

 <p>UniSR Università Vita-Salute San Raffaele</p>	<p>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</p>	<p>MO 20-5 ed. 01 del 21/02/2025 PO 20 Page 4 of 9</p>
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PROJECT

Supervisor: Prof. Alberto Briganti

Title: Exploiting the Role of Extracellular Vesicles in Modulating the Tumor Microenvironment: An Innovative Approach in Prostate Cancer.

Curriculum: Clinical and Experimental Medicine

Link to the personal page of the University or relevant hospital site website: __ <https://www.unisr.it/docenti/b/briganti-alberto> __

Description of the Project (max 3,000 characters including spaces)

Background and gap of knowledge

Prostate cancer (PCa) is the most common malignancy in men and a major cause of cancer-related death. High-risk PCa is particularly aggressive and creates an immunosuppressive tumor microenvironment (TME), limiting the effectiveness of current therapies (1). Despite advances in diagnosis and treatment, the mechanisms driving immune evasion and progression in high-risk PCa are not fully understood (2, 3). Innovative strategies are needed to address this gap and improve clinical outcomes (4).

Rationale and hypothesis

Extracellular vesicles (EVs) are key mediators of cancer progression, transferring proteins, RNA, and metabolites that influence cell communication and the TME (5). Tumor-derived EVs (TDEVs) support tumor growth and immune suppression (6). In PCa, expressed prostatic secretion (EPS)-urine is enriched with prostate-specific EVs, offering a valuable source for exploring their role in tumor biology.

Objectives and aims

This project investigates the role of prostate-derived EVs in high-risk PCa, with the goal of translating these findings into therapeutic applications (7). The study is divided into three aims.

Aim I focuses on the deep molecular characterization of prostate-specific EVs. By isolating EVs from EPS-urine using prostate-specific markers, we aim to reduce sample heterogeneity and improve specificity. Samples from patients with clinically significant and non-significant PCa (n=40 each) will be analyzed. Cutting-edge platforms such as the Cellenion CellenOne and the Orbitrap



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Università Vita-Salute
San Raffaele

**APPLICATION TO ACT AS SUPERVISOR AND
RESEARCH PROJECT PROPOSAL**

MO 20-5
ed. 01 del 21/02/2025
PO 20
Page 5 of 9

Astral mass spectrometer will be used for high-sensitivity multi-omics, including transcriptomic profiling. This will provide a comprehensive molecular map of prostate-derived EVs and identify candidate biomarkers and signaling pathways involved in disease progression (8).

Aim II validates the tumorigenic and immunomodulatory potential of these EVs in patient-derived xenograft (PDX) models. EVs from PCa patients will be tested on PDX-derived cells, with and without co-cultures of immune cells, to assess their effects on T-cell function and tumor growth. We will examine their interaction with MDSCs and TAMs, evaluating immune-suppressive mediators such as CD73, CD39, IL-6, and TGF- β . Functional assays and single-cell transcriptomics will be used, alongside pharmacological inhibition of the purinergic signaling pathway, to identify therapeutic targets.

Aim III explores the development of engineered EVs (engEVs) as targeted therapeutic tools (9). EVs will be bioengineered to display PSMA-binding peptides and deliver inhibitors of purinergic signaling identified in Aim II. These engEVs will include pH-sensitive components for tumor-specific release and will be produced in bioreactors. Their efficacy in modulating the TME, restoring immune response, and halting tumor progression will be tested in PDX models.

Expected outcomes

This project will provide new insights into the role of EVs in PCa progression and immune evasion. By combining in-depth EV profiling with functional validation and therapeutic engineering, it aims to support the development of innovative diagnostic and immunotherapeutic approaches for high-risk PCa.

Skills that the student should acquire (max. 600 characters including spaces):

The student will gain expertise in extracellular vesicle isolation, single-cell transcriptomics, proteomics, and multi-omics integration. They will develop skills in advanced technologies such as mass spectrometry and EV engineering, and gain hands-on experience with patient-derived xenograft models and immune cell co-cultures. The project will also enhance competencies in cancer biology, immunology, and translational research methodologies.

References (max. 15)

- 1 The Tumor Microenvironment and Immune Responses in Prostate Cancer. Jennifer L Bishop et al. *Nature Reviews Urology*, 2021.
- 2 How to Turn Up the Heat on the Cold Immune Microenvironment of Prostate Cancer. S. M. Sha et al. *Prostate Cancer and Prostatic Diseases*, 2021
- 3 The Immune Microenvironment in Prostate Cancer. M. A. Sfanos et al. *Cancer Immunology Research*, 2023
- 4 Prostate Cancer Reshapes the Secreted and Extracellular Vesicle Protein Landscape" A. M. Thind et al. *Nature Communications*, 2023
- 5 Extracellular Vesicles and Prostate Cancer Management. R. L. Delk et al. *Journal of Extracellular Vesicles*, 2022.



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San Raffaele

**APPLICATION TO ACT AS SUPERVISOR AND
RESEARCH PROJECT PROPOSAL**

MO 20-5

ed. 01 del 21/02/2025

PO 20

Page 6 of 9

6 Tumor-Derived Extracellular Vesicles Predict Clinical Outcomes in Prostate Cancer. I. Vardaki et al. *Clinical Cancer Research*, 2021.

7 Engineered Extracellular Vesicles: A New Approach for Targeted Cancer Therapy. Y. Wu et al. *Journal of Nanobiotechnology*, 2023.

8 Extracellular Vesicles as a Source of Prostate Cancer Biomarkers in Liquid Biopsies. M. Sequeiros et al. *British Journal of Cancer*, 2021.

9 Engineered Extracellular Vesicles as a Targeted Delivery Platform for Overcoming Drug Resistance in Cancer. C. Baulch et al. *Journal of Nanobiotechnology*, 2023