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 : U1151 **Intitulé Equipe : Cell growth control by nutrients** **ED d'appartenance : Bio SPC** **Responsable de l'Equipe : Mario Pende**	**Responsable du Stage : Mario Pende** **Contacts** Adresse : 160 rue de Vaugirard Email : mario.pende@inserm.fr Tel : 0632831839

Titre du projet : Glycerol 3 Phosphate accumulation triggers senescence by rewiring lipid metabolism

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

Cellular senescence impacts many physiological and pathological processes. A durable cell cycle arrest, a pro-inflammatory secretory phenotype and metabolic reprogramming characterize it. Identifying common and specific metabolic liabilities in senescence subtypes provide novel inroads to exploit senescence targeting for health benefits. In cultures of normal, human diploid fibroblasts, we used dynamic analyses of transcriptome and metabolome profiles in senescence subtypes to reveal a homeostatic switch of glycerol-3-phosphate (G3P) and phosphoethanolamine (PEtn) accumulation linking lipid metabolism to the senescence gene expression program. G3P accumulation by Glycerol kinase (GK) overexpression drives the senescence program, while scavenging by G3P phosphatase (G3PP) overexpression counteracts senescence. In this research proposal, we will address: 1) the expression and regulation of these enzymes in in vitro and in vivo models of senescence; 2) the signal transduction elements mediating cell cycle arrest and the inflammatory secretory phenotype upon G3P accumulation; 3) the pharmacological and genome editing strategies to modulate G3P accumulation in pathophysiology of cancer, aging or wound healing. The student will combine state-of-the-art approaches in metabolomics, biochemistry, genome editing in vivo and in vitro to reveal the molecular mechanisms and the therapeutic potential of these metabolic determinants of the senescent state.

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

1 Tighanimine, K. *et al.* A homoeostatic switch causing glycerol-3-phosphate and phosphoethanolamine accumulation triggers senescence by rewiring lipid metabolism. *Nat Metab* **6**, 323-342, doi:10.1038/s42255-023-00972-y (2024).
2 Bonucci, M. *et al.* mTOR and S6K1 drive polycystic kidney by the control of Afadin-dependent oriented cell division. *Nature communications* **11**, 3200, doi:10.1038/s41467-020-16978-z (2020).
3 Rashid, T. *et al.* Lipin1 deficiency causes sarcoplasmic reticulum stress and chaperone-responsive myopathy. *The EMBO journal* **38**, doi:10.15252/embj.201899576 (2019).
4 Barilari, M. *et al.* ZRF1 is a novel S6 kinase substrate that drives the senescence programme. *The EMBO journal* **36**, 736-750, doi:10.15252/embj.201694966 (2017).
5 Aguilar, V. *et al.* S6 kinase deletion suppresses muscle growth adaptations to nutrient availability by activating AMP kinase. *Cell metabolism* **5**, 476-487, doi:10.1016/j.cmet.2007.05.006 (2007).