Proposition de sujet de thèse ED BIO SORBONNE PARIS CITE

Attention: deadline to contact the thesis director: Saturday May 21th midnight

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Thesis subject: Molecular mechanisms of degenerative processes in physiological and accelerated ageing

Keywords: ageing, epigenetics, mitochondria, cerebral organoids, oxidative stress

Summary (5 lines maximum):

We study the molecular mechanisms underlying the progeroid and neurodegenerative Cockayne syndrome and their link with regular ageing. We have evidences that this process involves mitochondrial dysfunction and large scale transcriptional and epigenomic reprogramming. To address these questions and the large clinical heterogeneity of this disease, we rely on patient-derived cells, iPSCs and redifferentiated cells and cerebral organoids, as well as isogenic cellular models that we have constructed.

Thesis Project

Ageing is dramatically accelerated in some rare genetic disorders like Cockayne syndrome (CS), which is mostly fatal, but the molecular mechanisms of this process have not been elucidated. We discovered a major defective pathway of this progeroid disease that implies mitochondrial dysfunction, generated by oxidative and nitrosative stress (PNAS 2015), and is distinct from a well-established DNA repair impairment in this disease. We rescued the defect in CS patient cells using a scavenger of oxidative/nitrosative stress paving the path to therapeutic perspectives that are missing to date. We recently reported that progeroid-linked molecular defects also occur during cellular senescence, a process associated with regular ageing (Nature Comms 2019), and have evidences of epigenetic modifications leading to these alterations (BioRxiv, 2021). We focus here on the underlying molecular mechanisms of CS and their occurrence during regular ageing. A major subject of this thesis project is to understand the link between, oxidative/nitrosative stress, epigenetic alterations and mitochondrial dysfunction in promoting accelerated and physiological ageing.

We plan to investigate CS molecular and mitochondrial defects also in the context of whole genome structure and expression, in collaboration with OMICS specialists. For this we count on cells from patients with different severity (in collaboration with CS clinicians) and on CRISPR/Cas9 isogenic models that we have constructed. Finally, this project aims to investigate the role of CSB, which is not only a DNA repair protein, but also a transcription and chromatin remodeling factor, in the homeostasis on normal cells and its impact in preventing ageing. As animal models poorly recapitulate the disease, and patient material is rare and mostly unavailable, we generate induced pluripotent stem cells (iPSCs) from cells of patient with different clinical severity. From iPSCs we are also deriving differentiated cells and cerebral organoids to assess molecular, cellular, and intercellular alterations that are responsible for the accelerated ageing-related degeneration in this disease. Part of this material is available, other material will be generated during this thesis project, aiming to understand underlying mechanism of degeneration linked to pathophysiological ageing.

5 recent publications:

- Crochemore C, Cimmaruta C, Fernández-Molina C, Ricchetti M (2022). Reactive species in progeroid syndromes and aging-related processes". Review. *Antioxidant and Redox Signaling* Jan 4. doi: 10.1089/ars.2020.8242.
- Crochemore C, Chica C, Garagnani P, Lattanzi G, Horvath S, Sarasin A, Franceschi C, Bacalini MG, Ricchetti M (2021). Epigenomic signature of the progeroid Cockayne syndrome exposes distinct and common features with physiological ageing. *BioRxiv 445308*
- Crochemore C, Fernández-Molina C, Montagne B, Audrey Salles A, Ricchetti M (2019). CSB promoter downregulation via histone H3 hypoacetylation is an early determinant of replicative senescence. *Nature Communications.* Dec 6;10(1):5576.
- Ricchetti M (2018) Replication stress in mitochondria. *Mutation research* 808**:** 93-102; doi:10.1016/j.mrfmmm.2018.01.005
- Chatre L Biard D, Sarasin A and Ricchetti M (2015). Reversal of mitochondrial defects with CSB-dependent serine-protease inhibitors in patient cells of the progeroid Cockayne syndrome. *Proc. Natl. Acad. Sci. U.S.A.* 112 (22): E2910-2919