



MASTER'S DEGREE IN BIOMEDICAL RESEARCH

Research Project Proposal

Academic year 2023-2024

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| Project Nº 57 ASIGNADO | |
| Title: Characterization of therapeutic vectors for the treatment of cancer | |
| Department/ Laboratory <i>Laboratory of Tumor evasion and New Targets. Area of Solid tumors. CIMA</i> | |
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| Summary <p>Adeno-associated vectors (AAVs) are non-pathogenic long-term expression vectors that are used in the clinic for the treatment of inherited monogenic diseases. In order to induce a targeted, potent immune antitumor response, we developed an AAV8 vector encoding a form of mutated human STING responsive to DMXAA (an agonist of murine STING but not of human STING). Intratumor injection of this vector (AAV.hSTINGmut) followed by intraperitoneal DMXAA administration in STING KO mice resulted in increased intratumor levels of IFNbeta (as expected) but unfortunately this was not accompanied by tumor regression of murine subcutaneous tumors. In order to increase the immune response, we generated and tested a series of synthetic promoters responsive to STING activation to control the expression of IL-12 (a potent immune-stimulatory cytokine). In this way, IFNbeta and IL-12 production would be restricted to the tissue in which we administered AAV8-hSTINGmut and AAV8-IL-12. In an initial screening, the vector for expression of murine IL-12 regulated by the ISREx4 promoter showed the best results. We developed variations of this vector, including bi-cistronic constructs that co-express IL-12 and other cytokines. The project will consist in the in-depth characterization of these vectors, biodistribution, biological activities, etc. The <i>in vitro</i> characterization will involve tissue culture, AAV production (bacterial culture, plasmid DNA obtention, cell transfection, AAV purification, titration by RT-PCR), application of different treatments to cultured cells, ELISA, as well as other biochemical and molecular biology techniques). In a second stage of the project, the therapeutic effect of these vectors will be tested in an <i>in vivo</i> model of metastatic cancer. This will involve manipulation of mice, including subcutaneous inoculation of tumor cells, intratumoral injection of AAVs, additional treatments, tumor growth follow, blood sampling, sacrifice and tissue obtention for further analysis.</p> | |
| yes | X |
| no | |
| Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator? | |