DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

42° Ciclo

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

Title of the research: Decoding DDR2-β-arrestin-1 circuit to modulate ECM-driven tumor progression and response to chemotherapy in ovarian cancer

Supervisor: Laura Rosanò

Tutor: Prof. Loretta Tuosto

Host Institution: Istituto di Biologia e Patologia Molecolari (IBPM)-CNR

Summary (max 500 words)

Ovarian cancer (OC) remains one of the deadliest gynecological malignancies, largely due to its late diagnosis, and extensive peritoneal spread. Many patients respond initially to chemotherapy with carboplatin and taxol, but the majority eventually relapse due to the development of drug resistance. A key reason behind this poor outcome is that OC grow in a tissue rich in fibrillar collagen collagen, a structural protein mainly secreted by fibroblasts. This collagen-rich, stiff niche profoundly influences cancer cell behavior, promoting epithelial–mesenchymal transition (EMT), invasion, mechanotransduction, and reduced chemotherapeutic efficacy.

This PhD project focuses on two molecules that play important roles in how ovarian cancer cells interact with this collagen-rich environment: DDR2, a receptor on the cell surface that becomes active when it senses fibrillar collagen, and β-arrestin-1, a protein that works both at the cell membrane and in the cell nucleus to control gene expression. In cancer, DDR2 is activated selectively by fibrillar collagen and drives epithelial to mesenchymal transition (EMT), survival, and drug resistance, while β-arr1 modulates transcriptional programs, fibroblast activation, ECM remodeling, and metastatic dissemination in OC. Preliminary data from our laboratory indicate that β-arr1 facilitates Src-dependent DDR2 phosphorylation in both ovarian cancer cells and fibroblasts, and that soluble factors from β-arr1-silenced fibroblasts decrease DDR2 activation in tumor cells, suggesting a bidirectional paracrine feedback mechanism that strengthens tumor/stroma communication.

The overall goal of this project is to understand how the DDR2/β-arrestin-1 axis helps ovarian cancer cells adapt to their environment and resist chemotherapy, and how fibroblasts contribute to this process.

The project is organized into three main objectives:

1. Understand how DDR2 and β-arrestin-1 influence the genetic programs that drive changes, and the transition toward a more invasive, mesenchymal state of OC cells.
2. Determine how these molecules influence the response to chemotherapy (carboplatin and taxol) by inhibiting DDR2 and reducing β-arrestin-1.
3. Investigate the role of fibroblasts and collagen architecture modulate by DDR2/ β-arrestin-1 affect cancer cell invasion, signaling, and drug response.

This project offers comprehensive training in cancer biology, cell-matrix interactions, and advanced laboratory models including 3D cultures. By integrating these approaches, the project aims to identify new mechanisms through which the tumor environment drives ovarian cancer progression and therapy resistance.

Pertinent Publications of the proponent (last 5 years)

1. Trono P, Masi I, Ottavi F, Rosanò L. Decoding collagen cues: the interplay of integrins and discoidin domain receptors in health and disease. J Biomed Sci. 2026;33:8.
2. Masi I, Ottavi F, Caprara V, Rio DD, Kunkl M, Spadaro F, Licursi V, Tuosto L, Bagnato A, Rosano' L. The extracellular matrix protein type I collagen and fibronectin are regulated by β-arrestin-1/endothelin axis in human ovarian fibroblasts. J Exp Clin Cancer Res. 2025; 44:64.
3. Pape J, Cheema U, Tocci P, Sestito R, Masi I, Loizidou M, Bagnato A, Rosanò L. Endothelin-1 receptor blockade impairs invasion patterns in engineered 3D high-grade serous ovarian cancer tumouroids. Clin Sci (Lond). 2024;138: 1441-1450.
4. Del Rio D, Masi I, Caprara V, Ottavi F, Albertini Petroni G, Salvati E, Trisciuoglio D, Giannitelli SM, Bagnato A, Mauri E, Spadaro F, Rosanò L. The β-arrestin1/endothelin axis bolsters ovarian fibroblast-dependent invadosome activity and cancer cell metastatic potential. Cell Death Dis. 2024;15:358.
5. Trono P, Ottavi F, Rosano' L. Novel insights into the role of Discoidin domain receptor 2 (DDR2) in cancer progression: a new avenue of therapeutic intervention. Matrix Biol. 2024;125:31-39.
6. Masi I, Ottavi F, Del Rio D, Caprara V, Vastarelli C, Giannitelli SM, Fianco G, Mozetic P, Buttarelli M, Ferrandina G, Scambia G, Gallo D, Rainer A, Bagnato A, Spadaro F, Rosanò L. The interaction of β-arrestin1 with talin1 driven by endothelin A receptor as a feature of α5β1 integrin activation in high-grade serous ovarian cancer. Cell Death Dis. 2023;14:73.
7. Del Rio D, Masi I, Caprara V, Spadaro F, Ottavi F, Strippoli R, Sandoval P, López-Cabrera M, Sainz de la Cuesta R, Bagnato A, Rosanò L. Ovarian Cancer-Driven Mesothelial-to-Mesenchymal Transition is Triggered by the Endothelin-1/β-arr1 Axis. Front Cell Dev Biol. 2021; 9:764375.
8. Masi I, Caprara V, Spadaro F, Chellini L, Sestito R, Zancla A, Rainer A, Bagnato A, Rosanò L. Endothelin-1 drives invadopodia and interaction with mesothelial cells through ILK. Cell Rep. 2021;34:108800.
9. Masi I, Caprara V, Bagnato A, Rosanò L. Tumor Cellular and Microenvironmental Cues Controlling Invadopodia Formation. Front Cell Dev Biol. 2020;8:584181.