Dipeptidyl Peptidase 4 (DPP4) as a new convincing target to eliminate cancer and senescent cancer cells

D. Daydé[1], V. Lelarge[1], G. Jouffroy[1], J. Chœur[1], T. Mathieu[1], E. Angevin[2], B. Le Calvé[1],

[1] Starkage Therapeutics, Lille, France, [2] Institut Gustave Roussy, Villejuif, France

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.

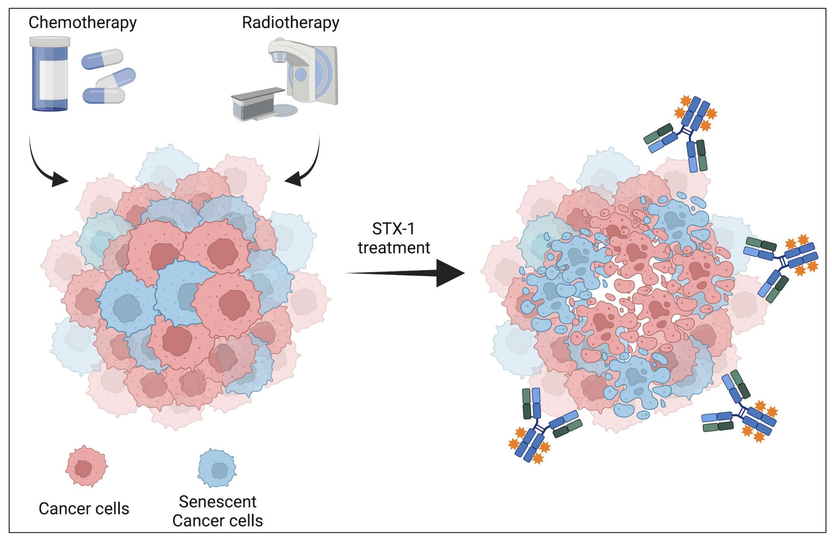

Fig.1: DPP4 (CD26) expression is boosted by senescence induction associated to conventional cancer therapies (chemotherapy and radiotherapy). Targeting DPP4 with an ADC allow elimination of both cancer and senescent cancer cells.

RESULTS

DPP4 is expressed in a wide range of solid cancers

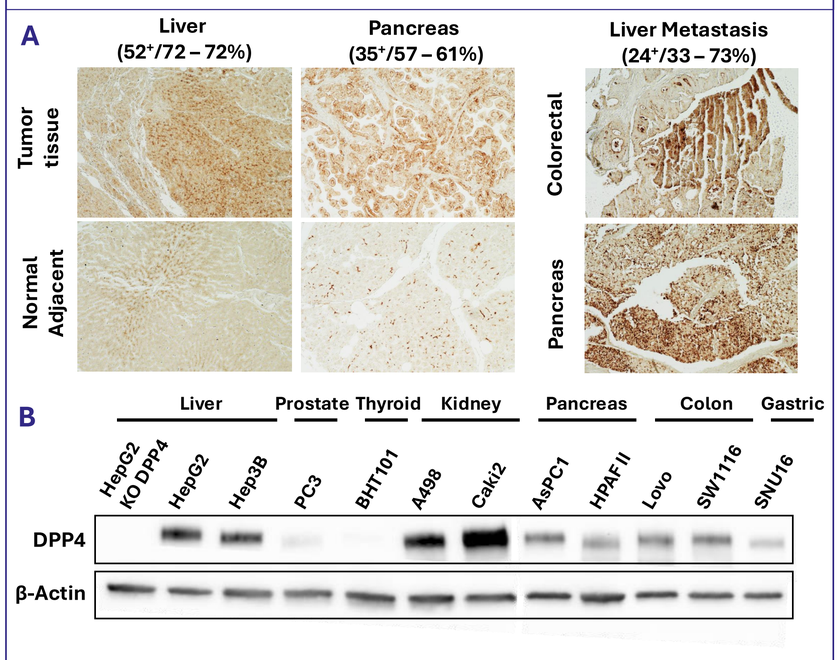

Fig.2: A/ DPP4 expression by IHC staining on TMA of human tumors and frequency of DPP4+ samples. B/ Western blot of DPP4 expression on various human tumor cell lines.

DPP4 is overexpressed in radiotherapy-induced senescence models

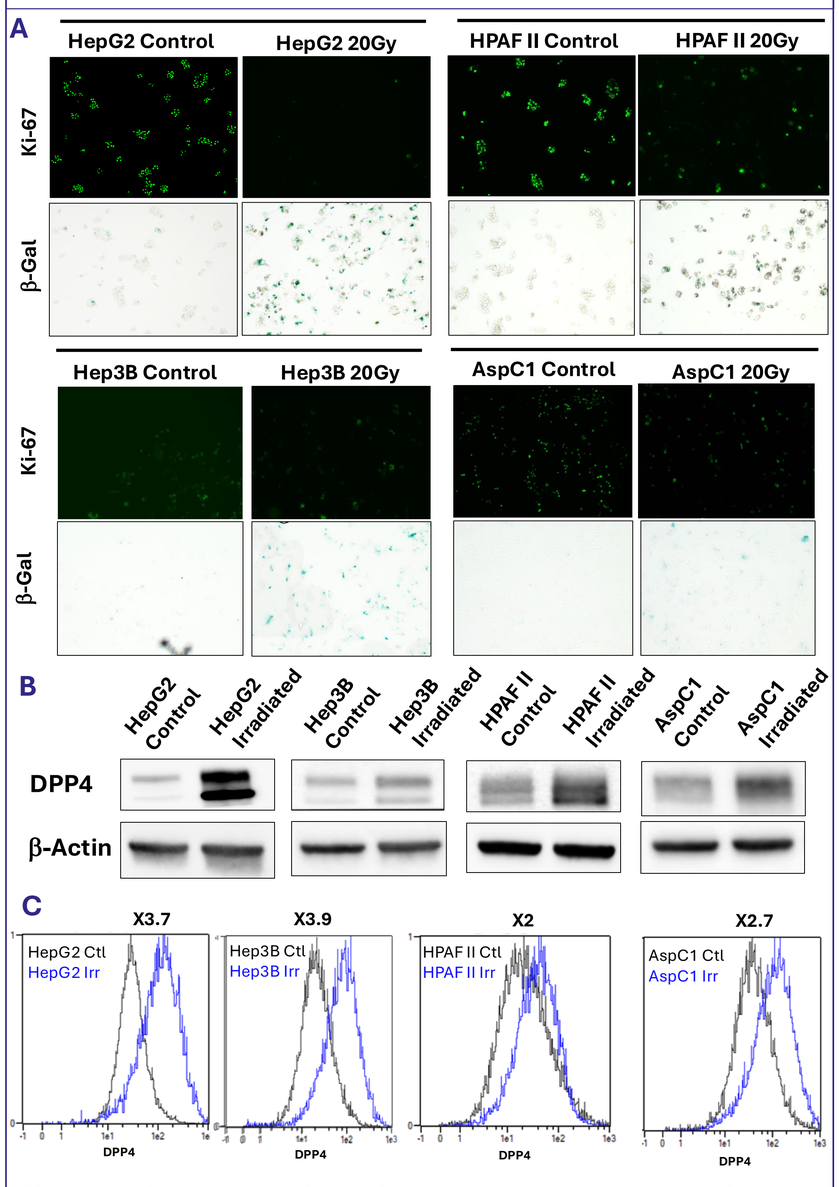

Fig.3: A/ Senescence induction of human tumor cell lines by radiotherapy leading to B/ overexpression of DPP4 (WB). C/ DPP4 expression is also increased at the plasma membrane (Flow Cytometry).

Screening of potential ADC Payloads

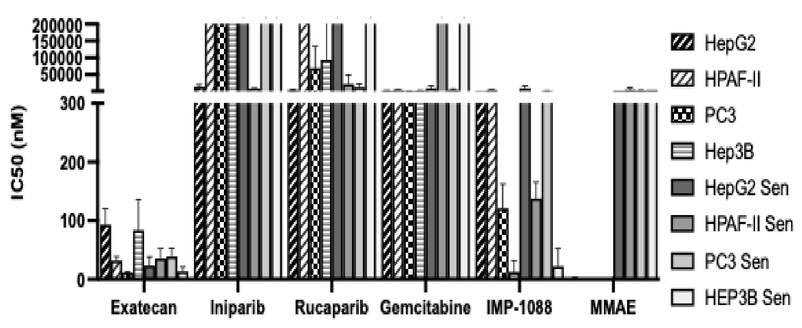

Fig.4: Screening of potential payloads associated to various mechanisms of action using a viability assay in several human cancer cell lines (Control or radiation-induced Senescent). IC50 were extrapolated from dose-response curves after 3 days of treatment.

STX-1, an ADC efficiently internalized

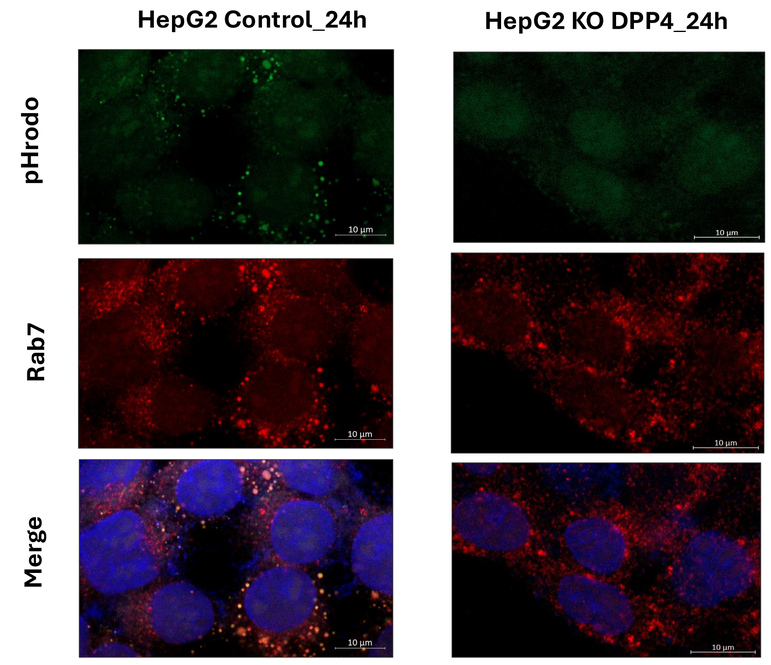

Fig.5: Internalization of STX-1 ADC after 24h in HepG2 and HepG2 KO DPP4 cells

STX1 reduces significantly tumor growth

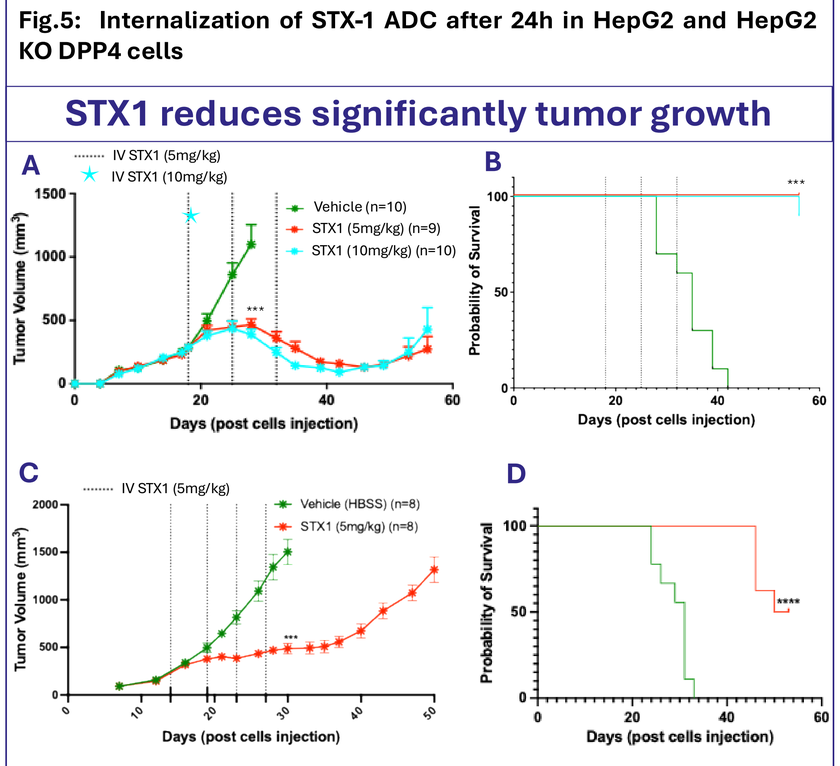

Fig.6: Tumor volume and survival of A,B HepG2 and C,D HPAF II cancer cells engrafted subcutaneously into the flank of NMRI nude mice and treated or not with STX-1.

Senescence induction potentiates STX-1 anticancer activity

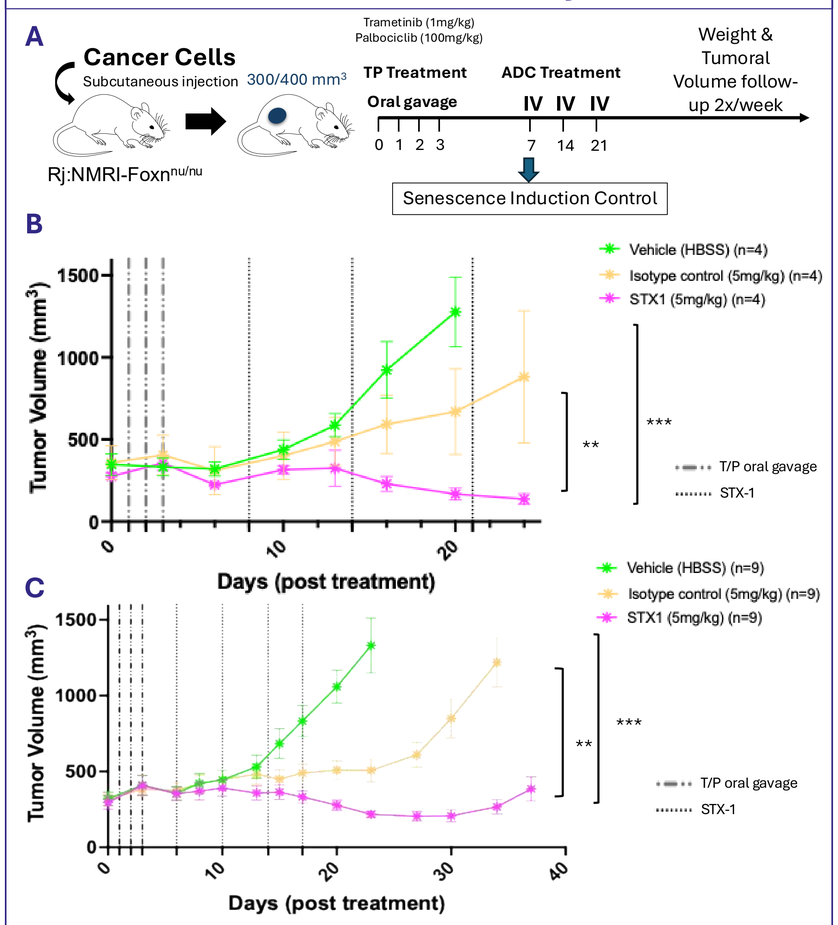

Fig.7: A/ Schema of HepG2 and HPAFII subcutaneous models treated with a combination of senescence inducers (Trametinib/Palbociclib) before injection of STX-1. B/HepG2 and C/HPAFII represent tumor progression for each models.

STX-1 is highly tolerated in hDPP4 mice

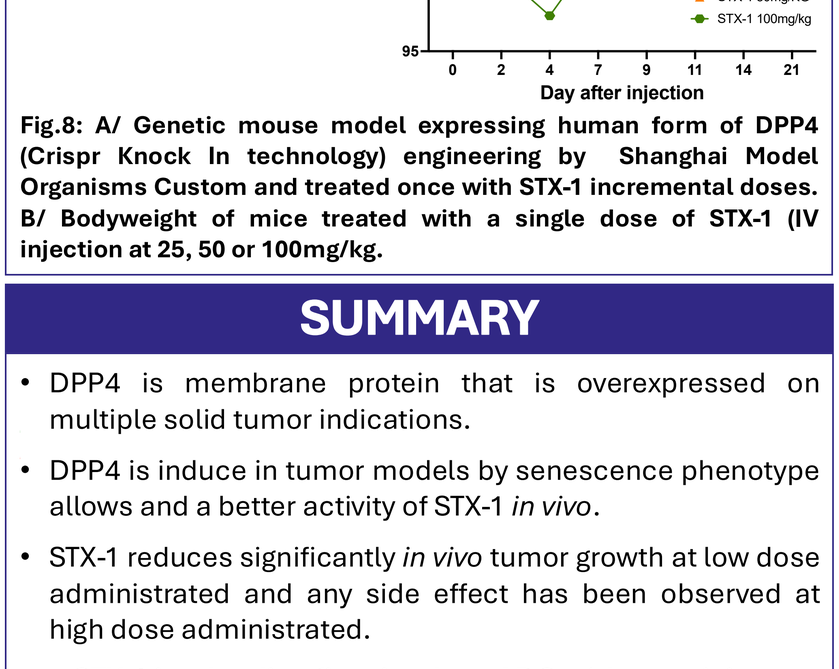

Fig.8: A/ Genetic mouse model expressing human form of DPP4 (Crispr Knock In technology) engineering by Shanghai Model Organisms Custom and treated once with STX-1 incremental doses. B/ Bodyweight of mice treated with a single dose of STX-1 (IV injection at 25, 50 or 100mg/kg.

SUMMARY

- DPP4 is membrane protein that is overexpressed on multiple solid tumor indications.
- DPP4 is induce in tumor models by senescence phenotype allows and a better activity of STX-1 *in vivo*.
- 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 cancer and senescent cancer cells