



# **A tumor-targeted CD40 agonistic DARPin<sup>®</sup> molecule leading to antitumor activity with limited systemic toxicity**

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## Disclosure Information



**I have the following financial relationships to disclose:**

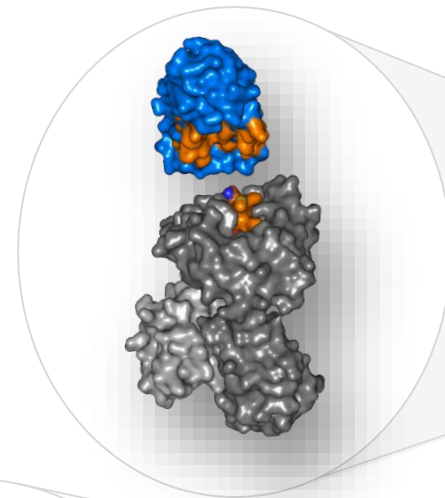
**Employe of: Molecular Partners AG, Schlieren-Zurich, Switzerland**

***- and -***

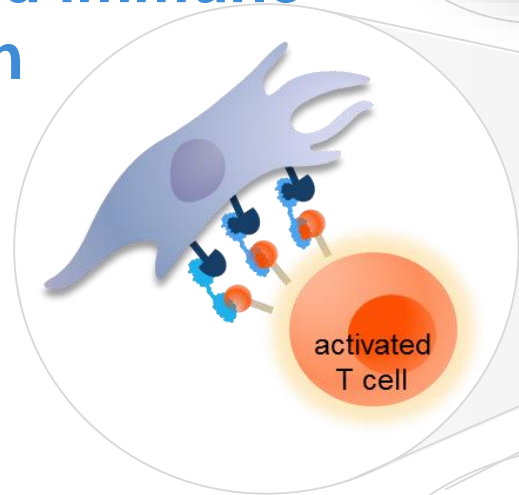
**I will not discuss off label use and/or investigational use in my presentation.**

# DARPin® platform

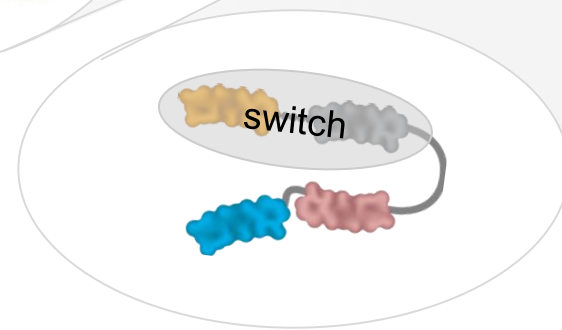
Targeting peptide  
MHC complexes  
**Poster 690**



Tumor-localized immune  
cell modulation  
**Poster 2273**

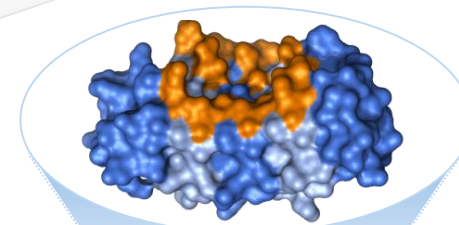


Next-generation  
T-cell engagers



## DARPin® Features

Rigid-body target binding



DARPin® domain

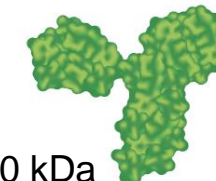
Multi-DARPin® formatting



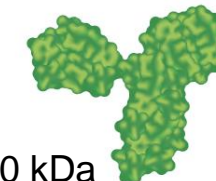
- High specificity and affinity
- Small size: 15 kDa
- Simple repetitive architecture: 1 polypeptide
- Tunable half-life

SCALE

15 kDa

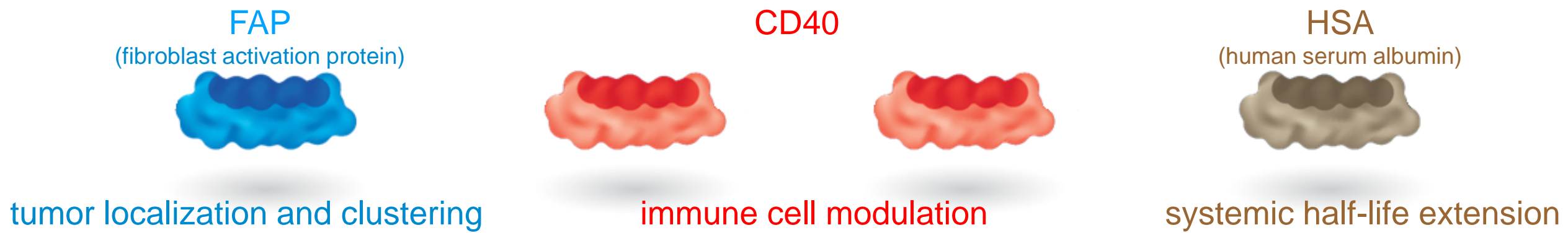


150 kDa

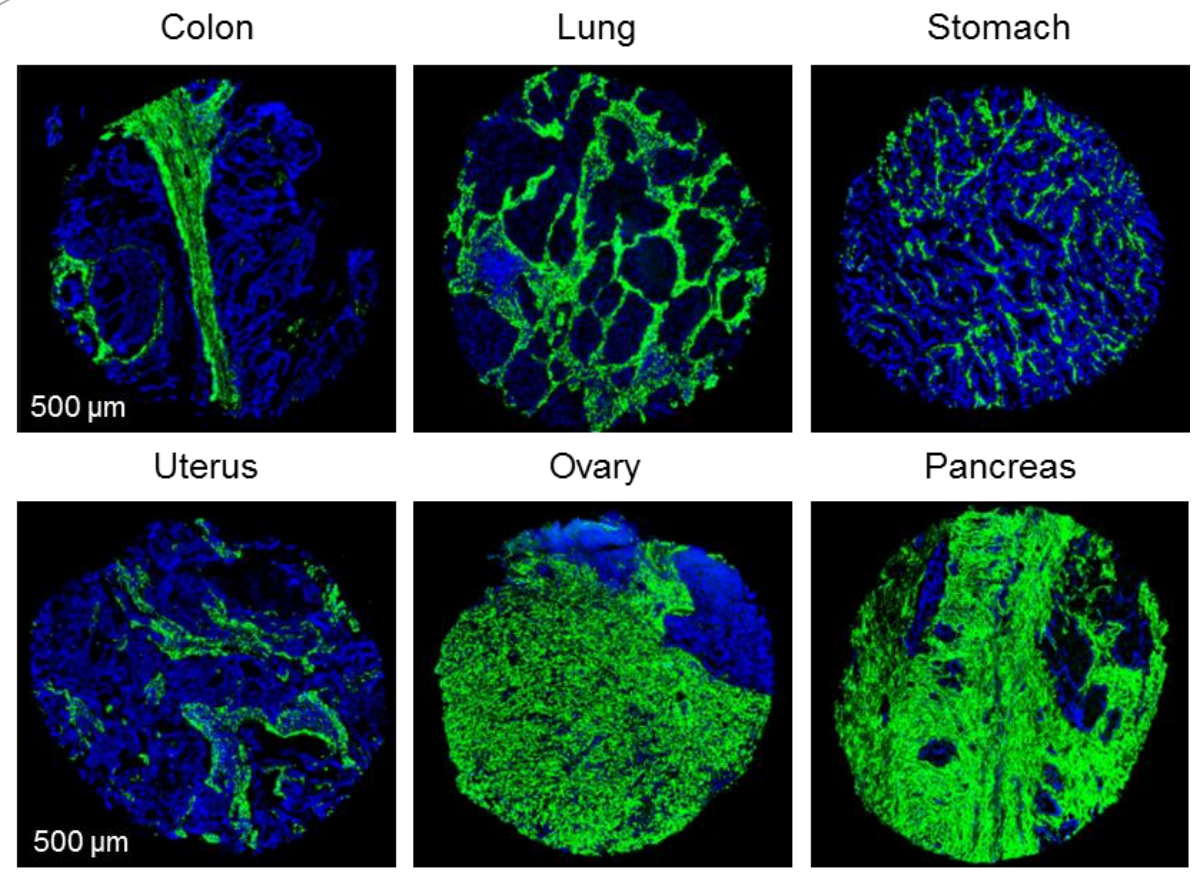




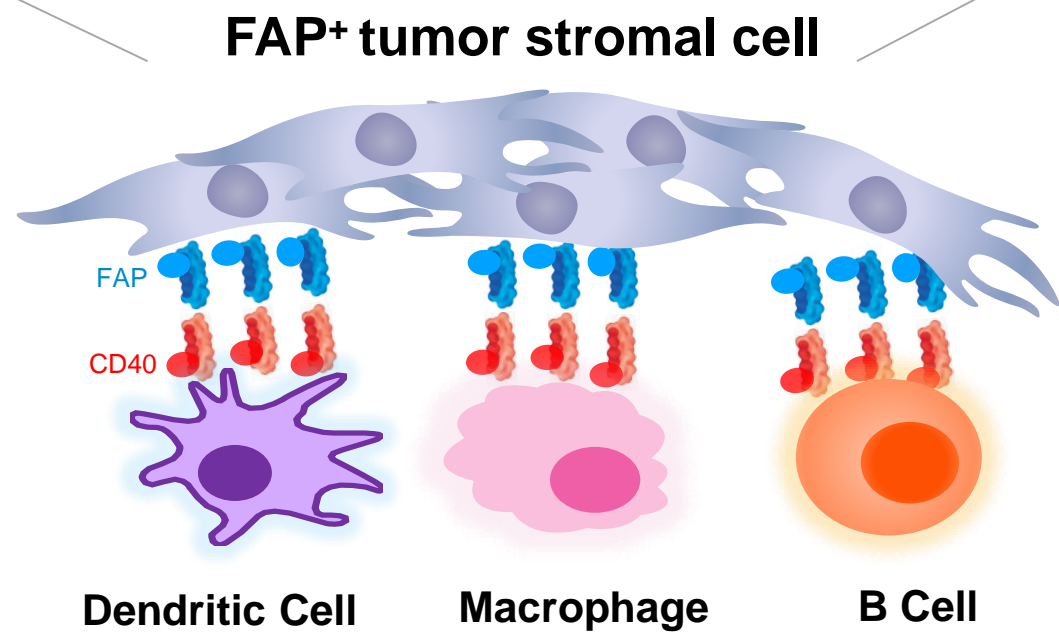
# MP0317, a multi-specific DARPin<sup>®</sup> molecule, designed to improve efficacy and safety via tumor localized CD40 agonism



## FAP expression in human tumor sections

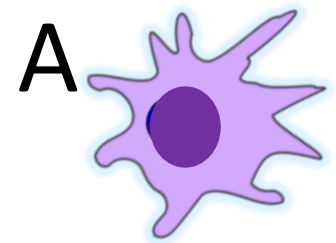


Human FAP, DAPI



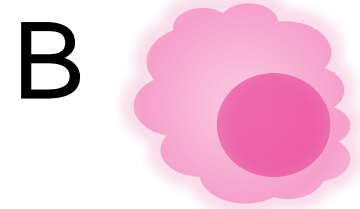
Tumor localized CD40 activation through cross-linking with FAP

# MP0317, a FAP-dependent MoA across different immune cell populations



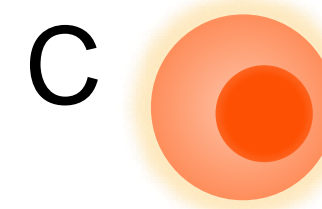
**A** Dendritic cells:

- CD86 ✓ IL-12 ✓
- CD83 ✓ CD80 ✓



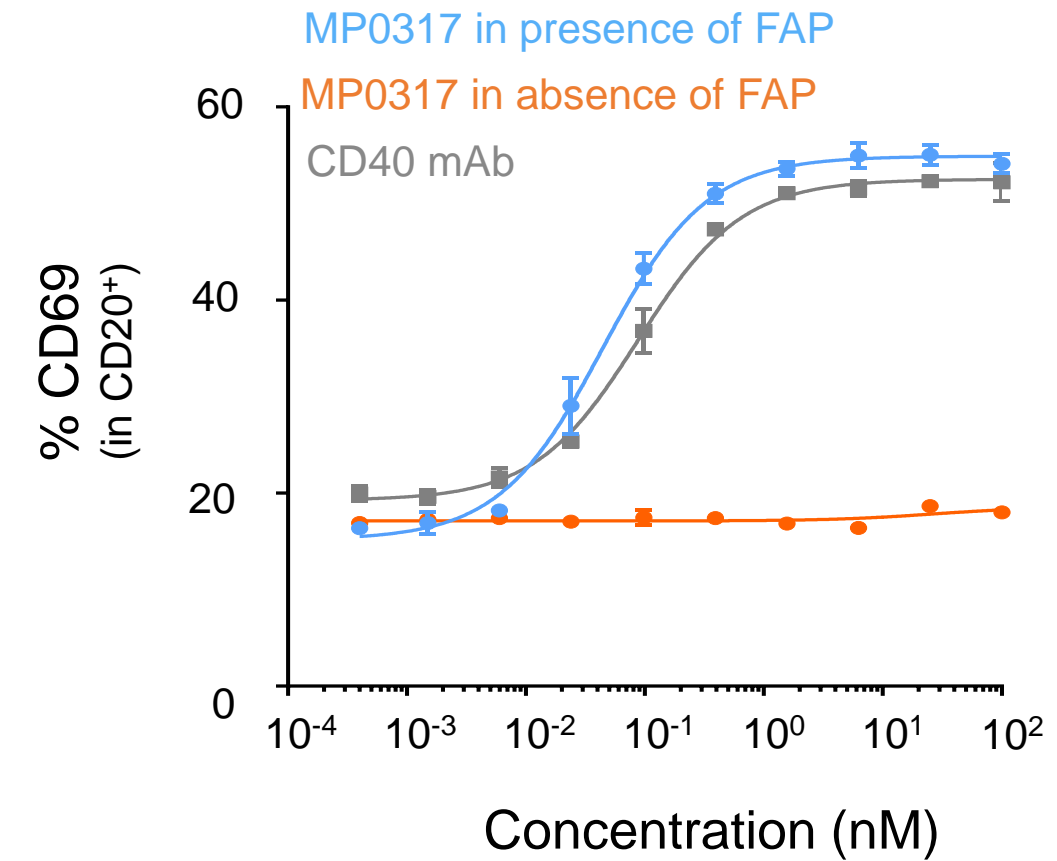
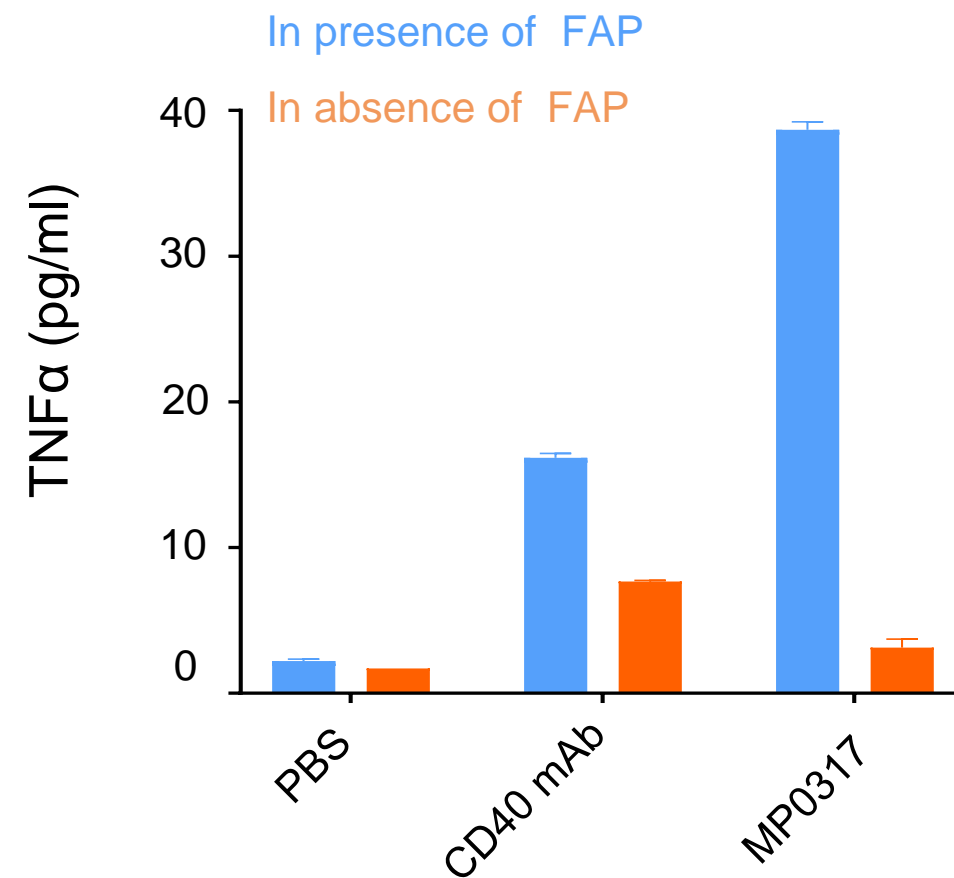
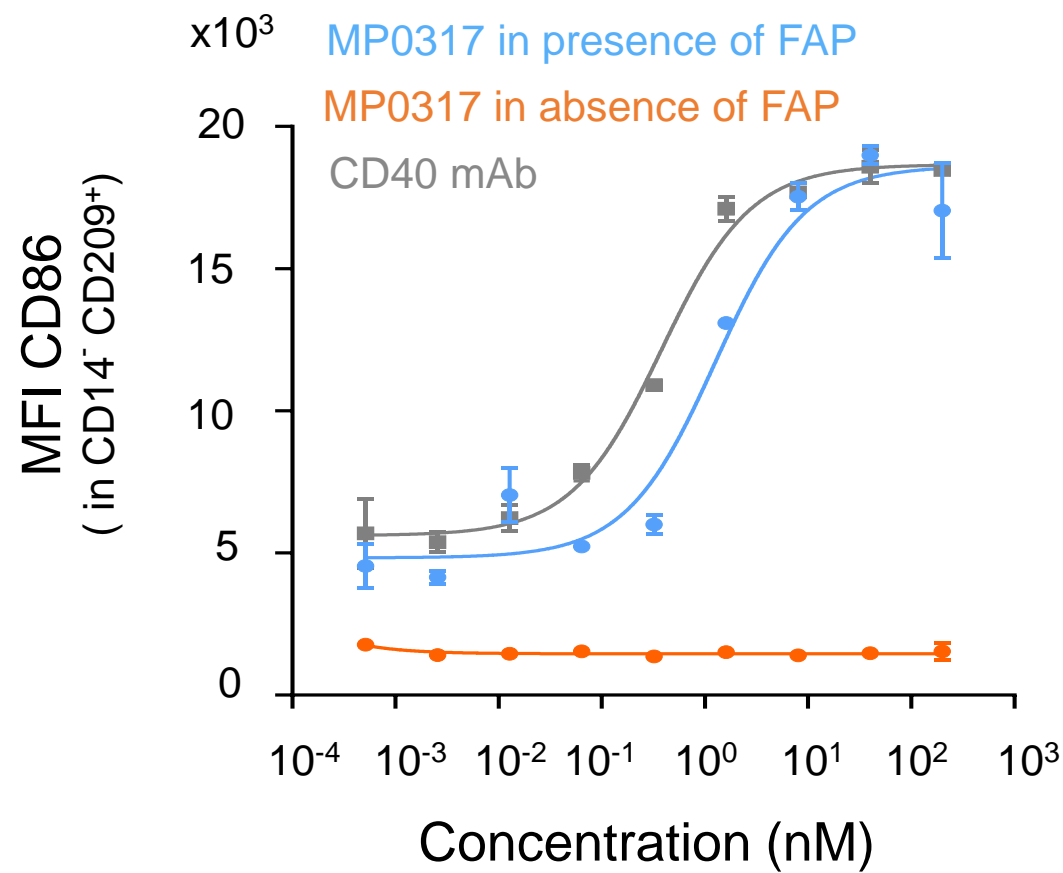
**B** Macrophages:

- TNF $\alpha$  ✓ IL-12 ✓
- IL-6 ✓ CCL17 ✓



**C** B cells:

- CD69 ✓
- CD86 ✓

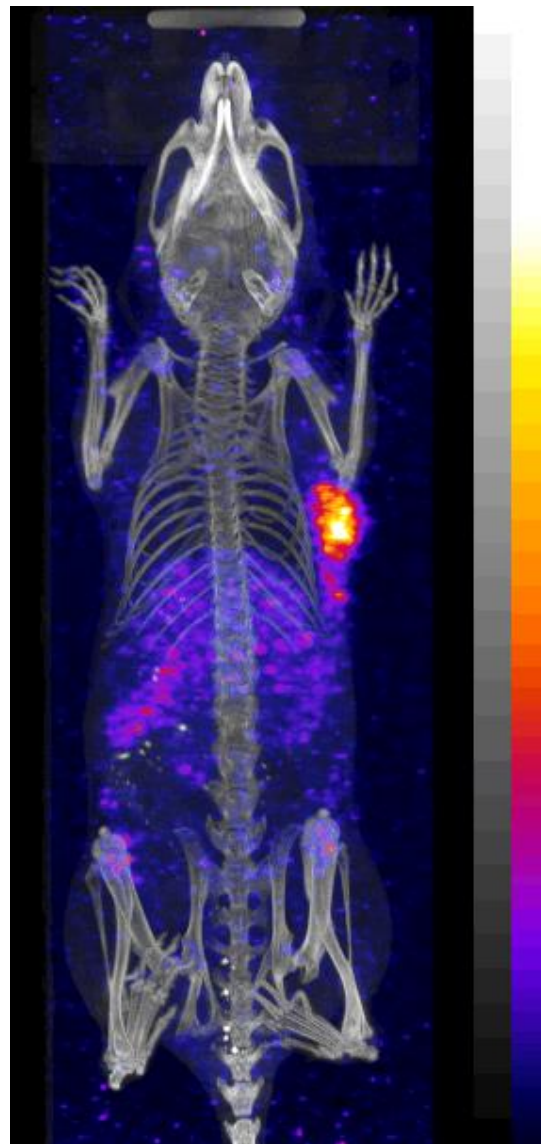




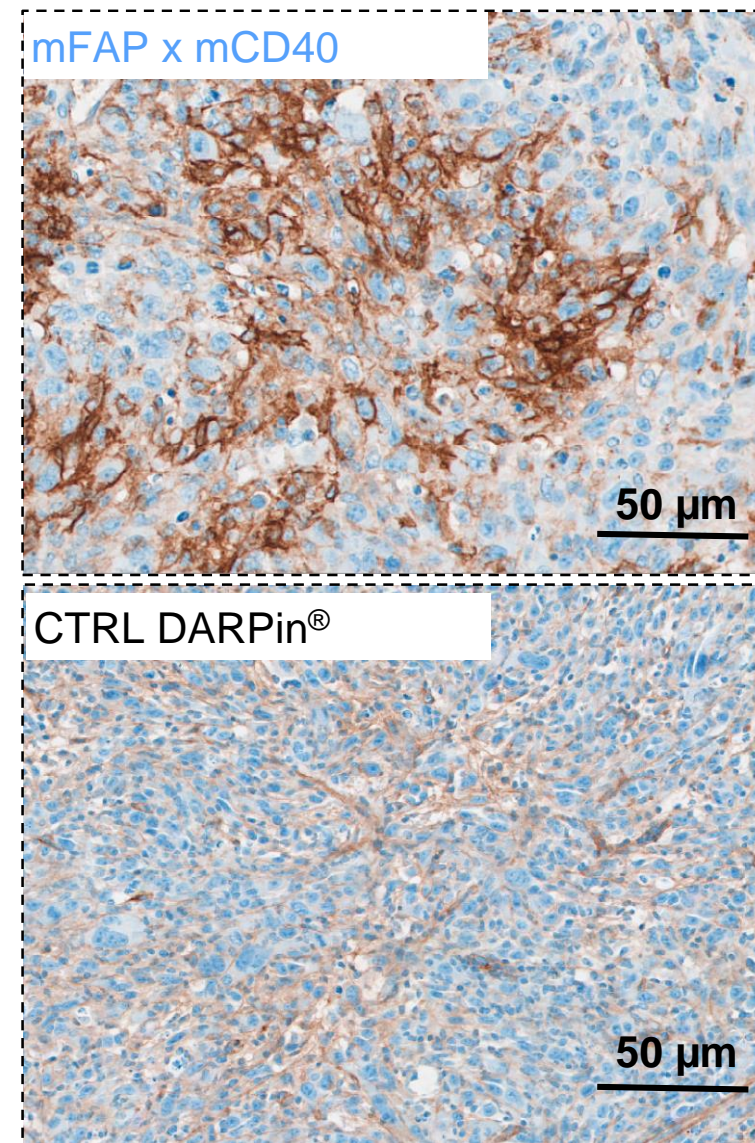
# Mouse-specific FAP x CD40 DARPin<sup>®</sup> molecule (mFAP x mCD40) localizes and accumulates to the FAP-transfected MC38 tumor (MC38-FAP)



**A** SPECT-CT study  
(mFAP x mCD40)

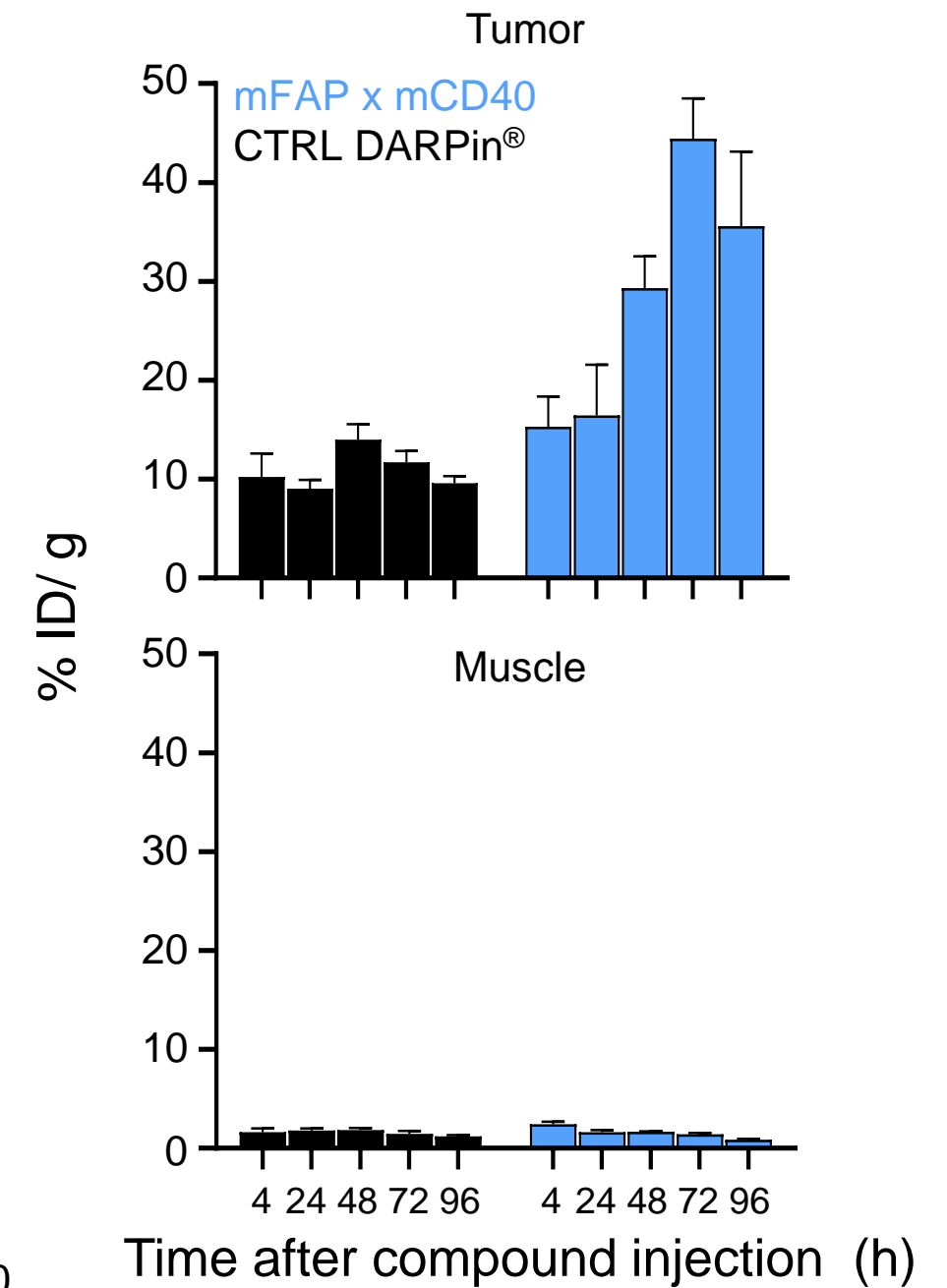


**B** Detection of the DARPin<sup>®</sup> in the tumor by IHC



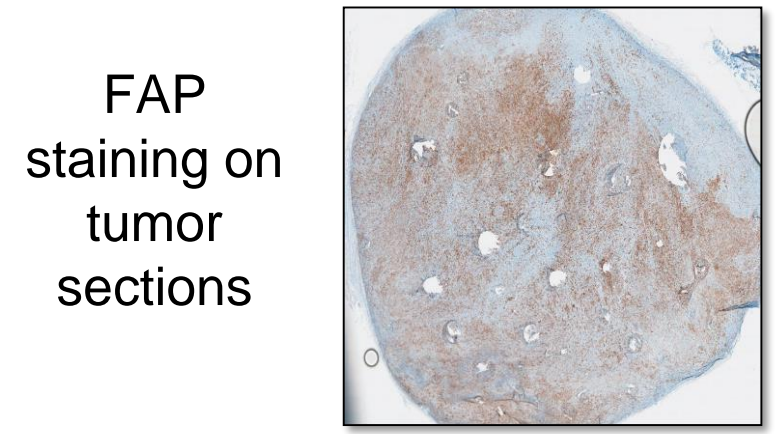
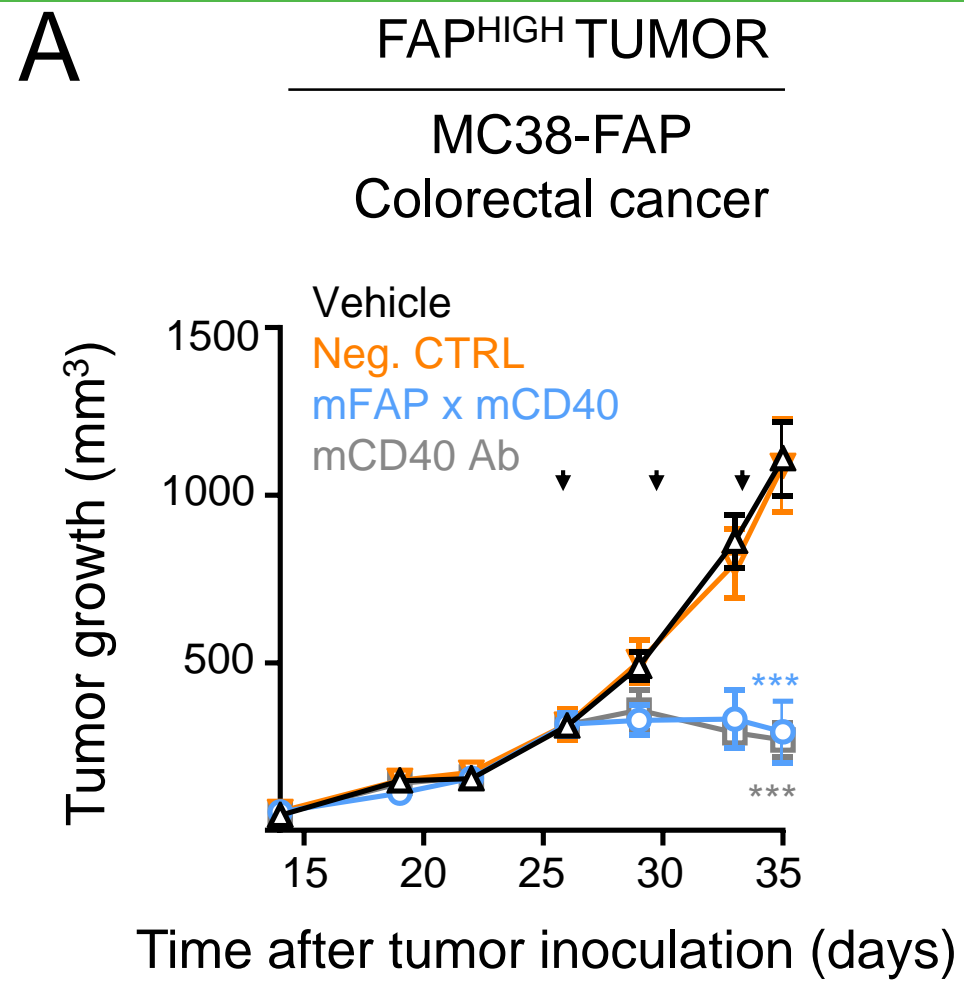
- CTRL DARPin<sup>®</sup> binding HSA, but neither FAP nor CD40

**C** Biodistribution study

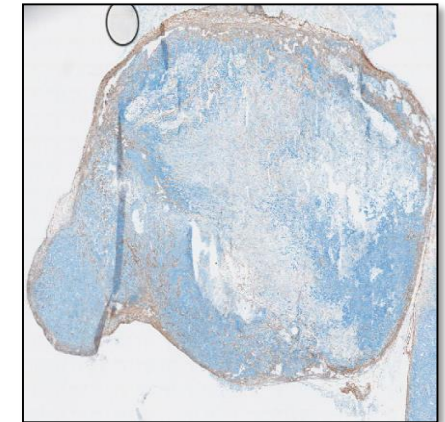
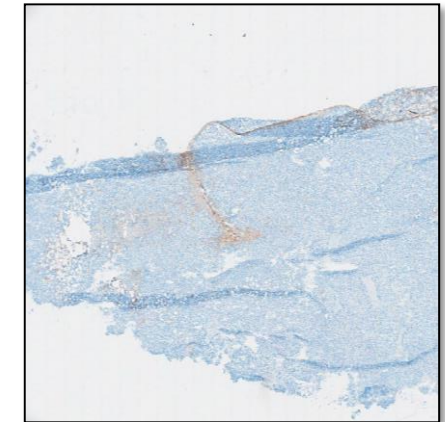
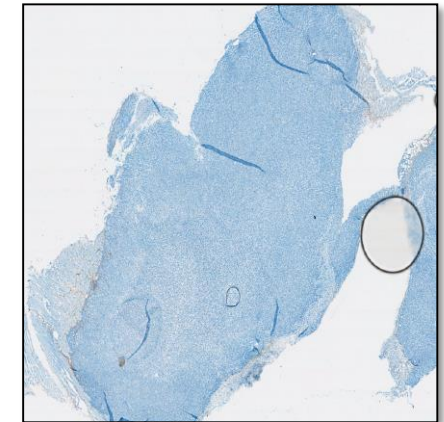
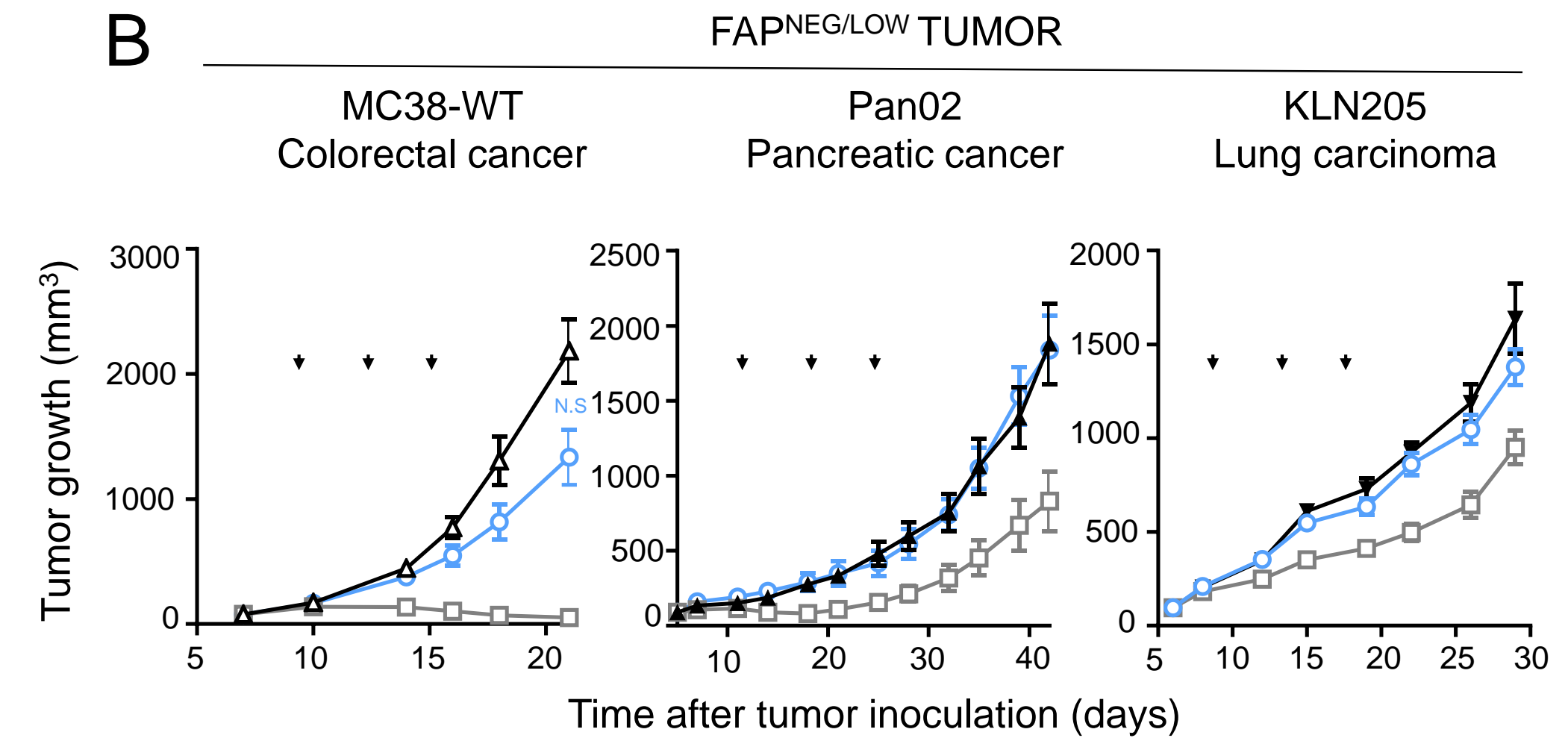




# mFAP x mCD40 restrains tumor progression in a FAP-dependent manner



Neg. CTRL, DARPIn<sup>®</sup> binding CD40 and HSA, but not FAP

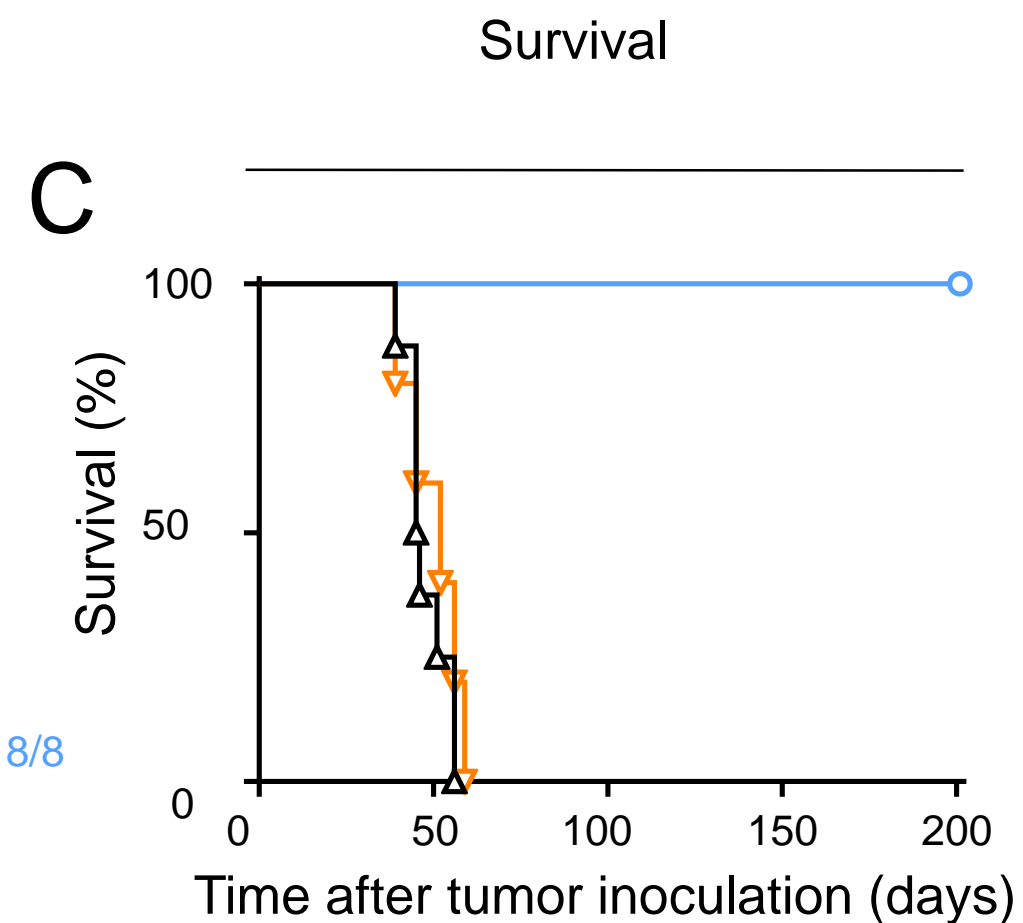
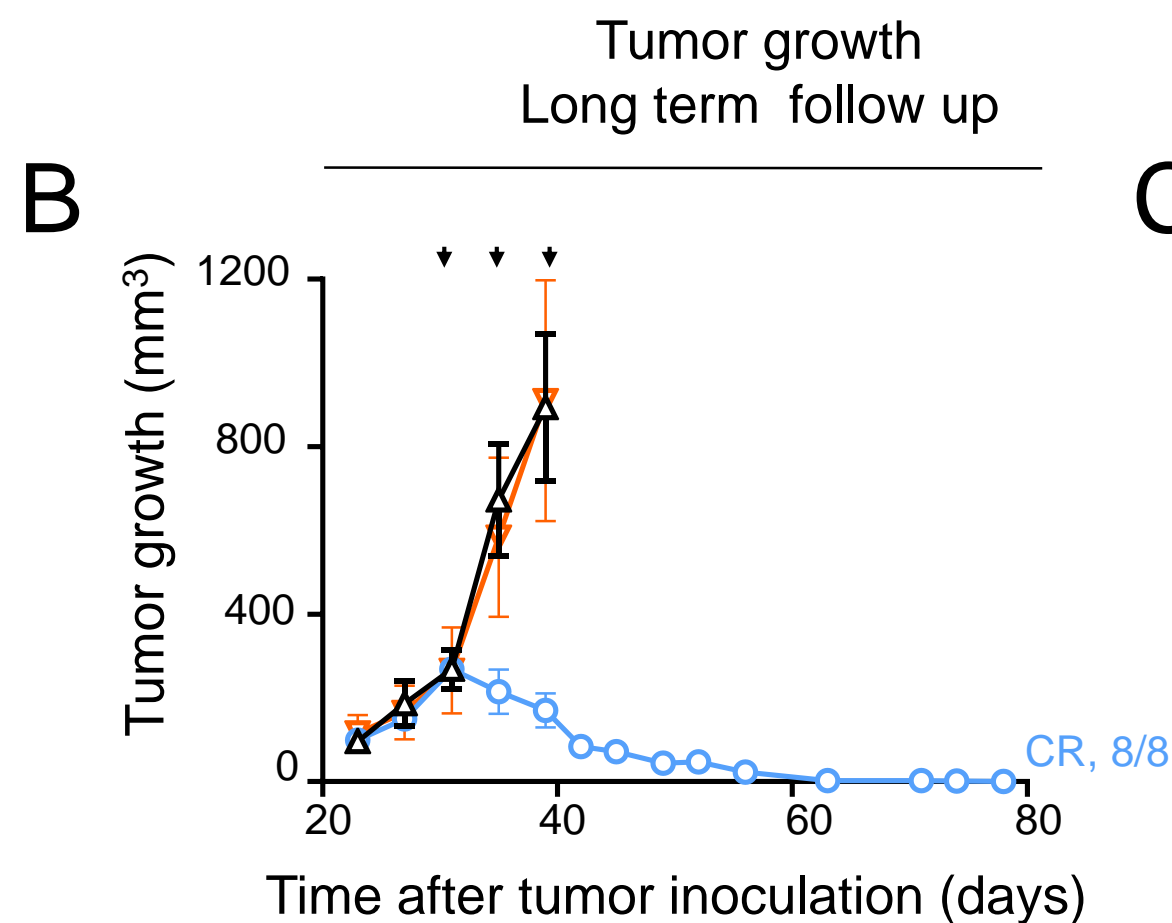
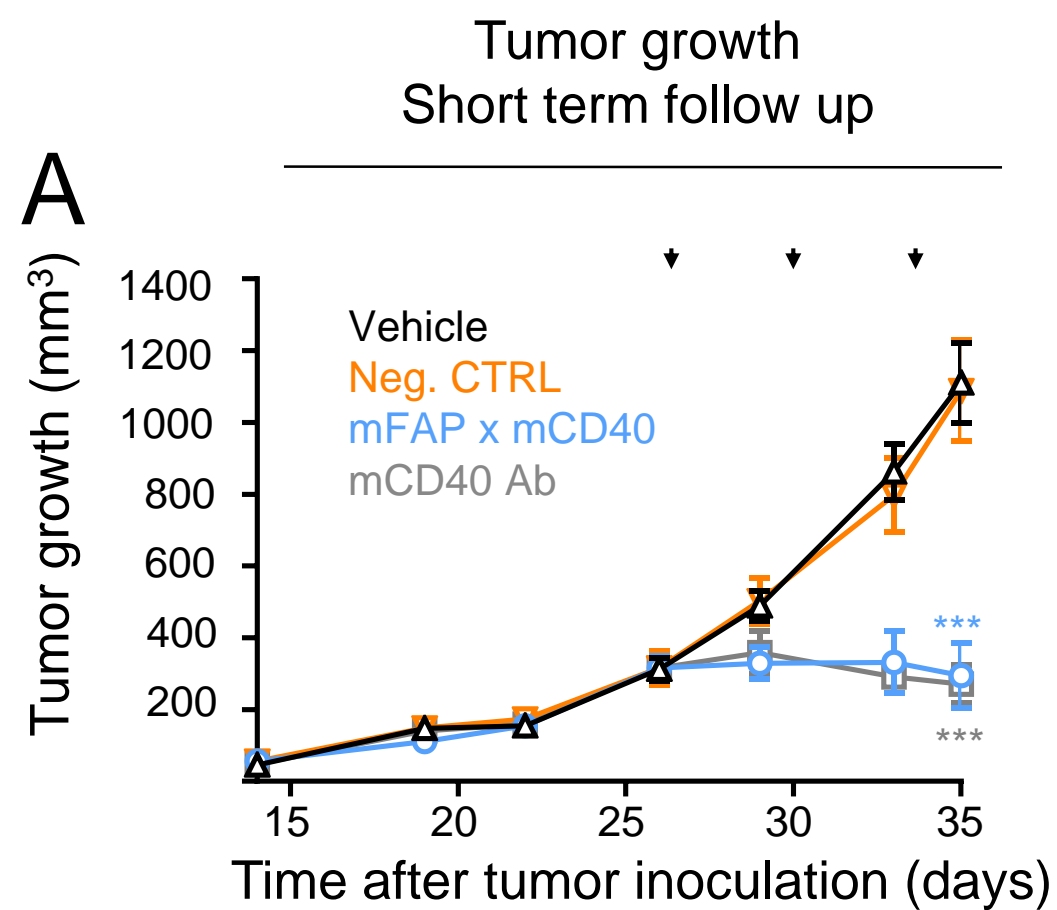


▼ =Treatments

# mFAP x mCD40 provides durable anti-tumor response in animals bearing FAP-transfected MC38 tumors

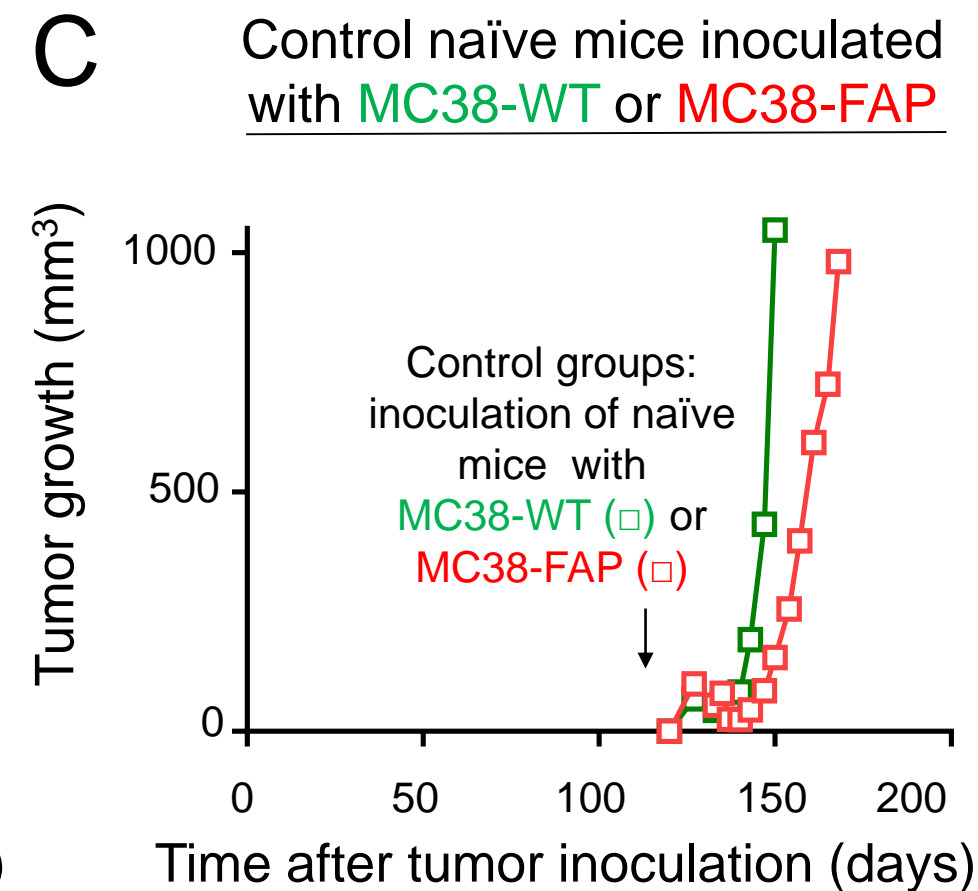
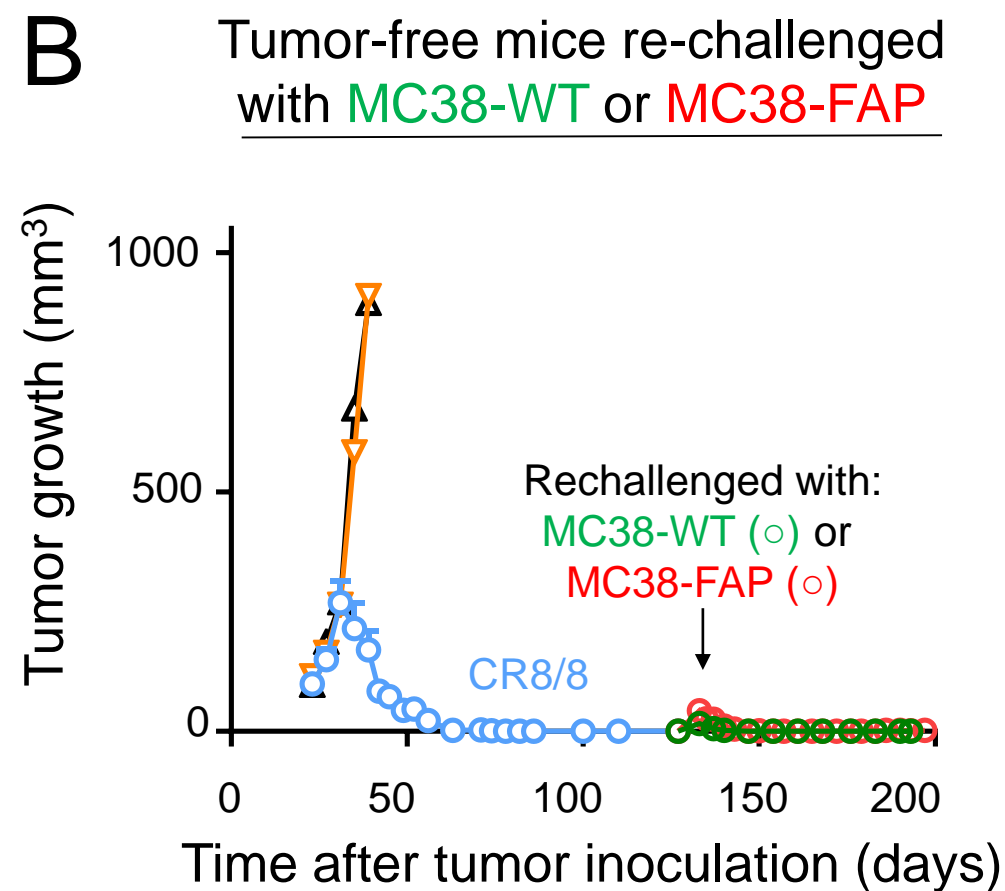
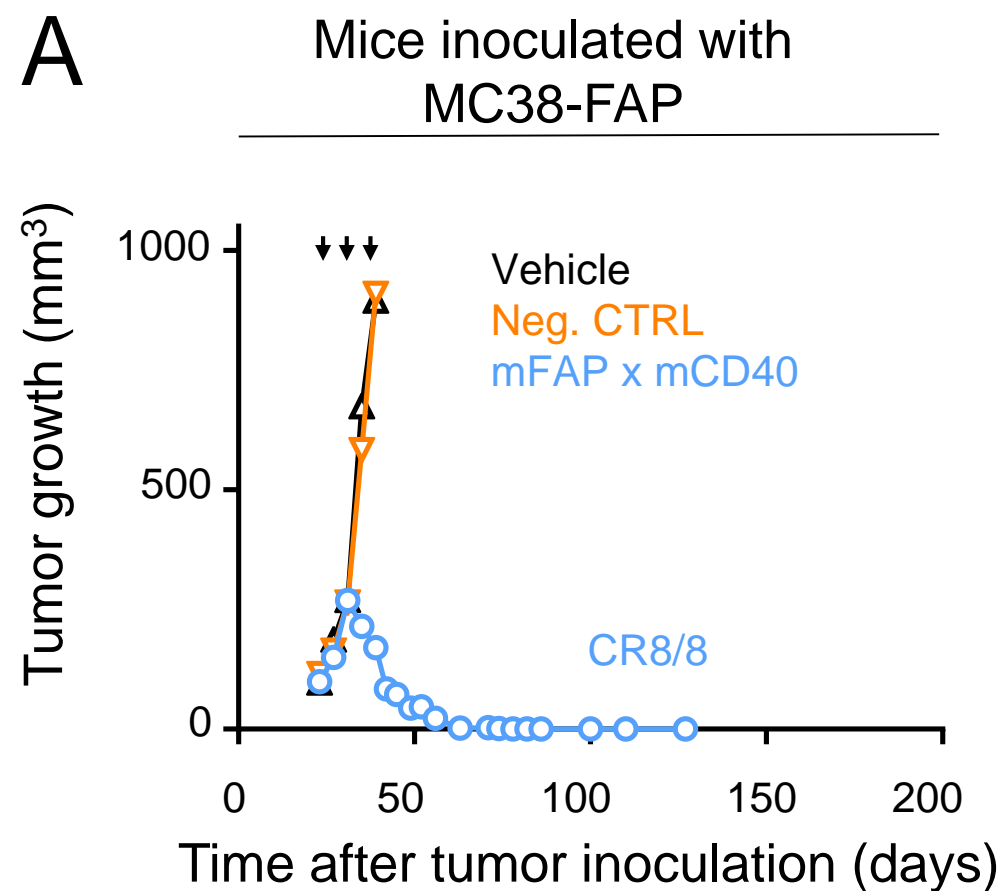


## MC38-FAP Colorectal cancer

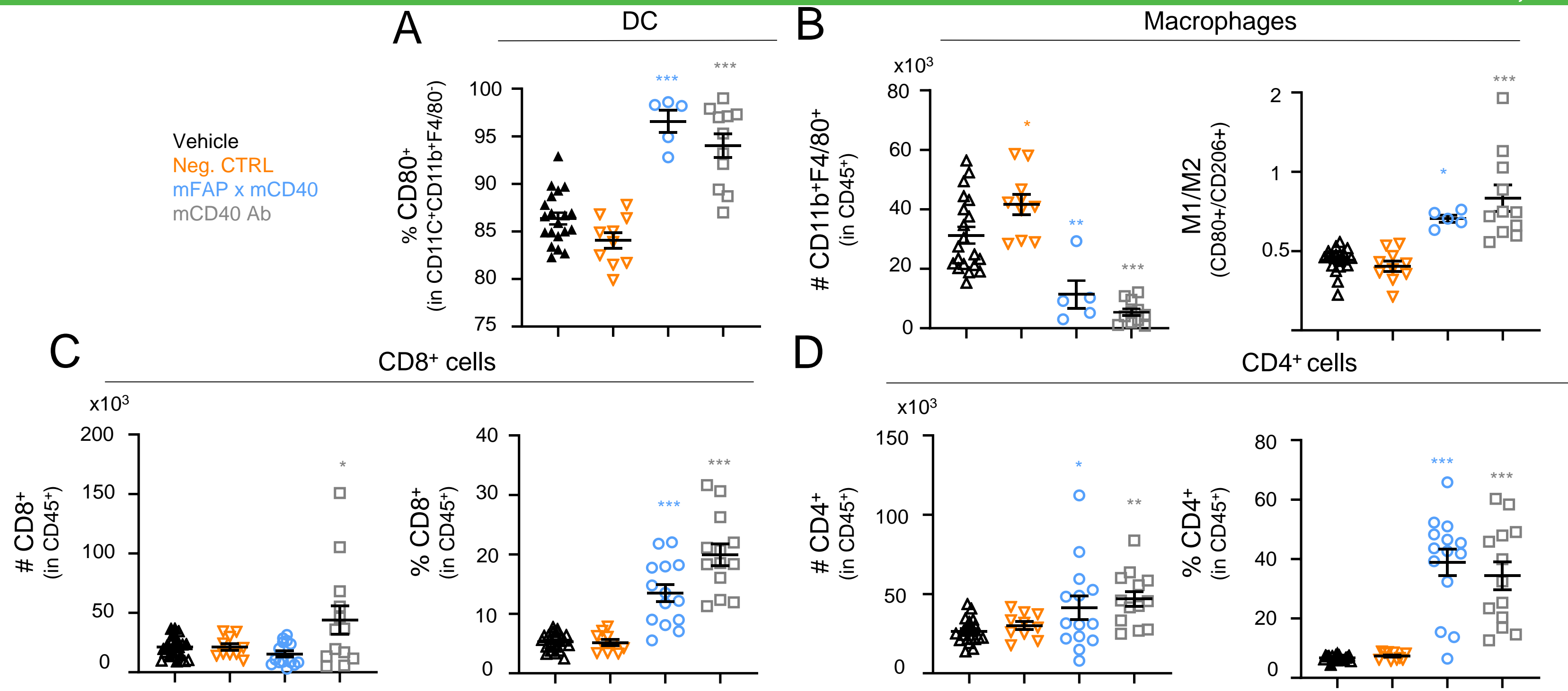




# mFAP x mCD40 induces a protective anti-tumor immunological memory that is not limited to the FAP antigen

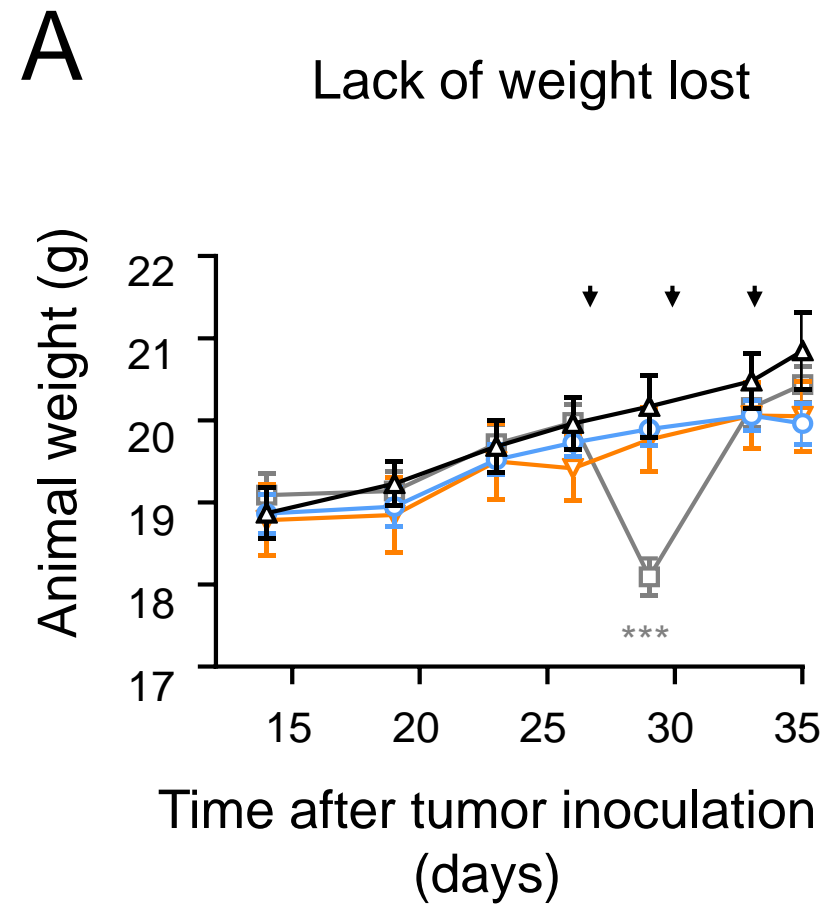


**In the TME, mFAP x mCD40 activates DC, increases the presence of M1-like macrophages and lymphocytes**



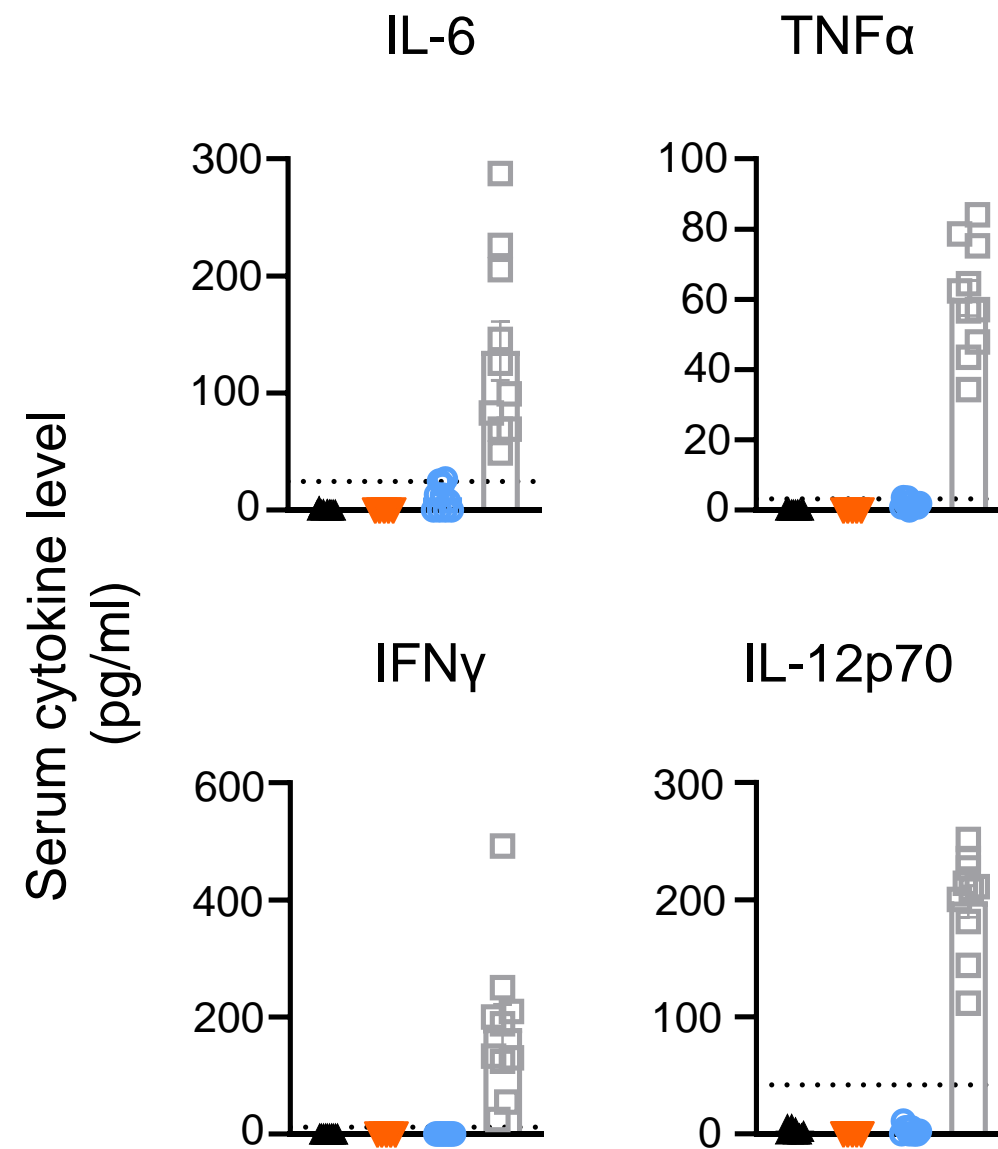


# Differently than CD40 Ab, mFAP x mCD40 does not show signs of systemic toxicity

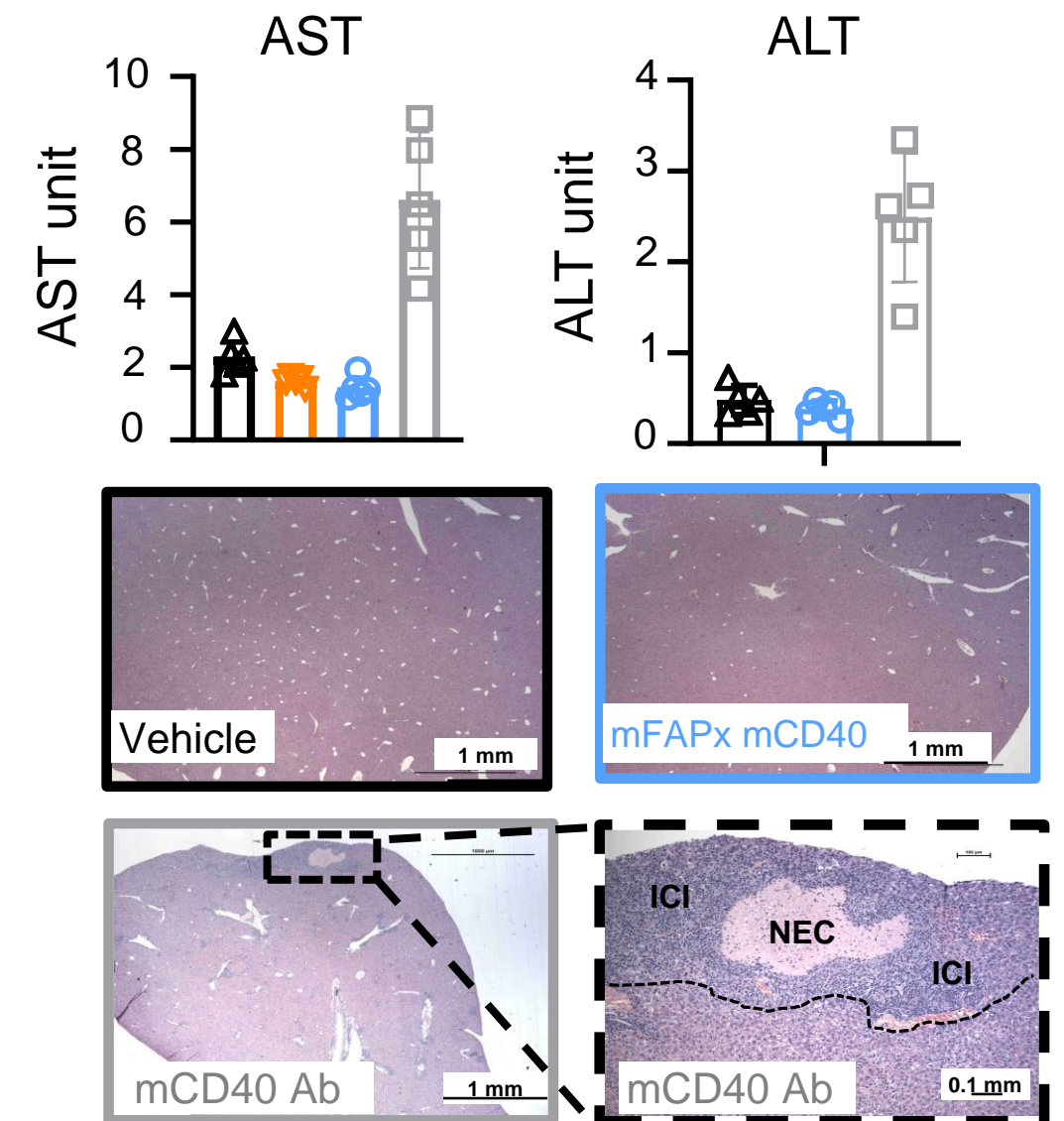


Vehicle  
 Neg. CTRL  
 mFAP x mCD40  
 mCD40 Ab

**B** Lack of increase of proinflammatory cytokines in the serum



**C** Lack of transaminase elevation in the serum and hepatocellular changes such as immune cell infiltration (ICI) and necrosis (NEC).



## Conclusions

- Double targeting FAP x CD40 DARPin<sup>®</sup> molecules activate in a FAP dependent manner different immune cell populations *in vitro* and induce a strong and durable antitumor response in FAP-positive tumors *in vivo* without showing signs of systemic toxicity
  - MP0317 activates *in vitro* 1) monocyte-derived dendritic cells 2) monocyte-derived macrophages and 3) B cells in a strictly FAP-dependent manner
  - Mouse mFAP x mCD40 shows a strong antitumor activity in FAP<sup>HIGH</sup> tumor-bearing mice, but has a negligible antitumor effect on FAP<sup>NEG</sup> or FAP<sup>LOW</sup> neoplasias confirming a FAP-specific MoA *in vivo*
  - mFAP x mCD40 generates anti-tumor immune memory response
  - mFAP x mCD40 affects the DC and macrophages and increases the percentage of lymphocytes in the TME
  - mFAP x mCD40, differently than the CD40 Ab, does not show signs of systemic toxicity





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