EFFICACY OF ART26.12, A NOVEL FATTY ACID BINDING PROTEIN 5 IHIBITOR, IN AN ORTHOTOPIC HCT-116-LUC HUMAN COLON CANCER MODEL

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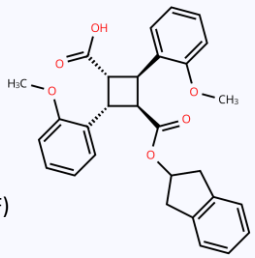
Introduction

Fatty acid binding protein 5 (FABP5) is overexpressed in a number of cancers including colorectal cancer, implicated in growth and metastasis. Pharmacological inhibitors of FABP5 have shown efficacy in preclinical models of prostate and lung cancer (Warren *et al.*, 2023). ART26.12, a potent and selective FABP5 inhibitor, has previously shown efficacy in oxaliplatin-induced peripheral neuropathy (Warren *et al.,* 2024). As colorectal cancer patients are a key population that receive oxaliplatin and go on to develop peripheral neuropathy (Cheng *et al.*, 2023), we sought to test the anti-tumoral efficacy of ART26.12.

The aim of this study was to test the direct anti-tumour effect of ART26.12 in an orthotopic HCT-116-Luc colon cancer model.

Methods

In vitro, cell viability was measured using CellTiter-Glo. HCT-116 cells were seeded in 10% FBS for one day in 384-well plates, and then grown for 3 days in 2.5% FBS during compound treatment. ART26.12 was tested in duplicate with a 10-point half-log dose response curve, with a top concentration of 100µM. *In vivo,* BALB/c nude mice were inoculated with $1x10^6$ HCT-116-luc cells, injected under the serosa membrane of the colon. On day 14 mice were randomly assigned to groups based on the bioluminescent signal of the tumour, using a computer-generated randomisation procedure. Treatment with ART26.12 (100 mg/kg p.o. BID), oxaliplatin (OXA, 2mg/kg i.v. twice weekly) and vehicle control was begun on day 15 (denoted day 1 in results) and continued for 34 days. Tumour growth was tracked weekly using bioluminescent imaging. Pain behaviour was assessed weekly using Von Frey (VF) measurements. Bodyweight was measured twice weekly.



Results

In vitro, ART26.12 killed HCT116 cells with an IC_{50} of 33.5µM. *In vivo*, ART26.12 (100mg/kg p.o. BID) significantly attenuated tumour growth by day 20 ($p<0.001$) compared to vehicle, with 3 animals tumour free at the end of study (Figs. 1A, 2). OXA (2mg/kg i.v. , twice weekly) did not have a significant effect on tumour burden (2 animals in particular did not respond to OXA). ART26.12 ameliorated weight loss compared to vehicle control from day 27 ($p<0.05$, Figure 1B). Tumour-bearing animals had reduced paw withdrawal thresholds compared to naïve mice, indicating induction of pain. Pain behaviour was improved in animals treated with ART26.12 compared with vehicle on days 6 ($p<0.05$), 20 ($p<0.001$) and 27 ($p<0.0001$)(Figure 1C).

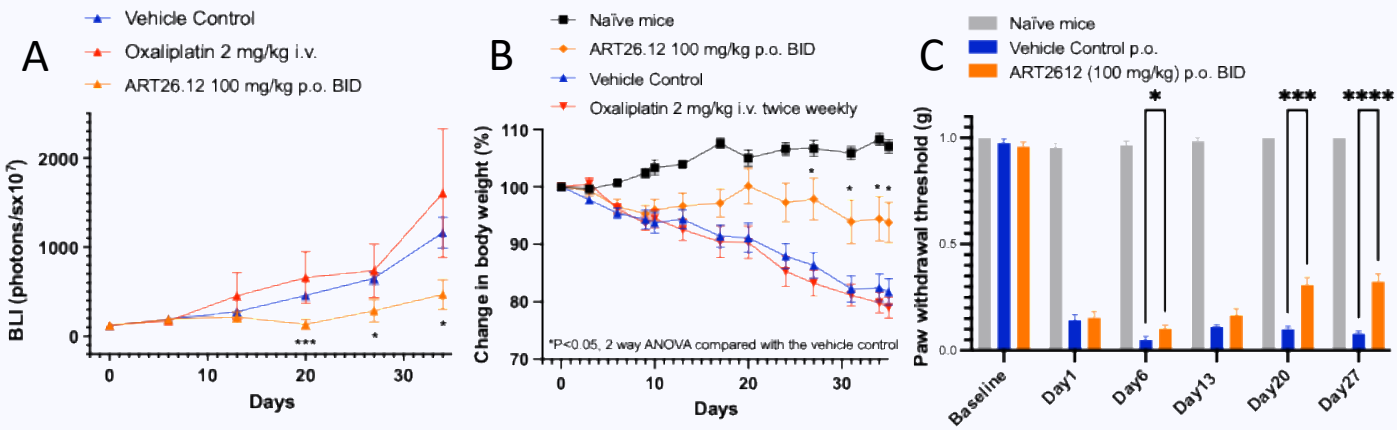


Figure 1. The effects of the FABP5 inhibitor ART26.12 in HCT-116-luc orthotopic xenograft. A) Tumour growth measured by bioluminescence imaging (BLI). B) Effect of tumour burden and treatments on body weight. C) Effect of tumour burden and treatments on paw withdrawal threshold, measured by Von Frey filaments. *<0.05 ***<0.001, ****<0.0001, 2 way ANOVA.

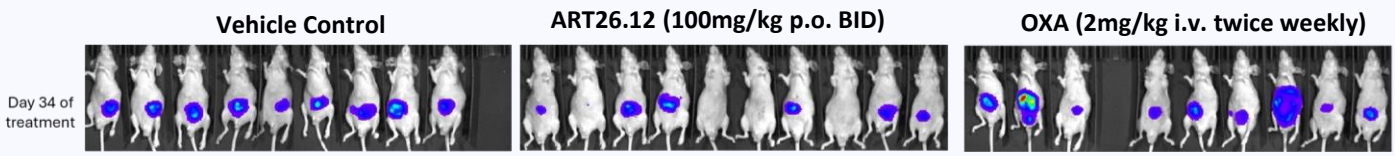


Figure 2. Bioluminescent readings of Tumour Burden on Day 34. Qualitative assessment of tumour burden highlights four well respondi mice to ART26.12, and two poorly responding mice to Oxaliplatin

Conclusions

In an *in vivo* orthotopic model of colorectal cancer, ART26.12 attenuated tumour growth, and ameliorated weight loss and cancer induced pain. This data supports the development of ART26.12 as a novel analgesic in oncology settings and establishes a direct anti-tumoral effect of FABP5 inhibition in colorectal cancer.

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