Universidad de Navarra
Facultad de Ciencias

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

Project Nº 51

Title: Therapeutic Splicing Modulation with U snRNP Super-binders (ERASMUS)

Department/ Laboratory RBAT/406/CIMA

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Summary

Alternative splicing (AS) is a fundamental post-transcriptional regulatory mechanism that enables a single gene to produce multiple mRNA and protein isoforms by variably including or excluding specific exons. Dysregulation of AS has been implicated in numerous diseases, including monogenic disorders and various forms of cancer, making it an attractive target for therapeutic intervention. In the context of malignant tumors, cells can acquire functions that provide them with anti-apoptotic, proliferative and drug resistance functions thanks to the development of aberrant AS events. The cancer specificity of these transcripts and the "splicing addiction" phenomenon offer great opportunities for safe and efficient therapies. General inhibition of splicing by small molecules or methods to downregulate the expression of components of the spliceosome can exert antitumor effects, but important side effects are expected. Perturbation of specific oncogenic splicing using antisense oligonucleotides (ASOs) is perceived as a safer approach, but the design of potent molecules is a challenge. In this project we propose a method based on the expression of modular components. The antisense moiety directs the therapeutic RNA to the oncogenic transcript, whereas a spliceosome-binding domain recruits specific elements to modulate AS. We plan to obtain proof of concept of this technology by reverting the oncogenic splicing of Bcl-X and PKM genes. We will employ human and mouse hepatocarcinoma cells, as well as an immunocompetent mouse model. The delivery in the form of small plasmids encapsulated in non-viral vectors would allow efficient access to the tumor microenvironment, a relatively long-lasting effect and the possibility of re-dosing. We aim to demonstrate that this strategy is broadly applicable to different targets, which can be combined to increase the therapeutic effect and reduce the emergence of resistances. The approach could be used not only for the treatment of different types of tumors, but also for certain monogenic diseases caused or influenced by aberrant splicing.

yes	x
no	

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