ChemBiol4ferroptosis

2-years Post-Doctoral Position: Design & Development of Chemical biology tools to interrogate the potential link between ACSL4, ferroptosis and neurodegenerative diseases.

The team of Medicinal Chemistry (CMFA) of the Louvain Drug Research Institute (LDRI) at UCLouvain, Brussels, Belgium, is looking for a chemical biologist to contribute to the development of chemical biology tools to probe the acyl-CoA synthetase long-chain 4 (ACSL4) enzyme and establish the potential link between ACSL4, ferroptosis and neurodegenerative diseases.

The project proposal grounds on important preliminary findings generated in collaboration with the *Brain Biology and Chemistry team* (UMR 1172 Lille Neurosciences and Cognition, University of Lille, France). The post-doctoral researcher enrolled in this position will, in collaboration with the team of Lille, contribute to the optimization of ACSL4 inhibitors by chemical synthesis with the aim to discover novel selective pharmacological tools targeting ACLS4. The post-doctoral researcher will also investigate the binding of these tools to ACSL4 by biophysical methods such as Microscale Thermophoresis (MST) and Nuclear Magnetic Resonance STD and/or WaterLogsy. The researcher will set up and optimize an LC-MS/MS-based method to quantify oxidized arachidonic acid-containing phosphatidylethanolamine.

Summary of the project. Over the past decade, a number of regulated cell death (RCD) has been identified shaking up cell death paradigm in multiple pathologies including neurodegenerative diseases (NDDs). Particularly, ferroptosis was shown to have significant implications in both Alzheimer's and Parkinson's disease and in Amyotrophic Lateral Sclerosis (ALS). Ferroptosis is a RCD characterized by iron-dependent accumulation of lipid hydroperoxides associated with an insufficient capacity to eliminate these oxidation products. Hence, anti-ferroptotic agents including iron chelators and radical trapping antioxidants have attracted much attention lately.

A recent report uncovered acyl-CoA synthetase long-chain 4 (ACSL4) as a critical contributor to ferroptosis execution. This enzyme catalyzes the conversion of long-chain fatty acids to the acyl-CoA active form. Genetic and pharmacological inhibition of ACSL4 by thiazolidinediones (TZDs) were found to suppress ferroptosis. Therefore, ACSL4 inhibitors are emerging as attractive anti-ferroptotic agents.

The goal of our research program is to develop ACSL4 inhibitors to help establish the potential link between ACSL4, ferroptosis and NDDs. The research project will articulate according to three main objectives. The first one consists in a hit expansion approach around TZDs in order to identify potent ACSL4 inhibitors. The second one relies on a screening of the Selective Optimization of Side Activity (SOSA) library to identify alternative starting points followed by a "Break, Pick & Build" approach. Finally, we will set up an LC-MS/MS experiment for the dosage of intracellular lipidic ferroptotic signals.

Based on the complementary expertise of the partners, our emerging research program has the potential to deliver several ACSL4 inhibitors that would help establish the potential link between ACSL4, ferroptosis and NDDs and constitute a strong basis for the development of first-in-class drugs for NDDs therapy.

The Post-doctoral researcher will be enrolled by the Louvain University (https://uclouvain.be/en/research-institutes/ldri) under the supervision of Prof. Raphaël Frédérick and work in collaboration with researchers at Lille, France.

Candidate profile

The ideal candidate for this position is a highly motivated researcher with a PhD degree (awarded after **March 2016**) in chemical biology, or organic/medicinal chemistry. The candidate should enjoy the challenge of novel scientific concepts and methodologies notably in biophysics (MST, NMR, MS). We are looking for candidates interested to work in a multidisciplinary research environment, who have excellent communication skills and are self-motivated, critical and trustworthy. The candidate should be able to work well both independently and in an interdisciplinary team.

Good oral and written communication skills in English are essential.

Good organisational and planning skills are necessary.

Duration: **18-24 months** Contact information: to get more details please write to raphael.frederick@uclouvain.be

Offer starting date : immediately

Recent references of the team

1. Thabault, L.; Liberelle, M.; Koruza, K.; Yildiz, E.; Joudiou, N.; Messens, J.; Brisson, L.; Wouters, J.; Sonveaux, P.; Frederick, R., Discovery of a novel lactate dehydrogenase tetramerization domain using epitope mapping and peptides. J Biol Chem **2021**, 100422.

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5. Ameryckx, A.; Pochet, L.; Wang, G.; Yildiz, E.; Saadi, B. E.; Wouters, J.; Van Bambeke, F.; Frederick, R., Pharmacomodulations of the benzoyl-thiosemicarbazide scaffold reveal antimicrobial agents targeting d-alanyl-d-alanine ligase in bacterio. Eur J Med Chem **2020**, 200, 112444.

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8. Ameryckx, A.; Thabault, L.; Pochet, L.; Leimanis, S.; Poupaert, J. H.; Wouters, J.; Joris, B.; Van Bambeke, F.; Frederick, R., 1-(2-Hydroxybenzoyl)-thiosemicarbazides are promising antimicrobial agents targeting d-alanine-d-alanine ligase in bacterio. Eur J Med Chem **2018**, 159, 324-338.

9. Ravez, S.; Spillier, Q.; Marteau, R.; Feron, O.; Frederick, R., Challenges and Opportunities in the Development of Serine Synthetic Pathway Inhibitors for Cancer Therapy. J Med Chem **2017**, 60 (4), 1227-1237.