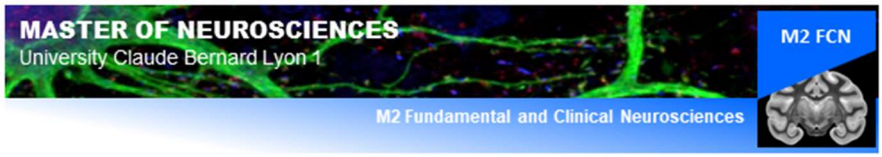

MASTER 2 Fundamental and Clinical Neurosciences

Internship proposal 2024-2025

(internship from January to June 2025)

Host laboratory:
CarMeN lab (Cardiovascular Metabolism Diabetology Nutrition)
Inserm U1060 Université Claude Bernard Lyon 1
Groupement Hospitalier EST
Bâtiment B13, IHU OPERA
59 boulevard Pinel
69500 BRON -FR

Host team :
IRIS team (Ischemia-reperfusion injury syndromes):
http://carmen.univ-lyon1.fr/equipe-3-ischemia-reperfusion-syndromes/

Internship supervisors :
Marlène Wiart, PhD
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Directeur de recherche Inserm
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Project title :
Investigating the effects of phagocytosis modulators on microglial phagocytosis in an *in vitro* model of ischemic stroke

Project summary : *approx 10 lines*

Acute ischemic stroke (AIS) occurs in 140,000 persons in France each year and is a major public health issue. Microglial phagocytosis is emerging as a therapeutic target in AIS. The core objective of our project is to provide the proof-of-concept (POC) that microglial phagocytosis is a druggable target which modulation improves AIS outcome. Our hypothesis is that enhancing phagocytosis will result in better brain cleaning, dampened inflammation and thus prevent secondary brain damage and improve stroke outcome. We aim to test this hypothesis in an *in vitro* model of ischemic stroke. We have recently set up an *in vitro* assay of microglial phagocytosis of apoptotic neurons based on former collaborative works.[1, 2] We have shown with confocal microscopy that microglial phagocytosis of apoptotic neurons increased in the first 24 hours in normoxic conditions and that this pattern was altered in ischemia-like conditions, with a decrease of microglial phagocytosis in time. The first aim of the internship

is to investigate the effects of phagocytosis modulators (inhibitors and agonists) in that model to test whether microglial phagocytosis is a druggable target. The second aim of the internship is to assess the effects of iron oxide nanoparticles (USPIO) on microglial phagocytosis of apoptotic neurons in that model. Specifically, we aim to evaluate: 1/ if microglial internalization of USPIO follow the same trend as microglial phagocytosis of apoptotic neurons in normoxic and ischemia-like conditions; 2/ if USPIO internalization is impacted by phagocytosis modulators (inhibitors and agonists) in these conditions; and 3/ if USPIO modulates the inflammatory response of microglia in terms of mortality, morphophenotype and cytokine secretions. The perspective of the internship is to test the best drug candidates in an *in vivo* murine model of AIS using UPSIO-enhanced MRI as an *in vivo* imaging biomarker of microglial phagocytosis.

Reference:

1. Hubert V, et al. *Adv Sci (Weinh)*. 2021:e2101433. https://doi.org/10.1002/advs.202101433
2. Beccari S, et al. *Autophagy*. 2023:1-30. https://doi.org/10.1080/15548627.2023.2165313

3-5 recent publications :

1. Tavakoli C, Cuccione E, Dumot C, Balegamire J, Si-Mohamed S, Kim J, Crola-da-Silva- C, Chevalier Y, Berthezene Y, Boussel L, Douek P, Cormode D, Elleaume H, Brun E, **Wiart M.** High-resolution synchrotron K-edge subtraction CT allows tracking and quantifying therapeutic cells and their scaffold in a rat model of focal cerebral injury and can serve as a reference for spectral photon counting CT. NanoTheranostics. 2023 :16;7(2):176-186.
2. Dumot C, Po C, Capin L, Hubert V, Ong E, Chourrout M, Bolbos R, Amaz C, Auxenfans C, Canet-Soulas E, Rome C, Chauveau F, **Wiart M**. Neurofunctional and neuroimaging readouts for designing a preclinical stem-cell therapy trial in experimental stroke. Sci Rep, 2022, **12**(1): 4700. https://doi.org/10.21203/rs.3.rs-1019878/v1
3. Hubert V, Hristovska I, Karpati S, Benkeder S, Dey A, Dumot C, Amaz C, Chounlamountri N, Watrin C, Comte JC, Chauveau F, Brun E, Marche P, Lerouge F, Parola S, Berthezène Y, Vorup-Jensen T, **Pascual O**, and **Wiart M**. Multimodal imaging with NanoGd reveals spatiotemporal features of neuroinflammation after experimental stroke. Adv Science 2021, e2101433. https://onlinelibrary.wiley.com/doi/10.1002/advs.202101433
4. Karpati S, Hubert V, Hristovska I, Lerouge F, Chaput F, Bretonnière Y, Andraud C, Banyasz A, Micouin G, Monteil M, Lecouvey M, Mercey M, Dey A, Marche, Lindgren M, **Pascual O**, **Wiart M**, Parola S. Hybrid Multimodal Contrast Agent for Multiscale In Vivo Investigation of Neuroinflammation. Nanoscale, 2021, **13**, 3767-3781
https://doi.org/10.1039/D0NR07026B
5. Basalay MV*, **Wiart M***, Chauveau F, Dumot C, Leon C, Amaz C, Bolbos R, Cash D, Kim E, Mechtouff L, Cho TH, Nighoghossian N, Davidson SM, Ovize M, Yellon DM. Neuroprotection by remote ischemic conditioning in the setting of acute ischemic stroke: a preclinical two-centre study. Sci Rep 2020 Oct 9;10(1):16874. *co-first authors