DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

40th CYCLE
Project proposal for a Sapienza PhD scholarship

Main research line

Title: Bispecific antibodies targeting CD28 and MUC1 for improving ovarian cancer Immunotherapy

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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.
This project aims to develop novel immunotherapeutic strategies based on the administration of CD28xMUC1 BsAbs in a free form and as decoration of ad-hoc nanoparticles (NGs) in combination with DDR2 blockade, in a reliable immunocompetent preclinical platform. By using HG-SOC cells, T cells, and 3D organotypic models, our specific aims will be to:
Aim 1. Assess the efficacy of combinatory CD28xTAA BsAbs and DDR2 inhibitor, as free therapeutics and as functionalization of engineered polymer nanoparticles, on tumour-specific T cell responses as well as on HC-SOC growth and progression, alone or in combination with anti-PD-1 Abs (nivolumab).
Aim 2. Evaluate the efficacy of combinatory CD28xTAA BsAbs and DDR2 inhibitor on human tumour-immune system interactions as well as on tumour growth, progression and invasion in organotypic HG-SOC. 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.

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.
2. Kunkl M, Amormino C, Tedeschi V, Fiorillo MT, Tuosto L. Astrocytes and inflammatory T helper cells: a dangerous liaison in Multiple Sclerosis. Front Immunol. 2022 Feb 8;13:824411. doi: 10.3389/fimmu.2022.824411.
3. Kunkl M, Amormino C, Caristi S, Tedeschi V, Fiorillo MT, Levy R, Popugailo A, Kaempfer R, Tuosto L. Binding of Staphylococcal Enterotoxin B (SEB) to B7 Receptors Triggers TCR- and CD28-Mediated Inflammatory Signals in the Absence of MHC Class II Molecules. Front Immunol.2021 Aug 13;12:723689. doi:10.3389/fimmu.2021.723689.
4. Kunkl M, Amormino C, Frascolla S, Sambucci M, De Bardi M, Caristi S, Arcieri S, Battistini L,Tuosto L. CD28 Autonomous Signaling Orchestrates IL-22 Expression and IL-22-RegulatedEpithelial Barrier Functions in Human T Lymphocytes. Front Immunol. 2020 Oct 14;11:590964.doi: 10.3389/fimmu.2020.590964.
5. Bucci E., Andreev K., Bjorkman A., Calogero R. A., Carafoli E., Carninci P., Castagnoli P., Cossarizza A., Mussini C., Guerin P., Lipworth B., Sbardella G., Stocki T., Tuosto L., van Tulleken C., Viola A. Safety and efficacy of the Russian COVID-19 vaccine: more information needed. Lancet. 2020 Oct 3;396(10256):e53. doi: 10.1016/S0140-6736(20)31960-7.
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9. Kunkl M, Mastrogiovanni M, Porciello N, Caristi S, Monteleone E, Arcieri S, Tuosto L. CD28 Individual Signaling Up-regulates Human IL-17A Expression by Promoting the Recruitment of RelA/NF-κB and STAT3 Transcription Factors on the Proximal Promoter. Front Immunol. 2019 Apr 24;10:864. doi: 10.3389/fimmu.2019.00864. eCollection 2019.
10. Porciello N, Grazioli P, Campese AF, Kunkl M, Caristi S, Mastrogiovanni M, Muscolini M, Spadaro F, Favre C, Nunès JA, Borroto A, Alarcon B, Screpanti I, Tuosto L. A non-conserved amino acid variant regulates differential signalling between human and mouse CD28. Nat Commun. 2018 Mar 14;9(1):1080. doi: 10.1038/s41467-018-03385-8.

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2. Bobisse, S., Genolet, R., Roberti, A., Tanyi, J.L., Racle, J., Stevenson, B.J., et al. Sensitive and frequent identification of high avidity neo-epitope specific CD8 (+) T cells in immunotherapy-naive ovarian cancer. Nat Commun (2018) 9:1092. doi: 10.1038/s41467-018-03301-0
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