# Master 1/2 - Research projects 2022-2023

## Antioxidant nanoparticles for *In Vivo* stroke therapy


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

The intern will join a group of researchers, composed of 2 postdocs, two PhD students, two M1/M2 interns, one biology engineer and one permanent position (J.-F. Berret, DR CNRS). Our research group develops novel functional structures, devices and systems with stimuli-responsive features at the nano and microscales. The three research themes of my group are cellular biomechanics, development of theranostic agents for nanomedicine and biophysics of lung function. Our objectives deal with applications in medicine, biology and in the environment (more information here).

**Project description**

Stroke is the second cause of mortality and the first cause of acquired disability in developed countries. About 80% of strokes are caused by a clot (or thrombus) occluding a cerebral artery. At present, r-tPA (recombinant tissue plasminogen activator), an enzyme with strong thrombolytic activity, remains the only pharmacological strategy available for the restauration of the blood flow. However, r-tPA has a limited time window (4 to 6 hours) and present side effects due to oxidative stress. All these factors have prompted researchers to seek better and safer approaches.

A blood clot occurring in a cerebral artery contains aggregated platelets, red blood cells and a mesh of cross-linked fibrin proteins. The use of r-tPA is based on the assumption that this enzyme induces fibrin degradation and clot dissolution [1]. Recently, neutrophil extracellular traps (NETs) have emerged as a new component in blood clots of various origins that may partly explain the failure of r-tPA to lyse the blood clot. NETs are decondensed nuclear DNA fibres supplemented with nuclear proteins, which are released by neutrophils during thrombus formation. Their integration into the fibrin scaffold results in a modified and stable clot structure that render clots resistant to r-tPA [2]. It was shown that the DNase-1 enzyme (deoxyribonuclease) degrades DNA fibers of NETs and accelerate the lysis by r-tPA of ischemic stroke patient thrombi [3].

Oxidative stress resulting from excess reactive oxygen species (ROS) is a major contributor to neuronal and vascular post-ischemic damage [4]. Cerium oxide nanoparticles were shown to display a broad range of antioxidant activities [5]. Recently, our group demonstrated that cerium oxide nanocrystals exhibit

strong enzyme-like mimetic catalytic activities [6-8] and that the content of $Ce^{3+}$ is critical to exhibit an effective and reproducible antioxidant activity [5,6].

In this project we aim to tailor all-in-one nanovectors combining cerium oxide nanoparticles (size < 5 nm) with powerful antioxidant properties with a series of attributes critical for targeting and dissolving stroke related thrombi. The rtPA and DNase-1 enzymatic activity will be assessed in static conditions by studying the clot dissolution kinetics. This will be achieved through a blood clot model using a microrheology technique on the rotation of magnetic wires developed in our group [9]. This technique allows to quantitatively measure the viscosity and elasticity of soft and gelled materials, such as a blood clot. The effect of nanoparticles coated with DNase-1 will be analyzed in a second step.

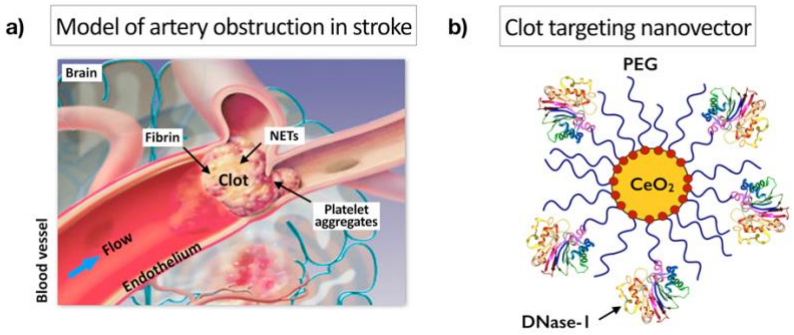


***Figure 1 : a)*** *Schematic illustration of ischemic stroke resulting from a blood clot (or thrombus) formation. The clot is made of platelets, red blood cells, cross-linked fibrin proteins and neutrophil extracellular traps (NETs) released by neutrophils.* ***b)*** *Functional nanoceria coated with PEG polymers for stability and with DNase-1 for targeting NETs in clots.*

## References on this work


[1] M. Hébert, F. Lesept, D. Vivien, R. Macrez, The story of an exceptional serine protease, tissue-type plasminogen activator (tPA), *Revue Neurologique*, 172 (**2016**) 186-197.
[2] T.J. Gould, T.T. Vu, A.R. Stafford, D.J. Dwivedi, P.Y. Kim, A.E. Fox-Robichaud, J.I. Weitz, P.C. Liaw, Cell-Free DNA Modulates Clot Structure and Impairs Fibrinolysis in Sepsis, *Arterioscler Thromb Vasc Biol*, 35 (**2015**) 2544-2553.
[3] C. Ducroux, L. Di Meglio, S. Loyau*, et al.*, Thrombus Neutrophil Extracellular Traps Content Impair tPA-Induced Thrombolysis in Acute Ischemic Stroke, *Stroke*, 49 (**2018**) 754-757.
[4] I. Margaill, M. Plotkine, D. Lerouet, Antioxidant strategies in the treatment of stroke, *Free Radical Biology and Medicine*, 39 (**2005**) 429-443.
[5] M.S. Lord, J.F. Berret, S. Singh, A. Vinu, A.S. Karakoti, Redox Active Cerium Oxide Nanoparticles: Current Status and Burning Issues, *Small*, n/a (**2021**) 2102342.
[6] V. Baldim, F. Bedioui, N. Mignet, I. Margaill, J.-F. Berret, The Enzyme-Like Catalytic Activity of Cerium Oxide Nanoparticles and its Dependency on Ce3+ Surface Area Concentration, *Nanoscale*, 10 (**2018**) 6971-6980.
[7] V. Baldim, N. Yadav, N. Bia, A. Graillot, C. Loubat, S. Singh, A.S. Karakoti, J.-F. Berret, Polymer-Coated Cerium Oxide Nanoparticles as Oxidoreductase-like Catalysts, *ACS Applied Materials & Interfaces*, 12 (**2020**) 42056-42066.
[8] G. Goujon, V. Baldim, C. Roques*, et al.*, Antioxidant Activity and Toxicity Study of Cerium Oxide Nanoparticles Stabilized with Innovative Functional Copolymers, *Advanced Healthcare Materials*, 10 (**2021**) 2100059.
[9] J.-F. Berret, Local viscoelasticity of living cells measured by rotational magnetic spectroscopy, *Nature Communications*, 7 (**2016**) 10134.