



Research Project Proposal
Academic year 2015-2016

Project Nº 3

Title: Production and application of High-Capacity adenoviral vectors in the treatment of gastrointestinal cancers

Department/ Laborator. Gene Therapy Program. CIMA

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Summary

The project involves the development of long-term gene therapy expression vectors based on adenovirus (High-Capacity, also called helper-dependent or “gutless” adenoviruses), and the characterization of their function in vitro and in animal models of cancer. High-Capacity adenoviruses (HC-Ad) are a special class of vectors obtained by substitution of the viral coding sequences with foreign genes (expression cassettes for therapeutic genes plus stuffer DNA). Production of these vectors is challenging, but they offer the opportunity to deliver long fragments of genetic material to an organism in vivo and achieve sustained gene expression. They are especially suited for liver-directed gene therapy applications.

Specific objectives:

- Improvement of methods for production of HC-Ads.
- Construction of HC-Ads for expression of therapeutic genes against cancer (immunostimulatory cytokines, molecules for modulation of the IGF-I pathway, etc.)
- Evaluation of the vectors in vitro (cell culture)
- Evaluation of the vectors in vivo:
 - Analysis of transgene expression
 - Analysis of antitumor effect using animal models of pancreatic, colon or liver cancer

Techniques:

- Molecular biology (subcloning, plasmid construction)
- Cellular biology
- Virology (virus rescue, amplification, purification and titration)

Animal models of disease (establishment of tumors in rodents, administration of gene therapy vectors, evaluation of antitumor effect and toxicity)



References

Hernandez-Alcoceba R, Sangro B, Berraondo P, Gonzalez-Aseguinolaza G, Prieto J. Cytokines for the treatment of gastrointestinal cancers: clinical experience and new perspectives. *Expert Opin Investig Drugs*. 2013 Jul;22(7):827-41

Gonzalez-Aparicio M, Mauleon I, Alzuguren P, Bunuales M, Gonzalez-Aseguinolaza G, San Martín C, Prieto J, Hernandez-Alcoceba R. Self-inactivating helper virus for the production of high-capacity adenoviral vectors. *Gene Ther*. 2011 Nov; 18(11):1025-33.

Gonzalez-Aparicio M, Alzuguren P, Mauleon I, Medina-Echeverz J, Hervas-Stubbs S, Mancheno U, Berraondo P, Crettaz J, Gonzalez-Aseguinolaza G, Prieto J, Hernandez-Alcoceba R. Oxaliplatin in combination with liver-specific expression of interleukin 12 reduces the immunosuppressive microenvironment of tumours and eradicates metastatic colorectal cancer in mice. *Gut*. 2011 Mar;60(3):341-9.

POSSIBILITY OF PhD

YES*

* (PhD grant required)