**THESIS TOPIC**

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| Thesis title: | Development of an innovative therapy based on adiponectin-enriched exosomes for diabetic patients | 3 keywords: | obésité, exosomes, innovative therapy, |

Unit / team: **INSERM UMRS 1063/SOPAM, Angers**

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*Socio-economic and scientific context (approximately 10 lines):*

EXOs, designing small extracellular vesicles exosomes, are recognized as important mediators of long distance intercellular communication. These bilayered-lipid vesicles are involved in a diverse range of biological processes by shuttling molecules between neighboring and distant cells. Many preclinical studies have proven that EXOs constitute efficacious drug delivery vehicles and target a large spectrum of organs. Clinical development using EXO carriers has so far focused on cancers, inflammatory diseases or regenerative medicine. Using exosomal system to deliver active forms of adiponectin - a well-known insulin-sensitizing hormone- in order to treat metabolic diseases such as type 2 diabetes Mellitus (T2DM) is unexplored. Adiponectin therapeutic development has so far been hampered by the difficulties encountered to produce this agent in its native oligomerized active forms. Data obtained from our laboratory demonstrating that fat-derived exosomes (EXOs) are highly enriched in adiponectin oligomers and can counteract obesity-associated IR in mice constitute the scientific basis of this project.

*Working hypothesis and aims (approximately 8 lines):*

**The overall aim of this project** is to develop an innovative pharmacological approach based on exosome delivery to provide metabolic active forms of the insulin-sensitizing fat hormone adiponectin for the treatment of Type 2 Diabetes Mellitus (T2DM), and the associated cardiometabolic morbidities.

**Research hypothesis:** Design of adiponectin or adiponectin-mimicking drugs has been so far hampered by the difficulties encountered to produce this therapeutic agent in its native oligomerized active forms. We previously demonstrated that fat-derived exosomes (EXOs), highly enriched in adiponectin oligomers, can counteract obesity-associated IR in mice constitute the scientific basis of this project.

*Main milestones of the thesis (approximately 12 lines):*

The thesis will articulate around three complementary aspects in order to pave the way for clinical use:

1- Beneficial cardiometabolic outcomes of adiponectin-enriched exosomes on T2DM (Proof-of-concept) This implies, first, to produce exosomes (EXOs) carrying or not adiponectin. Once characterized, investigation of adiponectin-associated EXOs cardiometabolic effects will be investigated.

2- Unraveling mechanisms of beneficial effects induced by exosomes carrying adiponectin in insulin-resistant (IR) animal models (better understand for the translation to the therapeutic use). To this mean, adiponectin-associated exosomes, their targeting and interaction with recipient cells as well as the cellular basis of adiponectin-enriched EXOs benefit will be explored.

3- Design of autologous adiponectin-enriched exosomes for personalized medicine for diabetic patients. In order to pave the way towards clinical translation, a proof of concept therapy for future treatment of insulin-resistance in diabetic patients will be envisaged.

*Scientific and technical skills required by the candidate (2 lines):*

Knowledge in physiology and with notions of physiopathology of obesity. Techniques: cell culture, biochemistry / molecular biology and functional explorations in rodents.

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

1- Extracellular vesicles as biomarkers and bioeffectors of metabolic syndrome.

Le Lay S, Martinez MC, Andriantsitohaina R.


National and international collaborations: