DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

41st CYCLE
Project proposal for a Sapienza PhD scholarship

Main research line

Title: Novel immunotherapeutic strategies for high-grade serous ovarian cancer.

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Summary
High-grade serous ovarian cancer (HG-SOC) is plagued by high rates of recurrence and rapid intraperitoneal dissemination. Despite HG-SOC exhibits an immunoreactive phenotype with tumour-infiltrating T lymphocytes (TILs), the response rates to immunotherapy based on immune checkpoint blockade have been disappointing. Recombinant bispecific antibodies (BsAbs) are now emerging as the next generation of immunotherapeutic approaches with the potential to improve clinical efficacy and safety of cancer immunotherapy. Tumour-targeted immunomodulatory BsAbs binding a tumour-associated antigen and CD28 costimulatory receptor on T cells stimulate only tumour infiltrating and tumour-specific effector T cells, and can promote T-cell cytotoxicity and long-term immunological memory. Recent studies have also shown that modifying the properties of the extracellular matrix (ECM) not only favours tumour progression, but also creates an immunosuppressive tumour microenvironment (TME), which affects the recruitment of TILs and the immune response. In this context, the collagen receptors discoidin domain receptors (DDRs), contribute to immune evasion by remodelling the collagen-enriched TME and the depletion of DDR2 increases sensitivity to anti-programmed cell death protein 1 (PD-1) immunotherapy.
HG-SOC also expresses a unique oncobioma characterized by the enrichment of pathogenic bacteria, including *Staphylococcus aureus*, which up-regulate the production of inflammatory cytokines and chemokines. Interestingly, Staphylococcus aureus produces toxin superantigens (SAgs), which bind the T cell receptor (TCR) and CD28 costimulatory molecule on T cells, thus stimulating the production of inflammatory cytokines and chemokines, which through NF-κB and STAT3 transcription factors may promote epithelial to mesenchymal transition (EMT). In this context, we recently identified a mimetic peptide that targets the CD28/SAgs interface resulting effective in inhibiting inflammatory cytokine production and EMT in cancer cells.
This project aims to develop novel immunotherapeutic strategies based on CD28xMUC1 BsAbs in combination with DDR2 blockade, in a reliable immunocompetent preclinical platform. In addition, how inflammatory T cells and SAgs empower metastatic HG-SOC cells and the inhibitory effects of mimetic peptide the will be also characterized.
Our proposal provides an innovative strategy for developing a novel immunotherapeutic tool for ovarian cancer and will provide the pre-clinical data required for further translation in animal models.

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Pertinent Publications of the proponent

1. Kunkl M, Amormino C, Spallotta F, Caristi S, Fiorillo MT, Paiardini A, Kaempfer R, Tuosto L. Bivalent binding of staphylococcal superantigens to the TCR and CD28 triggers inflammatory signals independently of antigen presenting cells. Front Immunol. 2023 May 3;14:1170821. doi: 10.3389/fimmu.2023.1170821.
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