016/j.jaci.2020.03.020. Epub 2020 Apr 10. PMID: 32283203.