Universidad de Navarra
Facultad de Ciencias

MÁSTER EN INVESTIGACIÓN BIOMÉDICA
Research Project Proposal
Academic year 2026-2027

Project Nº 63

Title: Combining mesothelin/CD3 and EGFR/4-1BB BiTEs to overcome T cell coinhibition in the mesothelioma tumor microenvironment: a dual signal approach

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Summary Mesothelioma is an aggressive malignancy with limited therapeutic options and poor prognosis. The recent approval of nivolumab plus ipilimumab as first-line therapy—the first meaningful advance in this disease in decades—has demonstrated that immunotherapy holds real potential in mesothelioma, encouraging the development of novel strategies to further harness T cell antitumor activity. However, T cell-based approaches remain limited by the highly immunosuppressive tumor microenvironment (TME), dominated by coinhibitory signals that impair T cell function and persistence. This project aims to evaluate whether tumor-restricted 4-1BB costimulation via an EGFR/4-1BB BiTE can potentiate mesothelin/CD3 BiTE-mediated T cell activation and antitumor activity in mesothelioma. The central hypothesis is that effective T cell activation requires both signal 1 (TCR engagement via mesothelin/CD3) and signal 2 (costimulation via EGFR/4-1BB), and that this dual strategy can overcome the coinhibitory TME, restoring T cell function and persistence. Mesothelin/CD3 and EGFR/4-1BB BiTEs will be engineered and produced via bacterial plasmid transformation and HEK293 cell transfection. Functional characterization will be performed using EGFR/4-1BB reporter systems co-cultured with mesothelin^{+}/EGFR^{+} mesothelioma cells. The combination will be evaluated *in vitro* with primary human T cells, measuring activation markers (IFN-γ, CD69, PD-1, 4-1BB) and cytotoxicity by real-time impedance (xCELLigence). *In vivo* efficacy will be assessed in a humanized immunodeficient murine model, measuring systemic IFN-γ and tumor growth control across dose combinations. Overall, this project represents a novel approach to costimulate mesothelioma-infiltrating lymphocytes through a dual BiTE strategy, potentially paving the way for more effective T cell-based immunotherapies in this challenging malignancy.

yes	x
no	

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?