Company/laboratory/public institution: Université Paris Cité, UTCBS

Address: Faculté de Pharmacie de Paris, 4 avenue de l'observatoire, 75006 PARIS

Supervision of trainee:

Name of tutor: Karine Andrieux

Position: Full Professor

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Internship period: 20 January - 18 July 2025

Title of the project: Nucleic acid delivery by lipid nanoparticles for preeclampsia treatment

General context and positioning of the project:
Preeclampsia (PE) is a hypertensive disorder of pregnancy associated with placental insufficiency occurring after 20 weeks of gestation. It is one of the major causes of extreme prematurity. There is currently no curative treatment available, and only childbirth and delivery of the placenta alleviate the mother's symptoms.

It is currently considered that preeclampsia is associated with maternal endothelial dysfunction induced by the release into the maternal circulation of a soluble form of the VEGF receptor 1, sFlt-1 in excess. In PE, the overproduction and secretion of sFlt-1 by the syncytiotrophoblast which is in direct contact with maternal blood within the intervillous chamber, leads to a capture of circulating VEGF and PlGF preventing their angiogenic actions in distant organs like the kidney and providing maternal proteinuria and hypertension. The increase of sFlt-1/PlGF ratio is then correlated with the PE severity and its decrease appears a promising therapeutic strategy.
Antisense modified RNA directed against sFlt-1 is an attractive therapeutic option to limit the overproduction of sFlt-1 by the syncytiotrophoblast. sFlt-1 is a family of truncated splice variants of the protein (VEGFR) lacking cytoplasmic and transmembrane domains6. Then the approach is to develop antisense modified RNA such as splice-switching oligonucleotides (SSOs). SSOs are short, synthetic, antisense, modified nucleic acids that base-pair with a pre-mRNA, disrupt the normal splicing step and finally block the production of a protein. Due to their antisense mechanism, SSOs appear promising to develop an antisense strategy against sFlt-1 but at this date, only siRNA sequences have been described in the literature.

Nanocarriers aim to modify the biodistribution of drugs, to increase their efficacy and decrease their side effects by carrying a larger part of these active molecules to the targeted tissues. They allow a protection of the carried degradable drug like nucleic acids, which have a very limited blood half-life. Nanocarriers such as lipid nanoparticles appear as a promising and original strategy to deliver an anti-sFlt-1 SSO to the placenta avoiding a large distribution into the mother's body and a passage into the fetus.

Objectives of the internship:
For this study, the intern will take part in the manufacturing of LNP loaded with anti-sFlt-1 SSO by microfluidics in order to be delivered specifically to the trophoblastic cells of the placenta. During the internship, the challenge is to develop an innovative delivery dosage form, to characterize the newly produced LNP (size, surface charge, lipid dosage), to test their internalization on placental in vitro and ex vivo model and evaluate their silencing efficacy in vitro on a new model yet established based on primary culture using Elisa kit.

Scientific/technical program:
The intern will learn about the diverse laboratory techniques:

- Formulation and characterization of LNP: Microfluidics, Nano SZ, vascoKin
- Cell biology: cell culture (cell line or primary)
- Biochemistry: western blot, Elisa dosage
- Imaging: confocal microscopy
- Analytical chemistry: UHPLC