Research projects 2020-2021

Master M1&M2 – PhD – Post-Doc

Antioxidant cerium oxide nanoparticles for in vivo stroke therapy

Supervisor:

Name: Jean-François Berret
E-mail: jean-francois.berret@univ-paris-diderot.fr
Phone: 01 57 27 61 47
Affliliation: Laboratory Matière et Systèmes Complexes, Université de Paris

Host Laboratory:

Affliliation: Université Université de Paris
Lab Name : Laboratoire Matière et Systèmes Complexes
Address : UMR 7057 Université de Paris/CNRS, Batiment Condorcet,
10 rue Alice Domon et Léonie Duquet, F-75205 Paris Cedex 13

Describe the team that the student will join for the project.

Our research group develops novel functional structures, devices and systems with stimuli-responsive features at the nano and microscales. Our objectives also deal with applications in medicine, biology and in the environment. It includes the development of tools for imaging and therapy in vivo, microfluidics and microrheology as well as the study of living system-machine interfaces.

Project description

Stroke is a leading cause of death worldwide for which doctors still lack therapeutic strategies. Ischemic stroke, one of the two major types of cerebral accidents results from the occlusion of a vessel in the brain, and it represents 80% of all worldwide recorded cases. Modern medicine tries to develop therapeutics that are personalized and adapted to each patient. To this aim, the mechanisms at the origin of the stroke pathophysiology, including perturbation of homeostasis, oxidative stress, inflammation must be studied. One approach consists in using follow-up of biomarkers associated with molecular imaging and therapeutic agents. The goal of our project is to develop innovative nanocarriers for *in vivo* experimentation combining imaging, vascular inflammation detection and oxidative stress reduction.

The nanocarriers targeted in this study are bimodal. They contain a healing agent to alleviate the stroke related biological damages and an efficient contrast agent for imaging. The healing agent is cerium oxide (or nanoceria) [1,2]. Recent studies have shown that nanoceria present unique antioxidant properties and protect cells against oxidative stress-related damage [3]. In particular, these nanoparticles were shown to display enzymes mimetic properties in which

the mechanisms underlying the catalytic activity depend on the particle physico-chemical properties such as size, morphology and Ce^{3+} fraction [1].

The nanostructures will be functionalized using advanced polymers and peptides for targeting the inflamed zones of the brain. Polymers are synthesized by the company Specific Polymers® (www.specificpolymers.fr) with which we have an exclusivity agreement for this study (Figure 2) [2]. The polymers contain poly(ethylene glycol) chains known for their bio-resistant properties and anchoring moieties (phosphonic acid) [4]. The contrast agents selected for the study are DOTA-Gadolinium complexes that will be grafted at the PEG end-groups of the functionalization layer (Figure 1b). For the targeting, peptide or antibody will be used. The peptide has a sequence of 10 amino acids that was shown to associate in the blood circulation to cell adhesion molecules (VCAM-1) located at the endothelial cell membrane.

In vitro cellular biology assays will be performed for testing targeting efficiency prior to the *in vivo* work. In vivo experiments will be carried out on a mouse model that will be treated to provoke an ischemic stroke, in collaboration with Isabelle Margaill group at the Université de Paris. MRI experiments will be performed at Paris-Tech on a 7 Tesla coil dedicated to small animal investigations [5,6]. The summary of the knowledge obtained by this study is that biocompatible polymers can be pursued as surface modifiers of nanoceria that can tune its enzymatic activities.

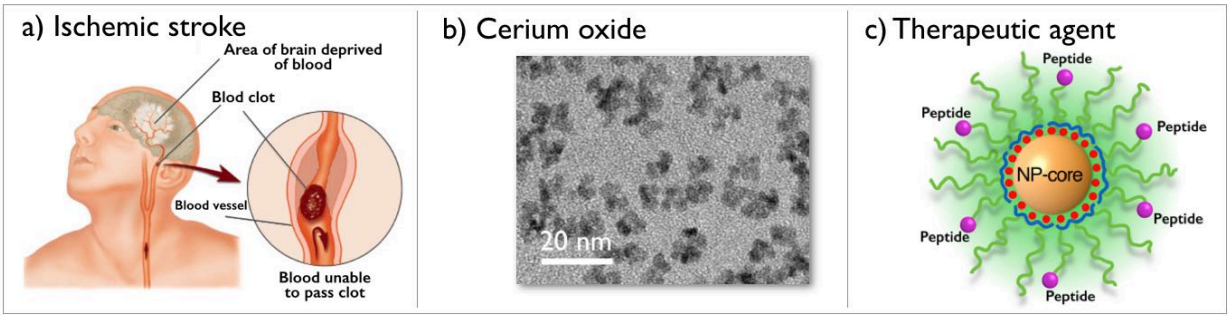

***Figure 1** : a) Representation of ischemic stroke, including the blockage of the blood vessel and the affected areas (ischemic core and penumbra). b) Transmission electronic microscopy image of nanoceria. c) Schematic presentation of therapeutic nanocarrier with functionalization corona.*

References

[1] V. Baldim, F. Bedioui, N. Mignet, I. Margaill, J.-F. Berret, *Nanoscale*, 10 (**2018**) 6971-6980.
[2] V. Baldim, N. Bia, A. Graillot, C. Loubat, J.-F. Berret, *Advanced Materials Interfaces*, 6 (**2019**) 1801814.
[3] I. Celardo, J.Z. Pedersen, E. Traversa, L. Ghibelli, *Nanoscale*, 3 (**2011**) 1411-1420.
[4] V. Torrisi, A. Graillot, L. Vitorazi, Q. Crouzet, G. Marletta, C. Loubat, J.-F. Berret, *Biomacromolecules*, 15 (**2014**) 3171-3179.
[5] G. Ramniceanu, B.T. Doan, C. Vezignol, A. Graillot, C. Loubat, N. Mignet, J.-F. Berret, *RSC Advances*, 6 (**2016**) 63788-63800.
[6] N. Giamblanco, G. Marletta, A. Graillot, N. Bia, C. Loubat, J.-F. Berret, *ACS Omega*, 2 (**2017**) 1309-1320.