

DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

42° Cycle

Project proposal for a PhD scholarship

Main research line

Title of the research: Exploring extracellular lipid droplets from lipid-storing cells as a novel mechanism of cell-to-cell communication

Supervisor: Dr. Stefano TACCONI (Department of Biology and Biotechnologies "C. Darwin", Sapienza University of Rome)

Co-supervisor: Dr. Sophie ROME (CarMeN Laboratory INSERM-INRAE, University of Lyon)

Summary (max 500 words):

Lipid-based vesicles such as extracellular vesicles (EVs) are important mediators of intercellular communication and play a key role in tissue homeostasis. EVs can shuttle lipids, proteins, and nucleic acids between cells, thereby influencing a wide range of physiological and pathological processes. Among these cargos, the role of EVs in lipid transfer between cells is only beginning to be explored. Recently, triacylglycerols (TGs) have been identified within EVs (ex-TGs), raising the question of a potential functional role for ex-TGs in recipient cells. Indeed, a previous study demonstrated that adipocyte-derived ex-TGs can be transferred to recipient macrophages. In tissues, certain macrophage subpopulations, such as TREM2-positive macrophages, are specialized in tissue clearance and are geared toward lipid uptake and storage, a process that promotes their polarization toward an M2-like phenotype. Therefore, understanding whether ex-TGs contribute to macrophage polarization and immune regulation is of major importance for many pathologies.

Recently, we discovered that fatty acid overload drives THP-1 M0 macrophages toward a LAM-TREM2 phenotype, which is accompanied by the accumulation of lipid droplets (LDs) rather than the utilization of free fatty acids for metabolism. More surprisingly, we found that LAM-TREM2 macrophages can export LDs into their extracellular environment, suggesting for the first time that extracellular LDs may represent a previously unrecognized source of ex-TGs. Whether these ex-TGs exert functional effects on recipient cells represents a fundamental unanswered question, and it remains unclear whether cell types other than macrophages can also export ex-TGs in extracellular LDs (ex-LDs). Based on these observations, we propose this PhD project to (i) establish a robust and reproducible strategies to isolate ex-LD to determine their composition and compare it to the composition of endogenous LDs, (ii) to determine whether LD secretion is a widespread and evolutionarily conserved process across different cell types and species particularly in a cancerous context, (iii) define the role of ex-LDs in transferring ex-TG but also phospholipids into recipient cells, particularly immune cells.

By redefining LDs as extracellular signaling entities, this work has the potential to reshape current understanding of LD biology and uncover new mechanisms linking lipid homeostasis to inflammation, metabolism, and cancer.

Pertinent Publications of the proponent (last 5 years):

- Tacconi S, Jalabert A, Berger E, Cotte C, Errazuriz-Cerda E, Bardot V, Leblanc A, Berthomier L, Dubourdeaux M, Rome S. Microvesicles from Turmeric Extracts Contain Curcuminoids and Modulate Macrophage Polarization and Migration. *Pharmaceutics*. 2025 Dec 3;17(12):1555. doi: 10.3390/pharmaceutics17121555. PMID: 41471070; PMCID: PMC12736489.
- Hakkar R, Brun CE, Leblanc P, Meugnier E, Berger-Danty E, Blanc-Brude O, Tacconi S, Jalabert A, Reininger L, Pesenti S, Calzada C, Gache V, Vasani SB, Pichon J, Larcher T, Errazuriz-Cerda E, Cassin C, Sung BH, Weaver A, Bongiovanni A, Rouger K, de Barros JP, Bouzakri K, Rome S. Sphingolipids in Extracellular Vesicles Released From the Skeletal Muscle Plasma Membrane Control Muscle Stem Cell Fate During Muscle Regeneration. *J Extracell Vesicles*. 2025 Sep;14(9):e70164. doi: 10.1002/jev2.70164. PMID: 40984725; PMCID: PMC12454923.
- Schifano E, Vari F, Buccini L, Karimova M, Syman K, Varnadyan D, Uccelletti D, Dinarelli S, Zuccotti M, Alfieri A, Sennato S, Mura F, Rossi M, Dini L, Tacconi S. A novel scalable method for the production of rennet-treated milk-derived extracellular vesicles for improved curcumin oral delivery. *J Nanobiotechnology*. 2025 Oct 10;23(1):656. doi: 10.1186/s12951-025-03724-0. PMID: 41074180; PMCID: PMC12514809.
- Tacconi S, Giudetti AM, Blangero F, Meugnier E, El-jaafari A, Longo S, Angilè F, Fanizzi FP, Canaple L, Jalabert A, Errazuriz-Cerda E, Cassin C, Zuccotti M, Alfieri A, Da Silva CC, Brun C, Gillet B, Hughes S, Rieusset J, Vidal H, Dini L, Rome S. LAM/TREM2 + macrophages release extracellular vesicles and extracellular lipid droplets which modulate the phenotype of recipient macrophages and homeostasis of skeletal muscle cells. *bioRxiv* 2025.01.26.634912.
- Moliterni C, Vari F, Schifano E, Tacconi S, Stanca E, Friuli M, Longo S, Conte M, Salvioli S, Gnocchi D, Mazzocca A, Uccelletti D, Vergara D, Dini L, Giudetti AM. *Lipotoxicity of palmitic acid is associated with DGAT1 downregulation and abolished by PPARα activation in liver cells*. *J Lipid Res*. 2024 Dec;65(12):100692. doi: 10.1016/j.jlr.2024.100692. Epub 2024 Nov 5. PMID: 39505261; PMCID: PMC11648247.
- Sbarigia C, Rome S, Dini L, Tacconi S. New perspectives of the role of skeletal muscle derived extracellular vesicles in the pathogenesis of amyotrophic lateral sclerosis: the 'dying back' hypothesis. *J Extracell Biol*. 2024 Nov 12;3(11):e70019. doi: 10.1002/jex2.70019. PMID: 39534483; PMCID: PMC11555536.
- Manganelli V, Dini L, Tacconi S, Dinarelli S, Capozzi A, Riitano G, Recalchi S, Caglar TR, Fratini F, Misasi R, Sorice M, Garofalo T. *Autophagy Promotes Enrichment of Raft Components within Extracellular Vesicles Secreted by Human 2FTGH Cells*. *Int J Mol Sci*. 2024 Jun 4;25(11):6175. doi: 10.3390/ijms25116175. PMID: 38892363; PMCID: PMC11172899.
- Tacconi S, Vari F, Sbarigia C, Vardanyan D, Longo S, Mura F, Angilè F, Jalabert A, Blangero F, Eljaafari A, Canaple L, Vergara D, Fanizzi FP, Rossi M, Da Silva CC, Errazuriz-Cerda E, Cassin C, Nieuwland R, Giudetti AM, Rome S, Dini L. *M1-derived extracellular vesicles polarize recipient macrophages into M2-like macrophages and alter skeletal muscle homeostasis in a hyper-glucose environment*. *Cell Commun Signal*. 2024 Mar 27;22(1):193. doi: 10.1186/s12964-024-01560-7. PMID: 38539237; PMCID: PMC10967050.
- Rome S, Tacconi S. High-fat diets: *You are what you eat...your extracellular vesicles too!* *J Extracell Vesicles*. 2024 Jan;13(1):e12382. doi: 10.1002/jev2.12382. PMID: 38151475; PMCID: PMC10752826.
- Sbarigia C, Tacconi S, Mura F, Rossi M, Dinarelli S, Dini L. *High-resolution atomic force microscopy as a tool for topographical mapping of surface budding*. *Front Cell Dev Biol*. 2022 Oct 12;10:975919. doi: 10.3389/fcell.2022.975919. PMID: 36313576; PMCID: PMC9597496.