Targeting arginase 2 to disrupt the immunosuppressive tumour microenvironment and promote gastric cancer response

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer death worldwide. Immunotherapy based on immune checkpoint inhibitors has undoubtedly revolutionized the treatment of some previously incurable cancers and has become one of the mainstays of innovation in cancer therapy [1]. However, only a small percentage of patients can benefit from immunotherapy due to the establishment of resistance mechanisms related to the type of tumour microenvironment that develops [2-4]. Recently, it has been reported that melanoma-associated fibroblasts impair CD8+ T-cell function and modify the expression of immune checkpoint regulators through increased arginase enzyme (ARG) activity [5]. In addition, ARG enzyme isoform 2 (ARG2) controls the metabolic fitness of regulatory T cells and correlates with their immunosuppressive function in cancer [5]. ARG2 is therefore a valuable target for T-cell-based cancer immunotherapies.

The aim of the present project is the design, synthesis, physicochemical characterization, and biological evaluation of new and more potent inhibitors targeting ARG2 to slow down the establishment of an immunosuppressive milieu in the tumour microenvironment and to forest the gastric cancer-specific immune response. The identification of new drugs targeting ARG2 would aid disease management, improve the success rate of immunotherapies, and contribute to the development of new patient-centred personalized therapies that can also be adapted to other tumour types.

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