PROJECT

Supervisor: _____ Prof Lorenzo Piemonti _____

Title: REPROGRAMMING THE IMMUNE METASTATIC NICHE IN PANCREATIC CANCER THROUGH MSC-MEDIATED CHEMOTHERAPY DELIVERY

Curriculum: Molecular Medicine / Basic and Applied Oncology

Link to the personal page of the University or relevant hospital site website: https://www.unisr.it/en/docenti/p/piemonti-lorenzo

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

Background/gap of knowledge

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, largely due to its resistance to immunotherapy. This resistance is driven by low tumor immunogenicity, a dense stromal barrier, and a highly immunosuppressive tumor microenvironment that limits T-cell infiltration and function. These challenges are exacerbated in liver metastases, where intrinsic hepatic immune tolerance further impairs effective anti-tumor immunity. Current treatments rely on systemic chemotherapy, which offers limited efficacy and significant toxicity. Thus, there is a critical need for strategies that both enhance drug delivery and reprogram the immune microenvironment of metastatic lesions.

Rationale and hypothesis

Mesenchymal stem cells (MSCs) represent a promising tumor-targeting platform due to their ability to home to tumor sites and deliver therapeutic agents locally. Preliminary data demonstrate that intraportal administration of MSCs loaded with nab-paclitaxel (MSC-n-PTX) significantly reduces liver metastases while minimizing systemic toxicity and promoting $CD8^+$ T-cell infiltration. We hypothesize that MSC-mediated chemotherapy delivery not only enhances local drug concentration but actively reshapes the metastatic niche, restoring T-cell function and enabling immune-mediated tumor control.

Objectives and specific aims

This project aims to define the immunological and therapeutic impact of MSC-n-PTX in metastatic PDAC through three objectives:

1.To determine whether therapeutic efficacy depends on adaptive immunity by comparing responses in immunodeficient and T-cell-depleted models, thereby distinguishing immune-mediated effects from direct cytotoxicity.

2.To assess whether MSC-n-PTX sensitizes tumors to immune checkpoint blockade by evaluating combination therapy with anti–PD-1, focusing on $CD8^+$ T-cell functionality, exhaustion, and survival outcomes.

3.To validate the translational robustness of this approach in clinically relevant models (Ferrara et al. Ann Surg Oncol, 2024), including primary tumors with multi-organ metastases, and to assess whether immune reprogramming extends beyond the liver.

Expected outcomes

This study is expected to demonstrate that MSC-mediated drug delivery acts as an immune-converting strategy rather than solely a chemotherapeutic approach. We anticipate defining a central role for $CD8^+$ T cells in therapeutic efficacy, showing that MSC-n-PTX can overcome immune resistance and synergize with checkpoint inhibitors. Validation in complex metastatic models will support the translational potential of this strategy, providing a strong rationale for clinical development of MSC-based combinatorial immunotherapy in PDAC.

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

The PhD student will gain expertise in metastatic PDAC preclinical models and develop technical skills in the following areas: in vitro studies (tumor and MSC cell culture, MSC characterization and drug loading), in vivo studies (such as animal handling, tumor induction, treatments with MSCs, IVIS), and ex vivo studies (IF, IHC, FACS, transcriptomics). He/she will acquire the ability to: i) independently design experiments for combination treatments; ii) analyze data obtained from the study of TME using rigorous statistical methods; iii) scientifically write abstracts and articles.

References (max. 15)

1- Siegel RL, CA Cancer J Clin. 2025 PMID: 39817679
2- Ju Y, NP J Precis Oncol. 2024 PMID: 39266715
3- Kung HC, Nat Rev Clin Oncol. 2025 PMID: 41044427
4- Yu J, Nat Med. 2021 PMID: 33398162
5- Nichetti F, JAMA Netw Open. 2024 PMID: 38190183
6- Sensebé L, Stem Cell Res Ther. 2013 PMID: 23751270
7- Aravindhan S, Cancer Cell Int. 2021 PMID: 33685452
8- Ferrara B, Ann Surg Oncol. 2024 PMID: 38869763