DIGNA BIOTECH

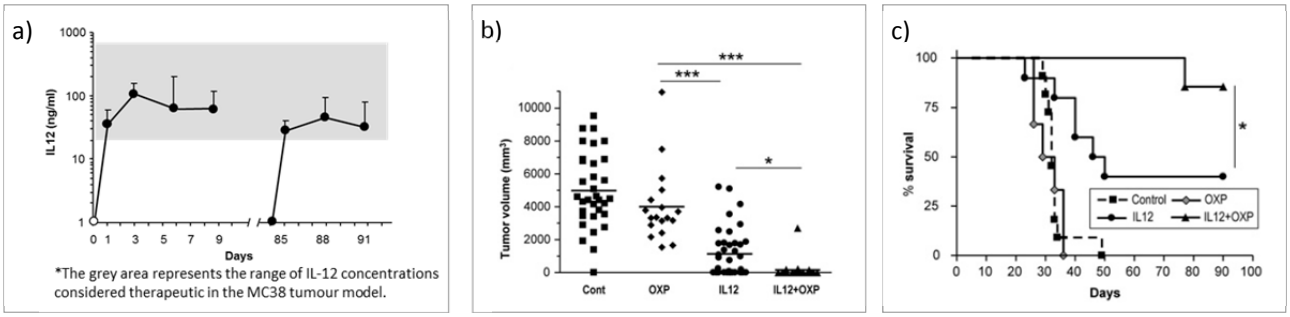
HC-Ad vectors:
High-capacity adenoviral vectors

- **High-Capacity adenoviral vectors (HC-Ad)**, also called helper-dependent or 'gutless' are a new class of gene therapy vectors that allow stable transfer of large DNA fragments *in vivo*.
- A **new method** for production of high-quality HC-Ad with potential applications in humans has been developed, based on a **self-inactivating adenovirus** acting as a helper virus (HV).
- **Indications**: monogenic diseases, cancer, liver cirrhosis and metabolic diseases.

HC-Ad Platform	This new method for production of HC-Ads will facilitate the use of these vectors in basic and applied research and in the clinical setting.
Competitive Advantage	· High transduction efficiency. · Maintenance of gene expression for long periods of time after a single administration of the vector without the need of integration in the genome. · Transfer of large DNA fragments (up to 36 Kb): Suitable for simultaneous expression of several therapeutic genes and incorporation of complex inducible systems
Therapeutic Approaches	· Gene supplementation in **monogenic diseases** when the DNA sequence required exceeds the cloning capacity of AAV vectors. · Controlled expression of imunostimulatory cytokines · Long-term expression of polypeptides with anti-angiogenic and anti-proliferative functions. · *In vitro* and *in vivo* gene correction through transference of specific recombinases together with genomic regions that facilitate the homologous recombination. · Expression of monoclonal antibodies with therapeutic properties.
Clinical Application	· Cancer: immunotherapy, anti-angiogenesis, inhibition of carcinogenic pathways. · Liver cirrhosis: controlled, liver-specific expression of IGF-1. · Metabolic diseases: porphyrias, hyperoxaluria, lysosomal storage diseases, hemophilia and alpha 1 anti-trypsin deficiency.

An example of HC-Ad: The HC-Ad/RUmIL-12 vector

- HC-Ad/RUmIL-12 vector, designed to fight against primary or metastatic liver cancer, contains a liver-specific, mifepristone-inducible system for the expression of IL-12 that allows a tight control on the intensity and duration of cytokine expression.
- Following vector administration, the induction regime is adjusted based on the response to a low dose of mifepristone, to compensate for differences in viral transduction.
- This individualized protocol allows several cycles of IL-12 expression in the therapeutic range (figure a).
- A single cycle consisting on 10 daily inductions significantly extended the survival of animals and achieved eradication of hepatic tumors in 50% of them.
- A single dose of the chemotherapeutic agents oxaliplantin (OXP) administered 3 days before the initiation of IL-12 induction increased the rate of tumor eradication above 80%, whereas the same dose of drug had no significant antitumor effect by its own in this aggressive tumor model (figures b and c).



Intellectual Property	· PCT/ES2009/070154. Self-inactivating helper adenoviruses for the production of high-capacity recombinant adenoviruses (licensed to Digna Biotech).
References	· Gonzalez-Aparicio M et al. Self-inactivating helper virus for the production of high-capacity adenoviral vectors. *Gene Ther*. 2011;18(11):1025-1033. · Gonzalez-Aparicio M et al. 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;60(3):341-349.

Contact: Jesús M. Hernández, MD, PhD | Email: jmhernandez@unav.es; Tel: + 34 948 194 700