

 <p>UniSR Università Vita-Salute San Raffaele</p>	<p>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</p>	<p>MO 20-5 ed. 02 of 16/01/2026 PO 20 Page 5 of 12</p>
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PROJECT

Supervisor: Rosanna Mezzapelle

Title: Investigating the role of TGF- β in mesothelioma pathogenesis

Curriculum: Cell and Molecular Biology

Link to the personal page of the University or relevant hospital site website: <https://research.hsr.it/en/divisions/genetics-and-cell-biology/chromatin-dynamics.html>

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

Background/gap of knowledge

Pleural mesothelioma (PM) is a rare and highly aggressive malignancy arising from mesothelial cells lining the pleural cavity and is strongly associated with chronic inflammation induced by asbestos exposure¹. Pleural mesothelioma is a highly heterogeneous disease, classified into epithelioid, biphasic, and sarcomatoid subtypes. These subtypes differ significantly in clinical behavior, prognosis, and therapeutic response¹. A key hallmark of mesothelioma is the presence of a complex and immunosuppressive tumor microenvironment (TME)², characterized by abundant cancer-associated fibroblasts (CAFs)³, tumor-associated macrophages (TAMs)⁴, and dense extracellular matrix deposition. Among the molecular regulators of tumor-stroma-immune interactions, Transforming Growth Factor- β (TGF- β) plays a central role. Another critical mediator of mesothelioma pathogenesis is HMGB1⁵, a damage-associated molecular pattern (DAMP) molecule actively secreted by tumor cells and released by dying cells. HMGB1 promotes chronic inflammation, supports tumor cell survival, and modulates immune responses^{6,7}.

Rationale and hypothesis

We hypothesize that TGF- β acts as a master regulator of mesothelioma tumor microenvironment remodeling by orchestrating interactions between tumor cells, fibroblasts, and immune populations, contributing to tumor progression and immune suppression.

Furthermore, we hypothesize that HMGB1 cooperates with TGF- β signaling to promote tumor cell plasticity and mesothelial-mesenchymal transition (MMT).

Objectives and specific aims



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This project addresses key questions related to the role of TGF- β in shaping the mesothelioma tumor microenvironment. It will define the principal cellular sources of TGF- β and elucidate how this pathway orchestrates the crosstalk among tumor cells, fibroblasts, and macrophages. Furthermore, it will investigate the functional interplay between TGF- β and HMGB1 in driving immune evasion and mesothelial-mesenchymal transition. Finally, it will evaluate whether targeting TGF- β can enhance the efficacy of immune checkpoint blockade.

Expected outcomes

This project is expected to generate a comprehensive and physiologically relevant understanding of the mesothelioma tumor microenvironment (TME), integrating multicellular modelling, molecular analysis, and in vivo validation.

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

The student will learn how to organize his work and his time, to think critically, to plan his/her experiments and solve and overcome problems.

He/she will work with cancer models developed in-house, including mice and 3D in vitro models; learn about immune responses to cancer and how to measure them using multiple assays, primarily flow cytometry and cell imaging.

He/she will work with a multi-disciplinary team involving bioinformaticians, pathologists and thoracic surgeons.

He/she will learn to present results to different audiences.

References (max. 15)

1. Brcic L, Kern I. Clinical significance of histologic subtyping of malignant pleural mesothelioma. *Transl Lung Cancer Res.* 2020 Jun;9(3):924-933. doi: 10.21037/tlcr.2020.03.38.
2. Désage, A.L., The Immune Microenvironment of Malignant Pleural Mesothelioma: A Literature Review. *Cancers* 2021, 13, 3205. doi:10.3390/cancers1313320
3. Obacz, J. et al. Single-cell transcriptomic analysis of human pleura reveals stromal heterogeneity and informs in vitro models of mesothelioma. *European Respiratory Journal* 63, 2300143 (2024); doi: 10.1183/13993003.00143-2023.



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4. Wu L., Defining and targeting tumor-associated macrophages in malignant mesothelioma. *Proc Natl Acad Sci U S A.* 2023 Feb 28;120(9):e2210836120. doi: 10.1073/pnas
5. Cottone L., Leukocytes recruited by tumor-derived HMGB1 sustain peritoneal carcinomatosis. *Oncoimmunology.* 2016 Jan 8;5(5):e1122860. doi: 10.1080/2162402X.2015.1122860.
6. Jube S., Cancer Cell Secretion of the DAMP Protein HMGB1 Supports Progression in Malignant Mesothelioma. *Cancer Res;* 72(13) July 1, 2012 doi: 10.1158/0008-5472.CAN-11-3481.2210836120.
7. Mezzapelle R., CXCR4 engagement triggers CD47 internalization and antitumor immunization in a mouse model of mesothelioma. *EMBO Mol Med.* 2021 Jun 7;13(6):e12344. doi: 10.15252/emmm.202012344.