



MASTER'S DEGREE IN BIOMEDICAL RESEARCH

Research Project Proposal

Academic year 2023-2024

Project Nº 40

Title: Engineering RNA devices for novel antitumor RNA immunotherapy.

Department/ Laboratory

Edificio CIMA, Departamentos de "DNA and RNA Medicine" and "Innovative Therapeutics".
Laboratories 4.06 and 3.06

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Summary

IL-12 is an immunomodulatory cytokine which possesses outstanding antitumoral potential. Unfortunately, antitumoral therapy with IL-12 is hampered by this protein's high toxicity. Uncontrolled levels after systemic delivery or gene therapy applications can lead to severe adverse events, including death. Therefore, tightly controlled expression of IL-12 would be of high interest for immunotherapy, especially in aggressive tumours with poor prognosis such as hepatocellular carcinoma (HCC).

Recently, at our lab we have developed a novel high-throughput technology to drive *in vitro* evolution of small RNA devices, in order to select RNA structures that function to fine-tune gene expression in response to a therapeutic drug. These RNA structures, located after the IL-12 mRNA, will impede expression by binding to a liver-specific miRNA. When the drug is administered, the RNA device will block miRNA binding and allow IL-12 production. Interestingly, the amount of IL-12 will mirror the amount of drug.

The final **aim** of this project is to test the **antitumoral efficacy in animal models**. The student will screen different RNA switches in cell cultures and produce Adeno-Associated viral vectors (AAV) armed with the best RNA devices. These vectors, with liver tropism, will be introduced in mice with HCC. IL-12 expression will be controlled with the amount of therapeutic drug administered to the animals, pursuing a protocol which combines an ideal safety profile and potent antitumor efficacy.

Methodology: Cloning, RNAi, RNA aptamer screening, RNA structure prediction, Cell culture, AAV production. In vivo: handling and conventional sample collecting and tumor growth evaluation in murine models.

yes	<input checked="" type="checkbox"/>
no	<input type="checkbox"/>

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