***DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO***

**XXXIX Cycle**

**Project proposal for a PhD scholarship (with no financial support from Sapienza)**

**Title of the research: Role of the extracellular vesicles in the development of muscle insulin resistance associated with metabolic diseases**

**Supervisor:** Luciana Dini (*luciana.dini@uniroma1.it*) / Sophie Rome (sophie.rome@univ-lyon1.fr)

Director of research, head of exosome/miRNA group (Human Nutrition)CarMeN Laboratory (UMR INSERM 1060/INRA 1397), Lyon-Sud Faculty of Medicine, University of Lyon, Pierre-Bénite, France; (possible co-tutored PhD)

**Host Institution:** Dip. Biologia e biotecnologie “Charles Darwin” – Sapienza/CarMeN Laboratory (UMR INSERM 1060/INRA 1397), Lyon-Sud Faculty of Medicine, University of Lyon, Pierre-Bénite, France

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**Summary**

The project studies the interaction between skeletal muscle and immune cells throughthe release of extracellular vesicles (EV) under metabolic stress.

In recent years, macrophage-derived EVs have emerged as vital mediators in immunoregulation, cancer, infections, and tissue repair, and may regulate glucose homeostasis in metabolic disorders characterized by dysregulated insulin secretion and/or signaling in peripheral tissues, such as skeletal muscle (SkM) and adipose tissue. SkM is the main tissue responsible for plasma glucose homeostasis and reduced insulin sensitivity in this tissue, known as insulin resistance (IR), is linked to metabolic diseases occurrence. Several studies have demonstrated that IR is often associated with tissue recruitment and infiltration of immune cells, primarily macrophages. Indeed, EVs derived from pro-inflammatory macrophages induce glucose intolerance and IR in adipocytes, myocytes, and hepatocytes by inhibiting the PPAR-γ signaling, a key modulator of insulin sensitivity. The functions of macrophage-derived EVs in various diseases have been extensively studied, and mounting evidence indicates that these EVs play a key role in disease progression. Therefore, a comprehensive understanding of the role of macrophage-derived EVs in pathologies associated with chronic high glucose and/or with excess of fatty acid is studied:

Aim1By combining co-culture experiments, molecular biochemical analyses andimaging techniques, we will define the effect of EVs released from myotubes onmacrophage activation under lipid overload.

Aim 2 By omics approaches, determining the effects of lipid excess on EV phospholipidcomposition released from myotubes.

Aim3 Investigating the role of the phospholipid component of myotube-derived EVs inthe interaction with recipient macrophages.

Aim4 Studying of the ability of EVs released from muscle cells to cross endothelialbarriers.

Aim5 Comparing *in vitro* results with those obtained by treating myotubes with circEVs isolated from blood of both healthy and diabetic patients (type 2 diabetes).

**Pertinent Publications of the proponent (last 5 years)**

1. [Rome, S.](https://www.scopus.com/authid/detail.uri?authorId=6701621800)[Muscle and Adipose Tissue Communicate with Extracellular Vesicles](https://www.scopus.com/record/display.uri?eid=2-s2.0-85132735363&origin=resultslist&sort=plf-f)[*International Journal of Molecular Sciences*](https://www.scopus.com/sourceid/25879?origin=resultslist), 2022, 23(13), 7052
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