

<b>Principal Investigator</b>	<b>TAMAGNONE LUCA</b>
<b>Institute of Affiliation</b>	Università Cattolica del Sacro Cuore
<b>Title of the proposed project:</b>	Extracellular Vesicle-Mediated Tumor Evolution and Adaptive Resistance in Advanced High-Grade Serous Ovarian Cancer
<b>Short description of the project</b>	<p>High-Grade Serous Ovarian Carcinoma (HGSOC) remains the deadliest gynecological malignancy, mainly due to extensive peritoneal dissemination, intra-tumoral heterogeneity, and the frequent developing of platinum-based chemotherapy resistance (PMID 37220750). Despite therapeutic advances, biomarkers able to predict aggressive disease behavior, therapy adaptation, and early relapse are still lacking. Increasing evidence suggests that chemoresistance is not primarily driven by genomic alterations, but is instead shaped predominantly by dynamic programs of cellular plasticity and tumor microenvironment (TME)-mediated signalling (PMID 37474499). Extracellular vesicles (EVs) from patient-derived biological fluids are emerging as promising tools to longitudinally capture adaptive resistant mechanism (PMID 41904344). We hypothesize that platinum-based chemotherapy reshapes EV-mediated communication within the peritoneal tumor ecosystem, promoting cellular states associated with disease progression and treatment failure. By comparing matched chemo-naïve and post-treatment ascitic fluid samples, we aim to identify EV-associated molecular signatures of tumor adaptation and uncover therapeutic vulnerabilities. This project aims to investigate the role of EVs in HGSOC evolution (FIGO 2014 stage III-IV) through a unique translational platform established at Università Cattolica/Poliniclinico Gemelli IRCCS. The hosting lab has collected over 270 ascitic fluid samples from advanced HGSOC patients since 2023 (NCT05067283) and is currently expanding a longitudinal cohort of matched chemo-naïve and post-treatment samples. These resources provide an exceptional opportunity to characterize dynamic changes associated with platinum exposure. The PhD candidate will contribute to the molecular characterization of EVs isolated from ascitic fluid, through integrated proteomic, transcriptomic, and single-cell/single-vesicle approaches, with the aim of identifying EV-associated signatures linked to therapy adaptation, metastatic progression, and unfavorable clinical outcomes. Patient-derived HGSOC cells and 3D-culture models will provide a complementary platform to support the biological interpretation of EV-associated molecular signatures (PMID 41731502; 41520487). This project aims to identify clinically relevant biomarkers and actionable mechanisms to improve risk stratification and identify novel therapeutic opportunities for patients with aggressive HGSOC.</p>
<b>Main research area for the project</b>	Cancer Biology

**5 keywords for the project**

Response and/or resistance to therapy - Ovarian ca. - Spheroids/3D cultures - Exosomes and/or endogenous microvesicles - Liquid biopsy

**LAB INFO**

**Main topic/s of the lab**

Molecular mechanisms controlling cancer progression and metastasis

**Short description of the lab activity**

Our lab studies novel molecular mechanisms controlling tumor progression. In previous years, the lab has discovered several novel signaling cascades active in the tumor microenvironment and controlling cancer cell behavior, angiogenesis, tumor inflammation, drug responsiveness and metastasis. In particular, the lab is at the forefront of research in semaphorin/plexin field at the international level. By exploiting experimental models in culture and in vivo, we previously shown that these signals regulate multiple steps of tumor progression, validating their relevance as targets for molecular therapy. Luca Tamagnone currently holds an H-index of 62, and his publications in peer-reviewed journals have so far gained over 17,000 citations (Google Scholar). In these years, he has supervised 16 PhD students and 19 Post-doctoral fellows in cancer biology field; at least six of these former trainees have become independent scientists in foreign institutions (in USA, UK, France, Belgium, Sweden, Spain). The Tamagnone lab is an international context, including foreign students and post-docs, and English is the official language for scientific reports and meetings. The laboratories and study rooms have been completely refurbished. The lab has access to state-of-the-art facilities at the Gemelli Science and Technology Park (<https://gstep.policlinicogemelli.it/#/VetrinaFacilities>). Notably, the presence of other groups, active in neuroscience and aging research, in the same university division led by Luca Tamagnone, ensures methodological cross-fertilization and scientific exchange in molecular medicine investigation. He is currently also the director of the Liquid Biopsy Facility on the campus. In recent years, the lab has been leading four collaborative studies, concerning: the role of PlexinB2 in metastatic cancers of unknown primary (Brundu et al., 2023), a Sema6C-dependent pathway controlling cancer cell viability (Fard et al., 2023), the role of PlexinB1 in the regulation of immune response in breast cancer microenvironment (Franzolin et al, 2024), and Neuropilin1-dependent control of the cargo of extracellular vesicles released by cancer cells (Palazzo et al, 2025). In the last three years the lab has been focusing on ovarian cancer, in collaboration with the gynecological oncology department at the Policlinico Gemelli Research Hospital. In particular, through an ongoing clinical trial, we have established a large collection of ascitic fluid liquid biopsies, yielding patient-derived HGSOC cellular models in culture and purified extracellular vesicles stocks. These samples are currently used for omic profiling, which will be correlated with clinical followup

	<p>data, to identify prognostic/predictive biomarkers (e.g. of drug-responsiveness) and putative novel targets for innovative therapeutic approaches. In vivo models in mice will be used for preclinical validation, including syngeneic murine cells transplanted in immunocompetent mice, and patient-derived xenograft platforms in immunodeficient mice.</p>
<b>Recent bibliography</b>	<p>Mutated axon guidance gene PLXNB2 sustains growth and invasiveness of stem cells isolated from cancers of unknown primary. <i>EMBO MOL MED</i> 2023 Mar; 15: e16104</p> <p>SEMA6C: a novel adhesion-independent FAK and YAP activator, required for cancer cell viability and growth. <i>CELL MOL LIFE SCI</i> 2023 Mar; 80: 111</p> <p>PlexinB1 inactivation reprograms immune cells in the tumor microenvironment, inhibiting breast cancer growth and metastatic dissemination. <i>CANCER IMMUNOL RES</i> 2024 Sep; 12: 1286</p> <p>Neuropilin1-dependent paracrine signaling of cancer cells mediated by miRNA exosomal cargo. <i>CELL COMMUN SIGNAL</i> 2025 Jan; 23: 54</p> <p>Single-cell transcriptome analysis of patient-derived organoids captures inter- and intratumor heterogeneity and uncovers targetable pathways in high grade serous ovarian cancer. <i>DRUG RESIST UPDATE</i> 2026 Mar; 85: 101354</p>
<b>Group composition</b>	<p>4 Postdocs 3 PhD students 2 undergraduate students 2 Technicians</p>
<b>Institutional page link</b>	<p><a href="https://docenti.unicatt.it/ppd2/it/docenti/59412/luca-tamagnone/profilo">https://docenti.unicatt.it/ppd2/it/docenti/59412/luca-tamagnone/profilo</a></p>