Master de Sciences et Technologies
Mention Biologie Intégrative et Physiologie
Parcours : Neurosciences
Responsable : Professeur Régis Lambert

Internship Proposal
Academic Year 2018-2019

1. Host team :

Research Unit (e.g. Department or Institute) : INSERM U1148
Research Unit Director : Didier LETOURNEUR
Research Team Director : Nathalie KUBIS & Marie-Christine BOUTON
Team name : Hemostasis, Thrombo-Inflammation, Neurovascular repair

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Supervisor of the Research Intern for this project : Nathalie KUBIS
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2. Internship project title:

Effects of human adipocyte mesenchymal stem cell transplantation in hypertensive mice with focal cerebral ischemia

3. Internship Description :

Stroke is currently the second leading cause of death in industrial countries. Among the living, 40% will be permanently disabled and 25% will manifest a significant cognitive decline, placing stroke as the second most common type of dementia after Alzheimer's disease. The only available treatment consists in pharmacological (rtPA) or mechanical (stent retriever) removing of the clot using, accessible to less than 10% of the patients, due to the short therapeutic window, thus remaining a major public health issue. Stem cell therapy could be efficient at the acute phase (neuroprotective properties), but also at the chronic phase by enhancing brain repair, and thus reduced sensori-motor disability.

However, preclinical studies rarely address the impact of cardiovascular risk factors on the benefit of cell therapy, which is ground truth. It is in this context that we have developed a work package of the European project H2020 RESSTORE, a European multicenter clinical and preclinical trial. Our goal is to evaluate - among other things - the effect of adipocytes-derived mesenchymal stem cells (AD-MSC) in ischemic stroke in hypertensive mice. Of all cell types / sources that have been pre-clinically tested in stroke, stromal / mesenchymal stem cells are easily derived from multiple sources including adipose tissue. These cells are easily accessible (liposuction), abundant, proliferate and differentiate easily. In addition, they exhibit low immunogenicity after allogeneic transplantation for safe use, including xenograft *(Kubis Neuroimage 2007, Guttierez J Trans Med 2013)*. Intravenous (IV) administration of these cells is noninvasive and easy to perform at the bedside in a translational point of view.

We will study, using an ischemic stroke model of hypertensive male mice, the consequences of IV AD-MSC administration at two different time points (Day 2 for early injection and Day 7 for late injection), with two different levels of hypertension (moderate and severe), models that involve or not the renin angiotensin system. Our hypothesis is that AD-MSC in hypertensive mice will reduce the infarct volume and the short-term sensori-motor deficit, and in the long term, memory disorders by limiting the development of hypertensive microangiopathy in these mice, which we have demonstrated to be associated with greater cognitive impairment (Cifuentes Hypertension 2015), and by promoting angiogenesis, which we have demonstrated to enhance neurogenesis (Nih EJN 2012, Hilal SCI 2018 in press).
The Master 2 student will be responsible for the induction of HTA in moderate and severe HTA murine models, weekly blood pressure measurement, evaluation of neurological deficit, AD-MSC cell culture, intravenous injections and blood sampling in mice, histology, immunohistochemistry and RT-PCR procedures. He will collaborate in the realization of the experimental cerebral infarction induction with PhD students. Finally, he will be in charge of the.

Bibliography

Gutiérrez-Fernández M, et al J Transl Med. 2015 1;13:46.
Hilal R et al (SCI 2018, in press).
Cifuentes D et al Hypertension. 2015;65(1):218-24.
Nih LR, et al Eur J Neurosci. 2012;35(8):1208-17.
Kubis N et al Neuroimage. 2007;34(1):1-11.