Universidad de Navarra
Facultad de Ciencias

MASTER'S DEGREE IN BIOMEDICAL RESEARCH
Research Project Proposal
Academic year 2024-2025

Project Nº 18

Title: Engineering of AAV-Based Vectors in combination with Radiotherapy for Immuno-gene Therapy of Cancer

Department/ Laboratory: Solid Tumors Program, Cancer Division at Cima.

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Summary

Radiotherapy (RT) primes the immune system against cancer but fails to trigger effective antitumor responses due to concomitant immunosuppressive mechanisms elicited by radiation. In preclinical mouse models, we have demonstrated that the combination of local RT and AAV-based delivery of IL-12 through an IFN-inducible promoter (AAV-iIL12) resulted in increased but restrained production of the cytokine. Importantly, the combination of RT + AAV-iIL12 caused a strong immune infiltration and reshaped the tumor microenvironment that was accompanied by local and systemic antitumor immunity with no systemic toxicity.
However, this approach allows us to include a second immunomodulatory element within the vector genome. The ultimate goal of the project is to explore antitumor effects of the new bicistronic vectors such as IL-12/IFNb, IL-12/IL-7, IL-12/IL-15 and IL-12/Bambi. The specific aims of this Research proposal are:
1. To **design and generate bicistronic AAV vectors** for IL-12/IFNb, IL-12/IL-7, IL-12/IL-15 and IL-12/Bambi. For this, the student will learn and use a series of techniques such as cloning, DNA purification, PCR and AAV production.
2. To **validate the AAV-mediated expression of the transgenes** *in vitro*. Different tumor cell lines will be irradiated, infected with the rAAV and stimulated with interferon. Transgene expression will be validated by ELISA and western blots.
3. To **demonstrate therapeutic potential** of the new AAV vectors. We will use murine tumor models (B16, LLC) to demonstrate therapeutic potential compared to AAV-iIL12. Tumor cells will be implanted into C57Bl6 mice and established tumors will be irradiated and inoculated with the different AAVs. The progress of the project will determine the number of models and vectors to attempt.

yes	x
no	

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