HC-Ad vectors:
High-capacity adenoviral vectors

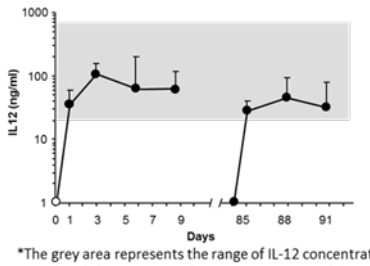
- **High-Capacity adenoviral vectors (HC-Ad)**, also called helper-dependent or 'gutless' are a new class of gene therapy vectors that allow stable transfer of large DNA fragments *in vivo*.
- A **new method** for production of high-quality HC-Ad with potential applications in humans was developed, based on a **self-inactivating adenovirus** acting as a helper virus (HV)(WO2009138544).
- **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, monoclonal antibodies and polypeptides with anti-angiogenic and anti-proliferative functions. · *In vitro* and *in vivo* gene correction through transference of specific nucleases together with genomic regions that facilitate the homologous recombination.
Clinical Application	· Cancer: immunotherapy, anti-angiogenesis, inhibition of carcinogenic pathways. · Metabolic diseases: urea cycle disorders, Wilson´s disease, porphyrias, hyperoxaluria, lysosomal storage diseases, hemophilia and alpha 1 anti-trypsin deficiency.

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

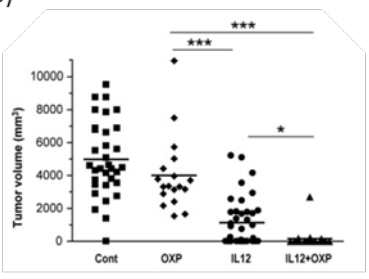
- HC-Ad/RUmIL-12 vector, designed to fight against primary or metastatic liver cancer, contains a liver-specific, mifepristone-inducible system for the expression of IL-12 that allows a tight control on the intensity and duration of cytokine expression.
- Following vector administration, the induction 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 mice harboring hepatic metastases of colon cancer and achieved eradication of tumors in 50% of them. The effect is enhanced when combined with chemotherapy (oxaliplatin, OXP), figure b.
- The vector is able to eradicate pancreatic cancer liver metastases in a Syrian hamster model (figure c)

a)

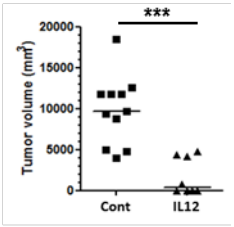


*The grey area represents the range of IL-12 concentrations considered therapeutic in the MC38 tumour model.

b)



c)



References

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- Gonzalez-Aparicio M et al. Self-inactivating helper virus for the production of high-capacity adenoviral vectors. *Gene Ther*. 2011;18(11):1025-1033.
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