COLLEGE ED BIOLOGIE DOCTORAL SANTE PAYS DE LA LOIRE

Year 2023/2024

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin:**
Thesis title: **Prevent intimal hyperplasia with a localized, multi-therapeutic and post-surgery solution.**		3 keywords: **Nanoparticle-based hydrogel, intimal hyperplasia, drug combination**
Unit / team: **MINT – INSERM U1066 / CNRS 6021**		
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Socio-economic and scientific context :

Intimal hyperplasia (IH) is a complex phenomenon, considered as hypertrophic scarring of the intima of the arterial wall, leading to narrowing of the artery to the point of occlusion (Déglise *Front Physiol* 2023; Lin *Arterioscler Thromb Vasc Biol* 2023). This stenosis or restenosis occurs rapidly after vascular surgery within the anastomosis of a bypass, after arteriotomy, after arteriovenous access for dialysis, or within the dilated zone after an endovascular recanalization technique. This is the major drawback of these common surgical procedures, which has yet not been resolved. The prevalence is high (> 90%), independent of surgical procedure, and has not improved for over 30 years (Miller *Am J Cardiol* 1993; Ruengsakulrach *Circulation* 1999; Cheung *J Am Soc Nephrol* 2017). Attempts at conventional pharmacological therapies have been doomed to failure, whether in the superacute, acute or chronic stages. The only therapeutic outcome is further surgery, which is always risky, invasive and costly (Melnik *Pharmacol Ther* 2022). It's time to think about preventive approaches to limit IH.

Working hypothesis and aims :

The project involves developing a hydrogel-type biomaterial that can inhibit the development of IH after vascular surgery. The biomaterial will be applied to the outer wall of blood vessels by the surgeon after vascular surgery. In order to limit the phenomenon of IH through a preventive action, the biomaterial will be able to sustainably deliver antiproliferative agents such as paclitaxel to limit the proliferation of vascular smooth muscle cells (VSMC). It could also release anti-Lamtor1 and/or pro-Nogo B agents, two signaling factors involved in IH, leading to inflammation, dedifferentiation of VSMC, their proliferation and migration, and the secretion of extracellular matrix into the vessel intima (Liu *Front Cell Dev Biol* 2021; Paszkowiak *Vascul Pharmacol* 2007; Kritz *Mol Ther* 2008), through a combination of siRNA and/or mRNA. This secondary prevention strategy is truly innovative and has never been considered before.

Main milestones of the thesis :

The methodology of this thesis project is based on a translational approach matching with the research activities of the host laboratory. The first part will focus on the formulation of lipid nanoparticles (LNps), with various surface modifications. In addition, LNps will be fluorescently FRET-labeled for distribution studies, and loaded with paclitaxel and/or anti-Lamtor1 siRNA and/or pro-Nogo B mRNA for pharmacological effect. A comprehensive physico-chemical characterization will be carried out. The second part will focus on the interaction of LNps with VSMCs (MOVAS cell line) in normal and IH contexts. After assessing the cytotoxicity of LNps, their internalization will be evaluated, as well as the antiproliferative effect thanks to the encapsulated drugs. A correlation will be established between the characteristics of LNps and cellular responses. The best LNps candidate will be selected for the development of hydrogel-based implants, as already carried out in tMINT laboratory. After their overall physico-chemical characterization, this third part will validate the use of these hydrogels on *ex vivo* (isolated arteries) and *in vivo* (murine model of IH) models. The distribution of LNps in the arterial wall will be assessed as a function of time. In addition, the ability to limit IH in the murine model will be established by anatomopathological analysis, as well as by the study of vascular functions (contraction and relaxation). A correlation between hydrogel stiffness and cellular responses will also be established.

Scientific and technical skills required by the candidate:

The candidate will have scientific and technical knowledges and skills in formulation and characterization of nanoparticles and/or in cell biology and *in vivo* experiments with murine models.

3 publications from the team related to the topic (last 5 years):

- ✓ **Gazaille C, Bozzato E, Madadian-Bozorg N, Mellinger A, Sicot M, Farooq U, Saulnier P, Eyer J, Préat V, Bertrand N, Bastiat G. Glioblastoma-targeted, local and sustained drug delivery system based on an unconventional lipid nanocapsule hydrogel. *Biomater Adv* 2023;153:213549.**
- ✓ **Pitorre M, Gazaille C, Pham LTT, Frankova K, Béjaud J, Lautram N, Riou J, Perrot R, Geneviève F, Moal V, Benoit JP, Bastiat G. Polymer-free hydrogel made of lipid nanocapsules, as a local drug delivery platform. *Materials Science and Engineering: C Materials for Biological Applications* 2021;126:112188.**
- ✓ **Gazaille C, Sicot M, Akiki M, Lautram N, Dupont A, Saulnier P, Eyer J, Bastiat G. Characterization of Biological Material Adsorption to the Surface of Nanoparticles without a Prior Separation Step: a Case Study of Glioblastoma-Targeting Peptide and Lipid Nanocapsules. *Pharmaceutical Research* 2021;38(4):681-691.**

National and international collaborations:

- ✓ **Pr Nicolas Bertrand, Faculté de pharmacie, Centre de recherche du CHU de Québec, Université Laval, Québec (QC), Canada.**
- ✓ **Pr Jean Piquet, Chef de service chirurgie thoracique et vasculaire, CHU d'Angers, Angers, France.**
- ✓ **Dr Sagrario Pascual, IMMM, Le Mans Université, Le Mans, France.**
- ✓ **Dr Daniel Henrion, CarMe / MitoVasc, Université d'Angers, Angers, France.**