Dipeptidyl peptidase 4 (DPP4) as a new senescence-associated target to eliminate cancer cells

Poster 14P

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Introduction

Background: Dipeptidyl Peptidase 4 (DPP4 or CD26) is a membrane glycoprotein involved in chemotactic and inflammatory responses, via its enzymatic activities. DPP4 is frequently overexpressed in primary tumors and metastases where its role remains still poorly understood. Recently, DPP4 has been identified as a novel biomarker of senescent cells. In cancers, the harmful effect of senescent tumor cells is well recognized and mediated by the Senescence Associated Secretory Phenotype (SASP) which can be induced by many chemotherapy and radiation treatments. This deleterious induction promotes tumor growth, invasion and neo-angiogenesis which can lead to treatment resistance, relapses, and poor prognosis in many cancers, especially at advanced stages.

Methods: Firstly, we generated original monoclonal antibodies against DPP4 human protein (patent WO2021058795A3) to design targeted therapies able to eliminate cancer and senescent cancer cells. Secondly, we screened several potential payloads by analyzing their activities on cancer and senescent cancer cells. The objective is to combine the most efficient payload with monoclonal antibody showing qualities for Antibody-Drug Conjugate strategy.

Finaly, STX-1 is a first-in-class Antibody-Drug Conjugate (ADC) coupling a chimeric anti-DPP4 monoclonal antibody with a topoisomerase I inhibitor (Exatecan/DAR8) payload via an enzymatically cleavable cathepsin-dipeptide linker.

A faire

Fig.1: DPP4 (CD26) expression is boosted by senescence induction associated to drug resistance and tumor relapse after failure of conventional cancer therapies. Targeting DPP4 with an ADC is leading to the internalization of the complex into the endolysosomal compartments and to the release of the payload. STX-1 is the first generation of ADCs specifically designed to eliminate senescent cancer cells.

RESULTS

DPP4 is expressed in a wide range of solid cancers

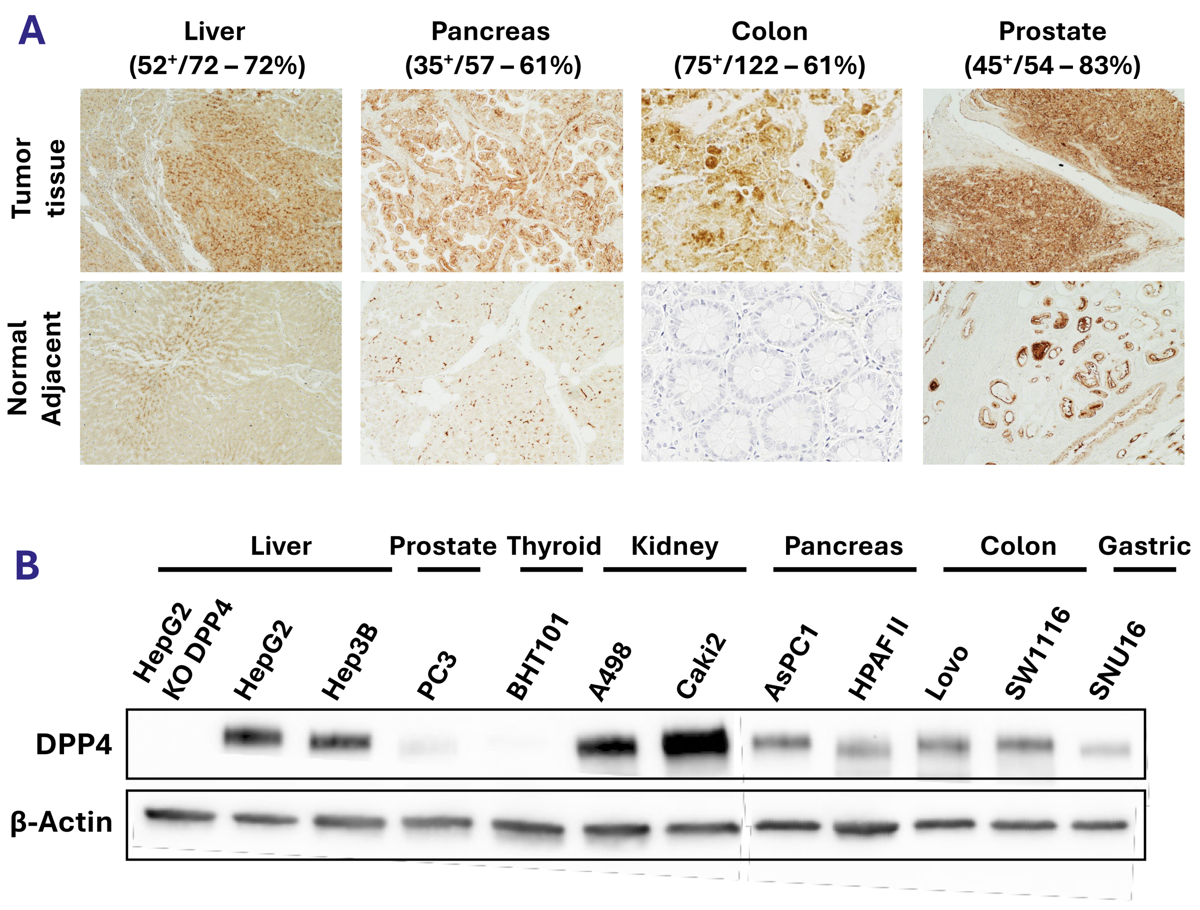


Fig.2: A/ DPP4 expression by IHC staining on TMA of human tumors and frequency of DPP4+ samples. B/ Western blot of DPP4 expression on various human tumor cell lines.

DPP4 is overexpressed in radiotherapy-induced senescence models

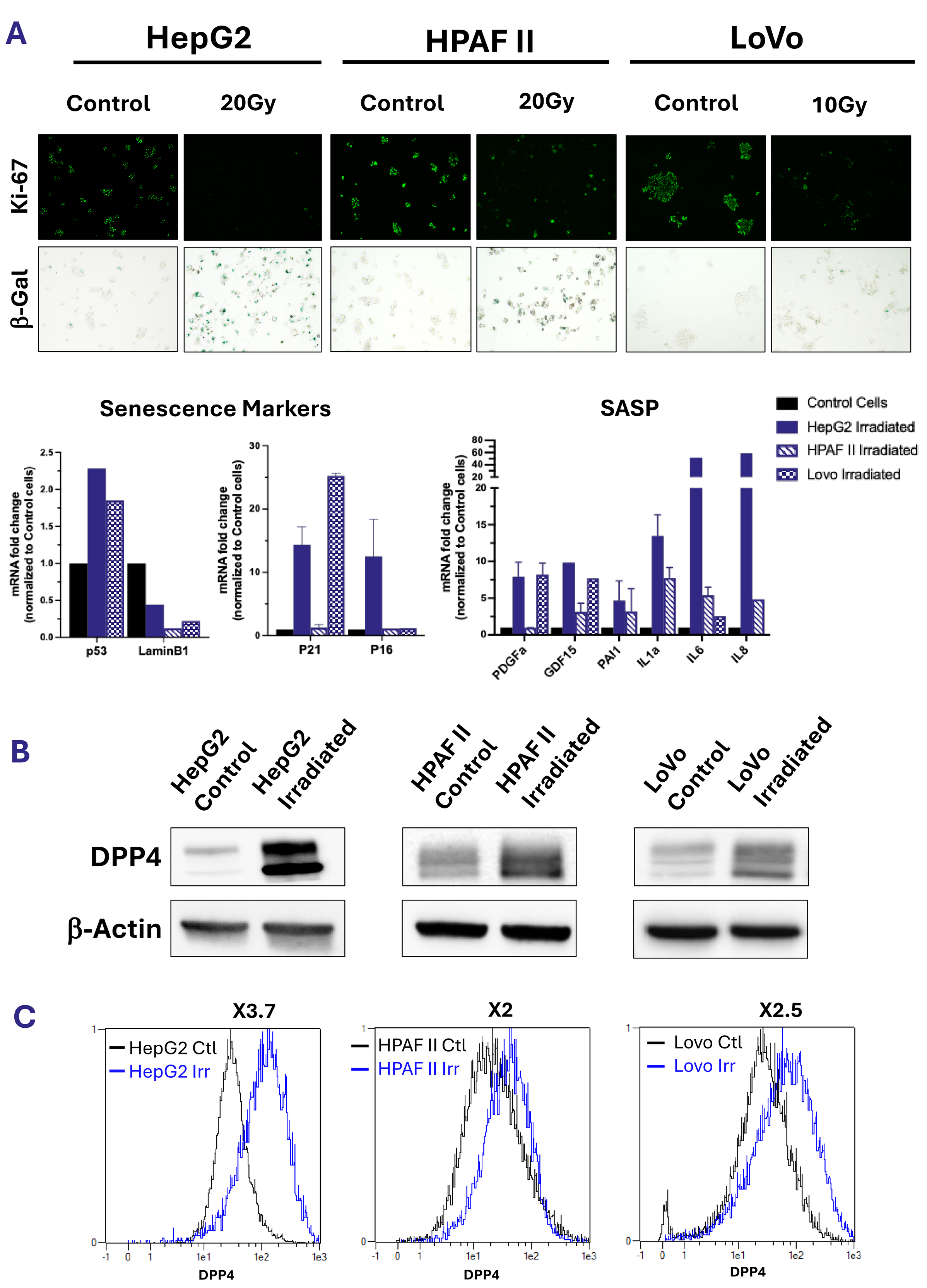


Fig.3: A/ Senescence induction of human tumor cell lines by radiotherapy (HepG2, HPAF II, LoVo) leading to B/ overexpression of DPP4 (WB). C/ DPP4 expression is also increased at the plama membrane (Flow Cytometry).

Screening of potential ADC Payloads

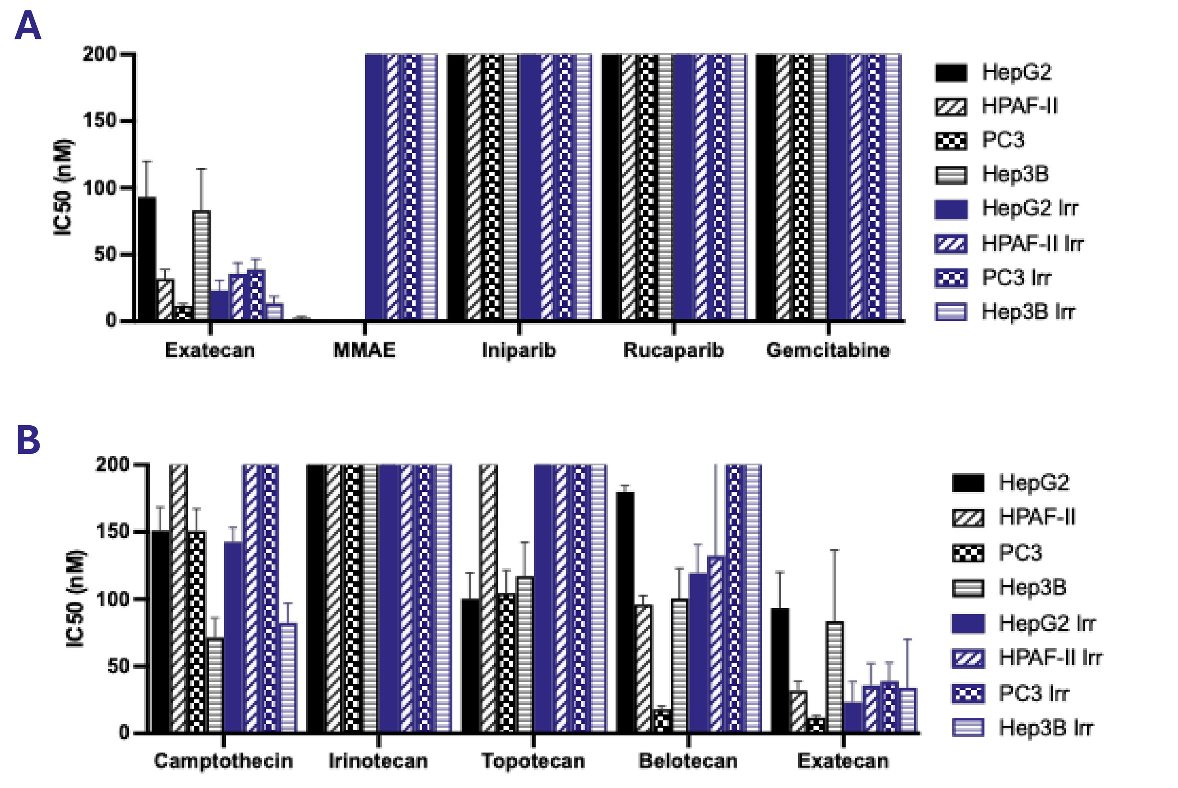


Fig.4: Screening of several A/ Senolytics and B/ Topoisomerase I inhibitors using a viability assay in several human cancer cell lines, Control or radiation-induced Senescent. IC50 were extrapolated from dose-response curves after 3 days of treatment. Values over 200 nM are undefined.

STX-1, an ADC efficiently internalized

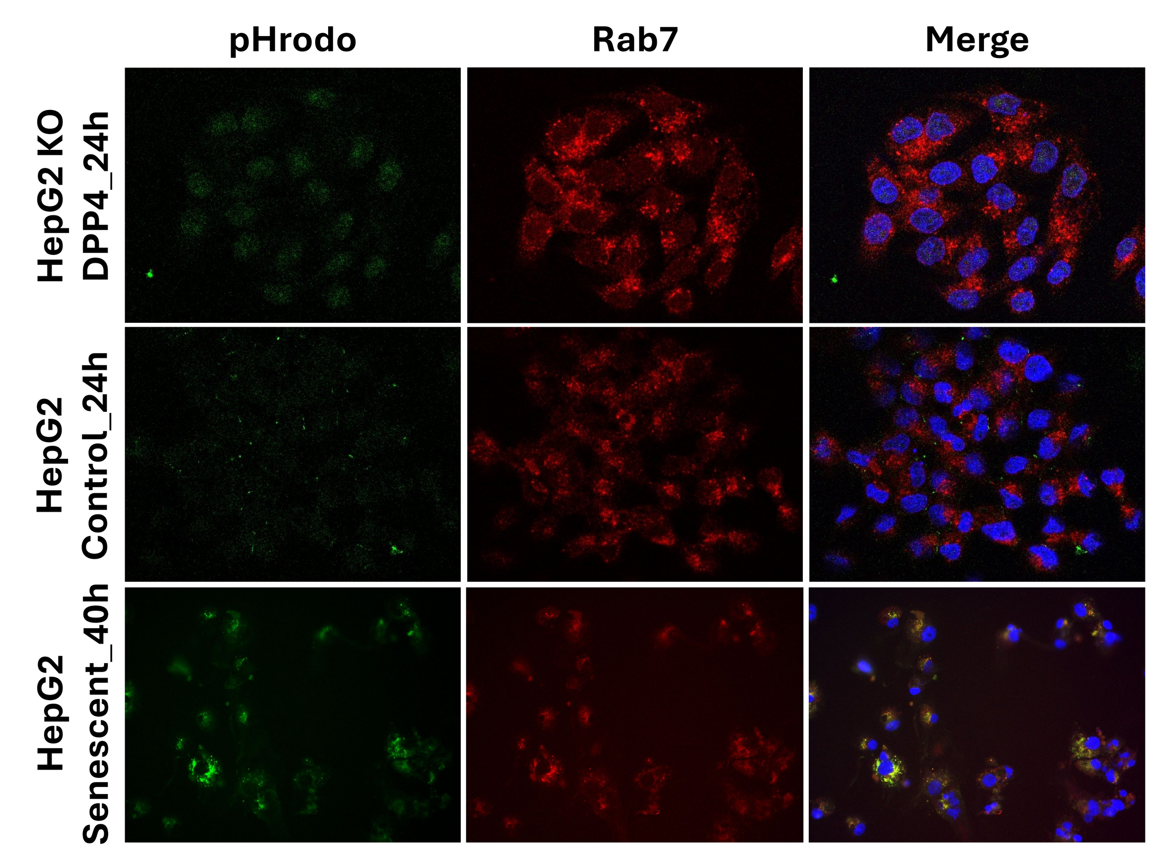
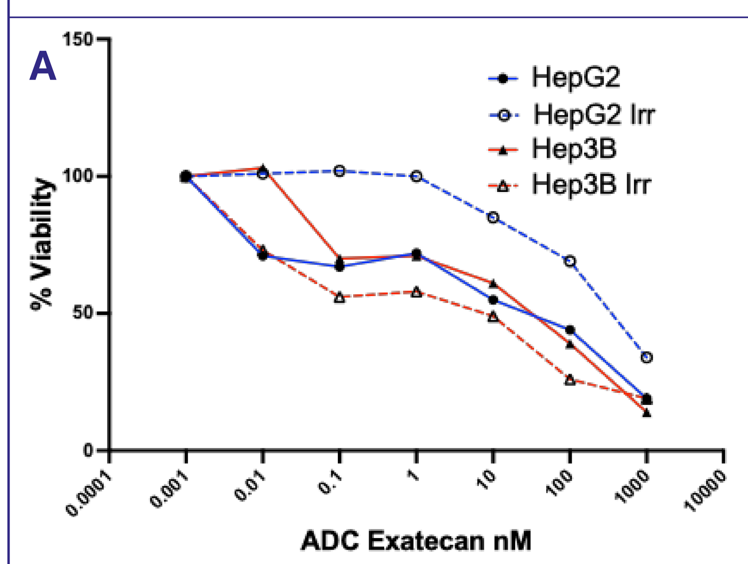


Fig.5: Internalization of STX-1 ADC after 24h in HepG2 and HepG2 KO DPP4 cells and after 40h in HepG2 senescent cells induced by 20 Gy radiation.

STX-1 is effective *in vitro* on cancer and senescent cancer cells



B

		HepG2	Hep3B
IC50 (nM)	Native	18.99	18.08
	Irradiated	50.55	0.02

Fig.6: A/ *In vitro* dose-response curves in human hepatocarcinoma models without and with senescence induction by radiotherapy. B/ IC50 (nM) after ADC-Exatecan treatment on cancer and Senescent cancer cells.

STX1 reduces significantly tumor growth

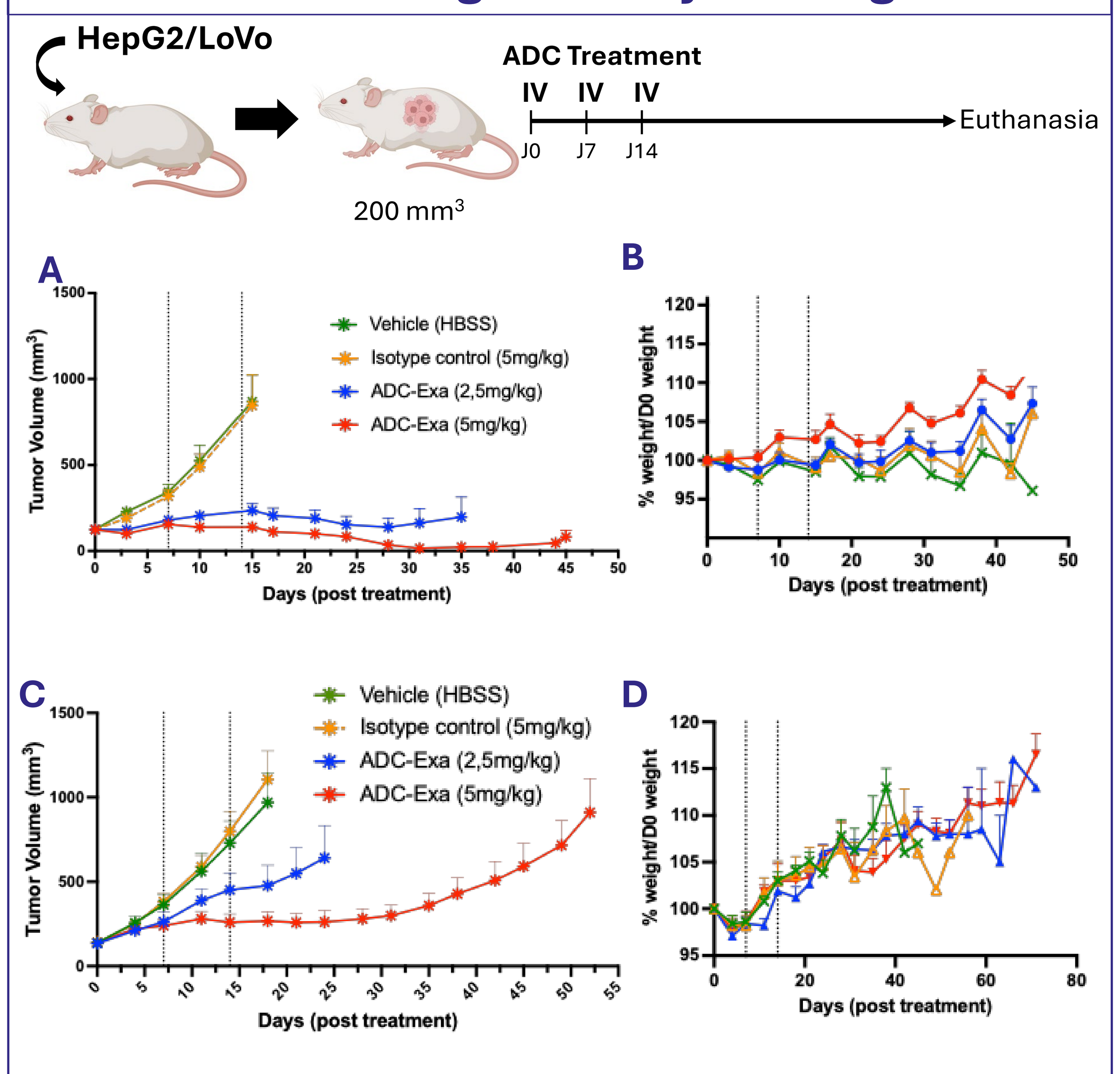


Fig.7: Tumor volume of A/ HepG2 and C/ LoVo cancer cells engrafted subcutaneously into the flank of NMRI nude mice. Vehicle, Isotype control and ADC-Exatecan have been administrated once a week during three consecutive weeks at 2,5 or 5 mg/kg. Percent body weight change calculated relative to animal weight at the start of the treatment shows ADC-Exatecan was well tolerated in both B/ HepG2 and D/ LoVo experiments.

STX-1 is highly tolerated in hDPP4 mice

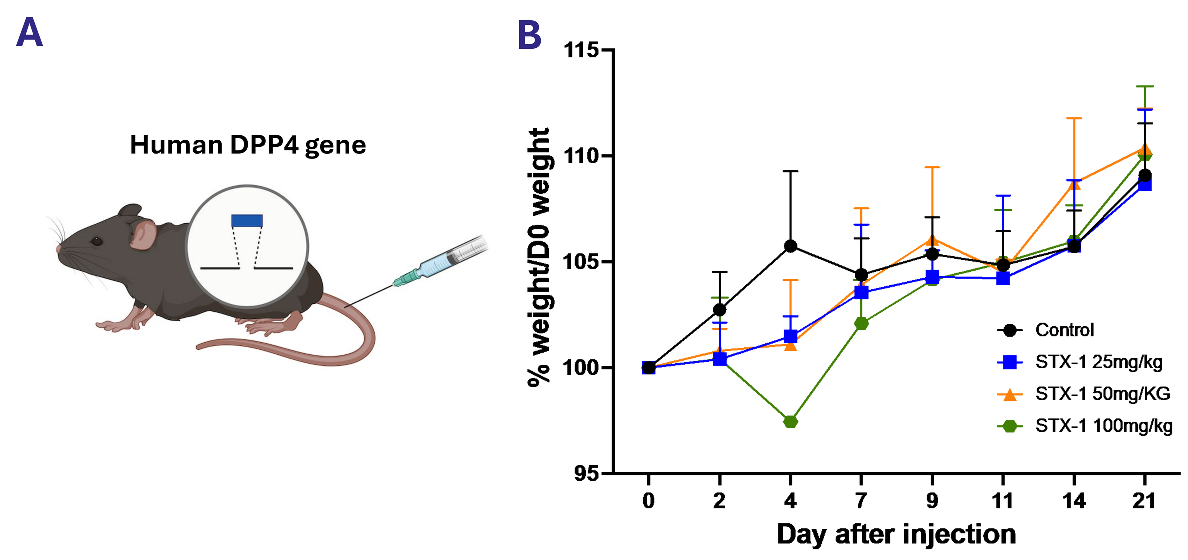


Fig.8: (A) Genetic mouse model expressing human form of DPP4 (Crispr Knock In technology) engineering by Shanghai Model Organisms Custom and treated once with STX-1 incremental doses. (B) Bodyweight of mice treated with a single dose of STX-1 (IV injection at 25, 50 or 100mg/kg.

SUMMARY

- DPP4 is a senescence marker that is overexpressed on multiple solid tumor indications.
- STX-1 demonstrates a rapid internalization and exhibits *in vitro* efficient cytotoxic activities against cancer and Senescent cancer cells.
- STX-1 reduces significantly in vivo tumor growth at low dose administrated and any side effect has been observed at high dose administrated

STX-1 is a leading first-in-class ADC with promising therapeutic developments to target DPP4 positive cancers