European School of Molecular Medicine

RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname: Ugo Cavallaro

* Affiliation IEO

PHD PROJECT DETAILS

* Title of the proposed project

The new role of Matrix Gla Protein in ovarian cancer stem cells and in their crosstalk with tumor microenvironment

* Short description of the project (up to 300 words)

Ovarian cancer stem cells (OCSC) account for dissemination, recurrence and therapy resistance in OC patient, thus emerging as main players in the high lethality rate of this neoplasm. Yet, very limited knowledge is available on the molecular and functional traits of this cell subpopulation, resulting in the lack of OCSC-targeted therapies. By capitalizing on patient-derived OC models, we have recently discovered Matrix Gla Protein (MGP), a molecule that prevents excessive calcification in the vasculature and in the skeletal apparatus, as a novel driver in OC stemness, which induces the stem-like phenotype in cancer cells and fuels OCSC-dependent tumorigenesis (Nieddu et al, 2023). Furthermore, our patient-derived 3D organotypic setting revealed that MGP (together with other stem-associated genes) is induced in OC cells upon contact with the peritoneal tumor microenvironment (TME), and is required for TME-enhanced stemness (Nieddu et al, 2023).
Building on these observations, the PhD student will explore the molecular mechanisms that underlie the novel role of MGP in OCSC and will define its function as a driver of TME-induced stemness. She/he will investigate the MGP interactome in order to identify candidate partners and pathways that act as MGP effectors in OCSC. These will be functionally validated in a series of cell biological assays as well as in *in vivo* models of OCSC-driven tumor development. Such a strategy is also expected to unveil potential vulnerabilities to be harnessed for OCSC-targeted treatments.
Furthermore, the student will employ patient-derived models, such as organotypic co-cultures, to define the functional role of MGP in the crosstalk between OCSC and the TME and will explore by multi-omics the molecular changes imparted by MGP on OCSC in the context of the TME niche.
This project is expected to advance our knowledge on ovarian cancer biology and to set the stage for innovative therapeutic treatments for such a devastating disease.

* Indicate the main research area for the project described above Cancer Biology

If needed indicate a second research area for the project described above Molecular & Cellular Biology

* Provide up to 3 key words for project:

Ovarian cancer; cancer stem cells; tumor microenvironment

YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

Molecular oncology of ovarian cancer; Pathophysiology of ovarian cancer stem cells; Tumor/microenvironment crosstalk.

* Short description of the lab activity (up to 500 words)

The Cavallaro lab has a long-standing interest in ovarian cancer (OC), with the ultimate objectives of unraveling the biological mechanisms that drive the aggressiveness of the disease and identifying vulnerabilities that could open new treatment approaches. The lab is pursuing such objectives through two main research lines.

1) Ovarian cancer stem cells (OCSC). OCSC have emerged as causal factors in OC progression, fueling tumor initiation, dissemination, relapse and therapy resistance. The lab is applying multi-omics strategies to investigate the molecular makeup of OCSC and a broad spectrum of molecular/cell biology methods to dissect their functional features.

2) Tumor/microenvironment crosstalk. The tumor microenvironment (TME) of OC modulates most aspects of neoplastic behavior, while at the same time cancer cells “educate” the TME towards a pro-tumoral niche. Yet, the molecular players and pathways that drive or are modulated by this interplay remain largely uncharacterized, and this is particularly true for the crosstalk of TME with OCSC. We have set up in vitro and in vivo models to mimic this crosstalk, and are currently applying them to investigate the interaction of OCSC with the peritoneal TME as well as with the vascular compartment. In this regard both systems-level (omics) and high-resolution studies are being carried out to identify and validate the determinants of the OCSC/TME interplay.

For the implementation of these studies, the Cavallaro lab capitalizes on a wide array of experimental settings, ranging from cell lines to patient-derived models (primary cells, organotypic co-cultures, mouse xenografts). The latter are routinely established thanks to the long-standing collaboration with the clinical staff of the Program of Gynecology at IEO (which includes the lab itself). This enables the group to address outstanding scientific and clinical questions in disease-relevant settings, thus increasing the translational value and the applicability of the results.

* Recent bibliography (max 5 references)

1. Franciosa G, Nieddu V, Battistini C, Caffarini M, Lupia M, Colombo N, Fusco N, Olsen JV, and **Cavallaro U.** (2025) Quantitative proteomics and phosphoproteomics analysis of patient-derived ovarian cancer stem cells. *Mol Cell Proteomics*, 24(5):100965. doi: 10.1016/j.mcpro.2025.100965.
2. Battistini C, Kenny HA, Nieddu V, Melocchi V, Decio A, Gatto A, Ghioni M, Porta FM, Giavazzi R, Colombo N, Bianchi F, Lengyel E, and **Cavallaro U.** (2024) Tumor microenvironment-induced FOXM1 regulates ovarian cancer stemness. *Cell Death Dis*, doi: 10.1038/s41419-024-06767-7.
3. Nieddu, V., Melocchi V., Battistini C., Franciosa G., Lupia M., Stellato C., Bertalot G., Olsen J.V., Colombo N., Bianchi F., and **Cavallaro U.** (2023) Matrix Gla Protein drives stemness and tumor initiation in ovarian cancer. *Cell Death Dis*, 14:220. doi: 10.1038/s41419-023-05760-w.
4. Battistini C. and **Cavallaro U.** (2023). Patient-Derived In Vitro Models of Ovarian Cancer: Powerful Tools to Explore the Biology of the Disease and Develop Personalized Treatments. *Cancers*, 15:368. doi: 10.3390/cancers15020368.
5. Lupia M., Melocchi V., Bizzaro F., Lo Riso P., Dama E., Baronio M., Ranghiero A., Barberis M., Bernard L., Bertalot G., Giavazzi R., Testa G., Bianchi F., and **Cavallaro U** (2022). Integrated molecular profiling of patient-derived ovarian cancer models identifies clinically relevant signatures and tumor vulnerabilities. *Int J Cancer*, 151(2):240-254. doi: 10.1002/ijc.33983.

* Group composition: total members, and roles distribution (PhD, postdoc, technician, etc.)

Total members: 11 (4 postdocs; 1 PhD student; 3 junior fellows; 1 bioinformatician; 2 research technicians)

Institutional page link

https://www.research.ieo.it/research-and-technology/principal-investigators/unit-of-gynecological-oncology-research/

Lab website link, if any

N.A.

Social media links, if any

https://www.linkedin.com/in/ugo-cavallaro-87454524/

If you prepare a video to promote your lab/project, please include the link below

N.A.