

# Logic-Gated Switch-DARPin T Cell Engager with CD2 Co-Stimulation for Improved Safety and Efficacy in MSLN and EpCAM Co-Expressing Ovarian Cancer – MP0632

Poster #1624

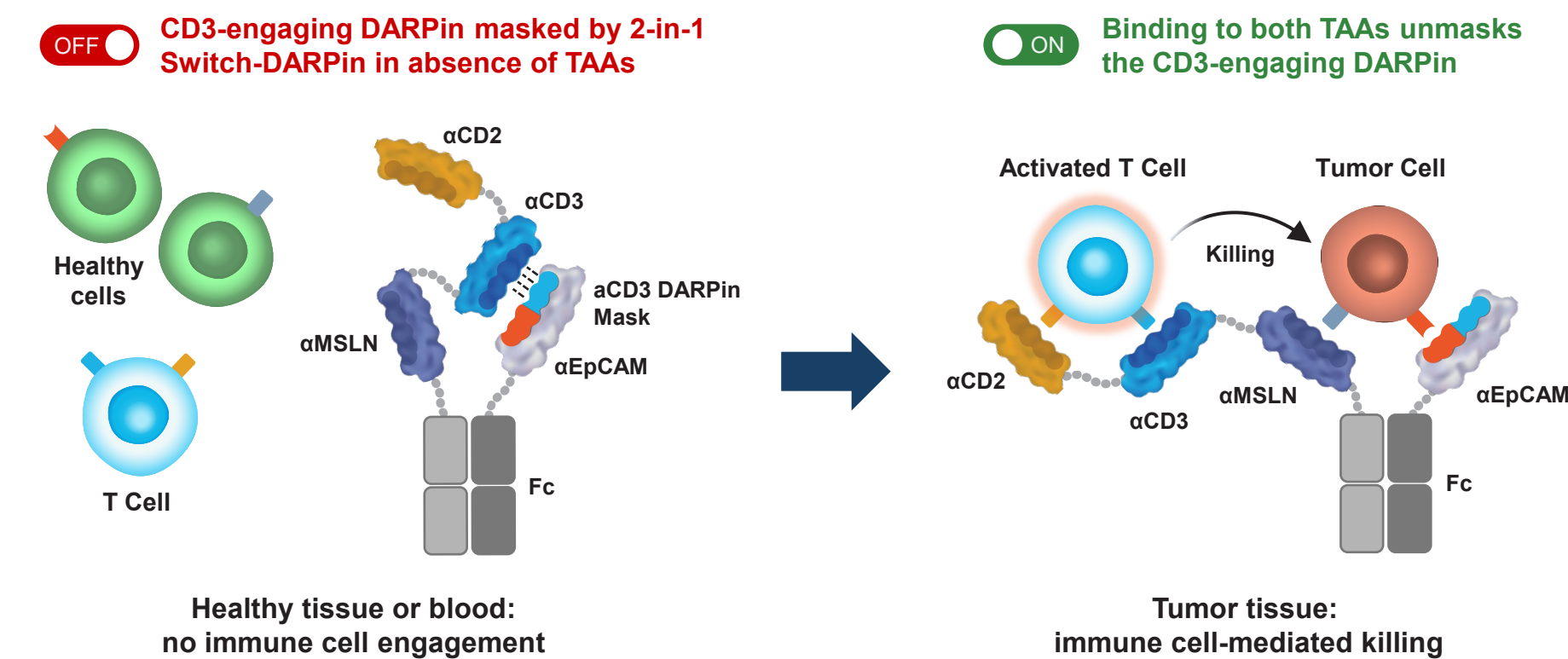
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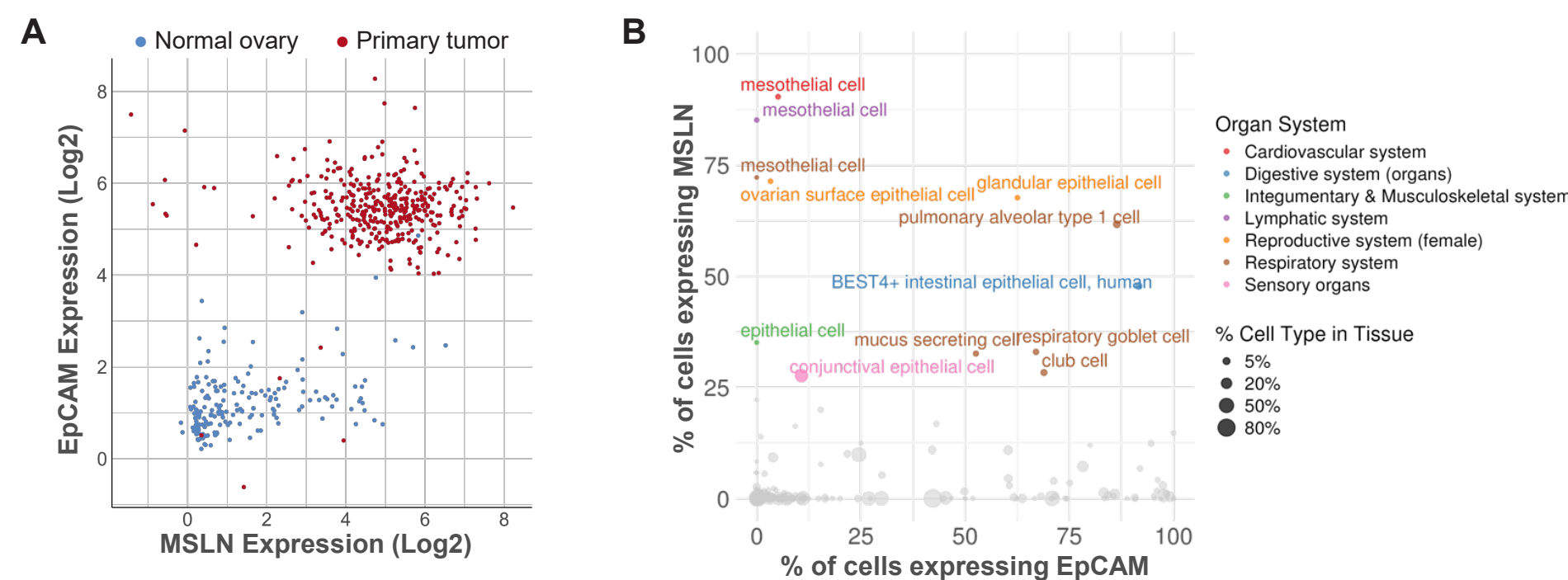
## Introduction

- Ovarian cancer (OC) remains the leading cause of cancer mortality in women, with a 5-year overall survival rate of ~51% due to late diagnosis and a high relapse rate.<sup>1</sup>
- Immunotherapy has shown limited success in OC, largely due to the scarcity of specific tumor-associated antigens (TAAs), the presence of dysfunctional T cells, and an immunosuppressive tumor microenvironment.<sup>2,3</sup>
- Particularly, the lack of “clean” TAAs has challenged the development of T cell engagers (TCEs) in OC, leading to on-target/off-tumor toxicity in normal tissues.
- To overcome these challenges, we developed MP0632: a multi-specific, logic-gated TCE targeting the TAAs mesothelin (MSLN) and EpCAM, with low-affinity CD3 engagement & CD2 co-stimulation.
- The conditional Switch-DARPin design employs an AND-gate mechanism, enabling CD3 engagement only upon simultaneous recognition of both TAAs.
- Our strategy aims to deliver sustained antitumor activity while minimizing systemic toxicity and off-tumor effects on single TAA-expressing healthy cells.

## MP0632: a MSLN/EpCAM AND-gated Switch-DARPin TCE with CD2 co-stimulation

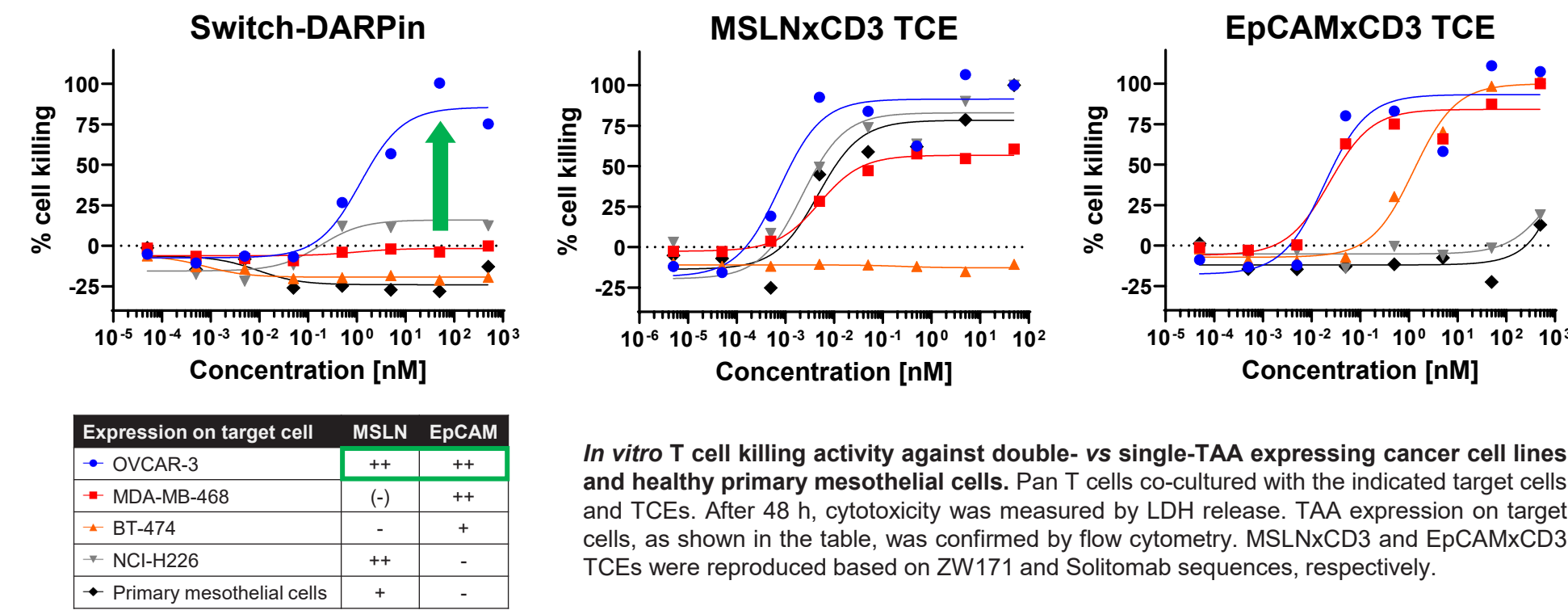


## MSLN & EpCAM are highly co-expressed in OC vs healthy tissues<sup>4</sup>

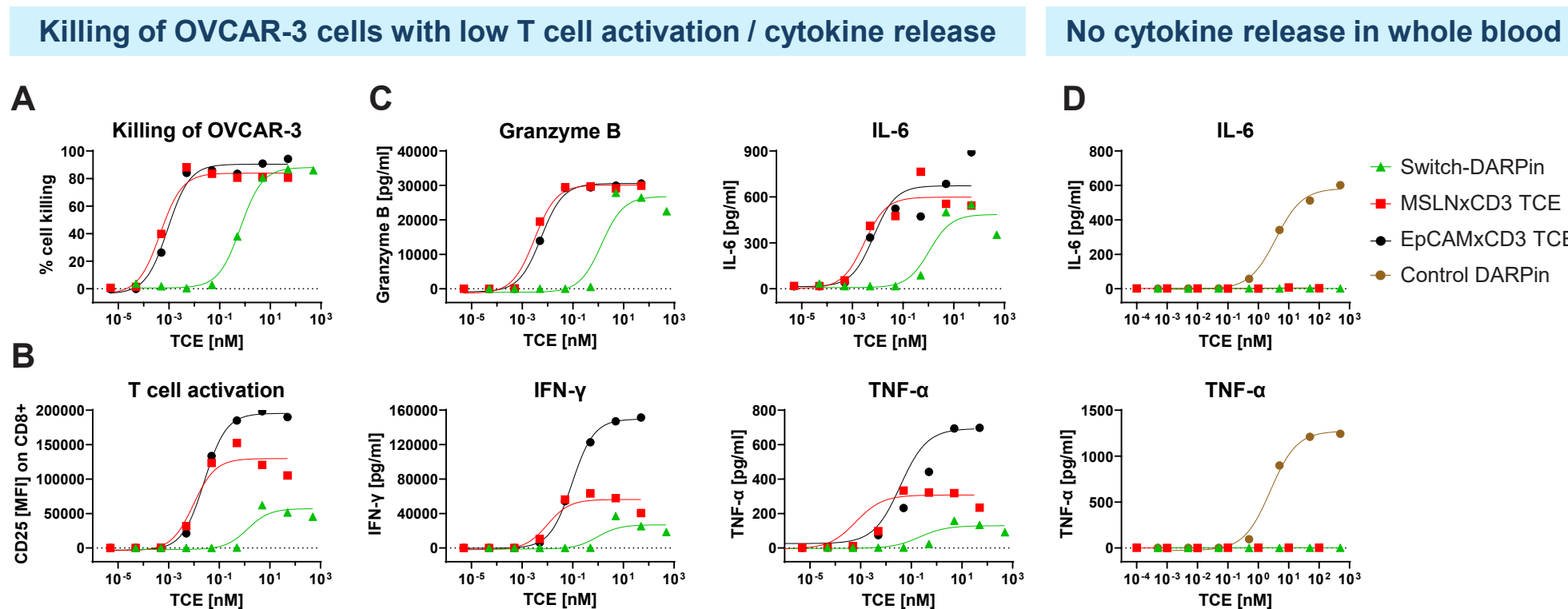


MSLN and EpCAM expression in OC and healthy tissues. (A) Tissue sample biopsies from TCGA and GTEx were analyzed for MSLN and EpCAM expression (RNAseq, bulk). (B) The Tabula Sapiens data set was analyzed to determine the fraction of cell types across different human healthy tissues expressing either MSLN, EpCAM, or both (RNAseq, single-cell).

## MP0632 selectively targets MSLNxEpCAM co-expressing cells

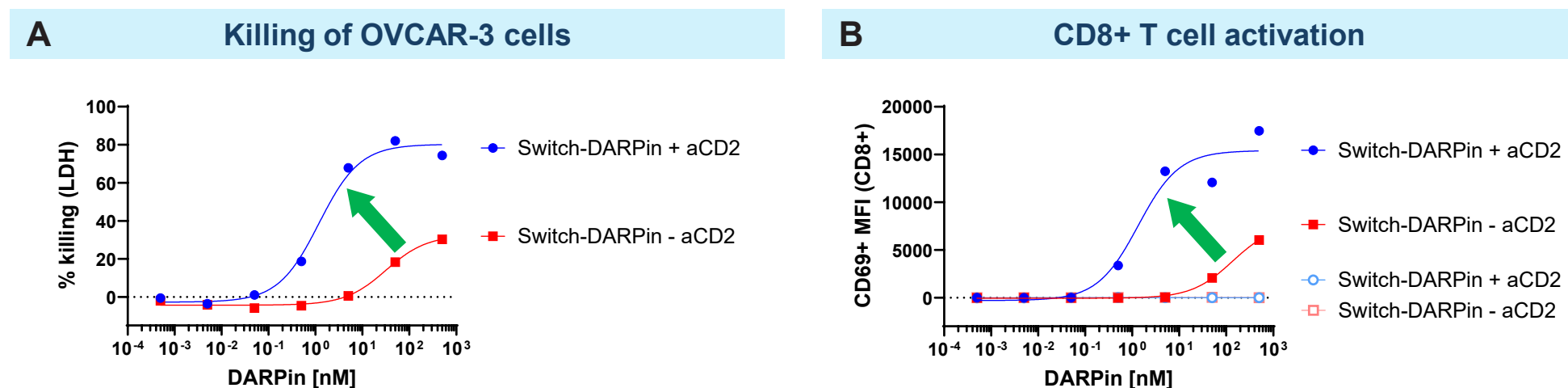


## MP0632 shows favorable cytotoxicity vs cytokine release profile



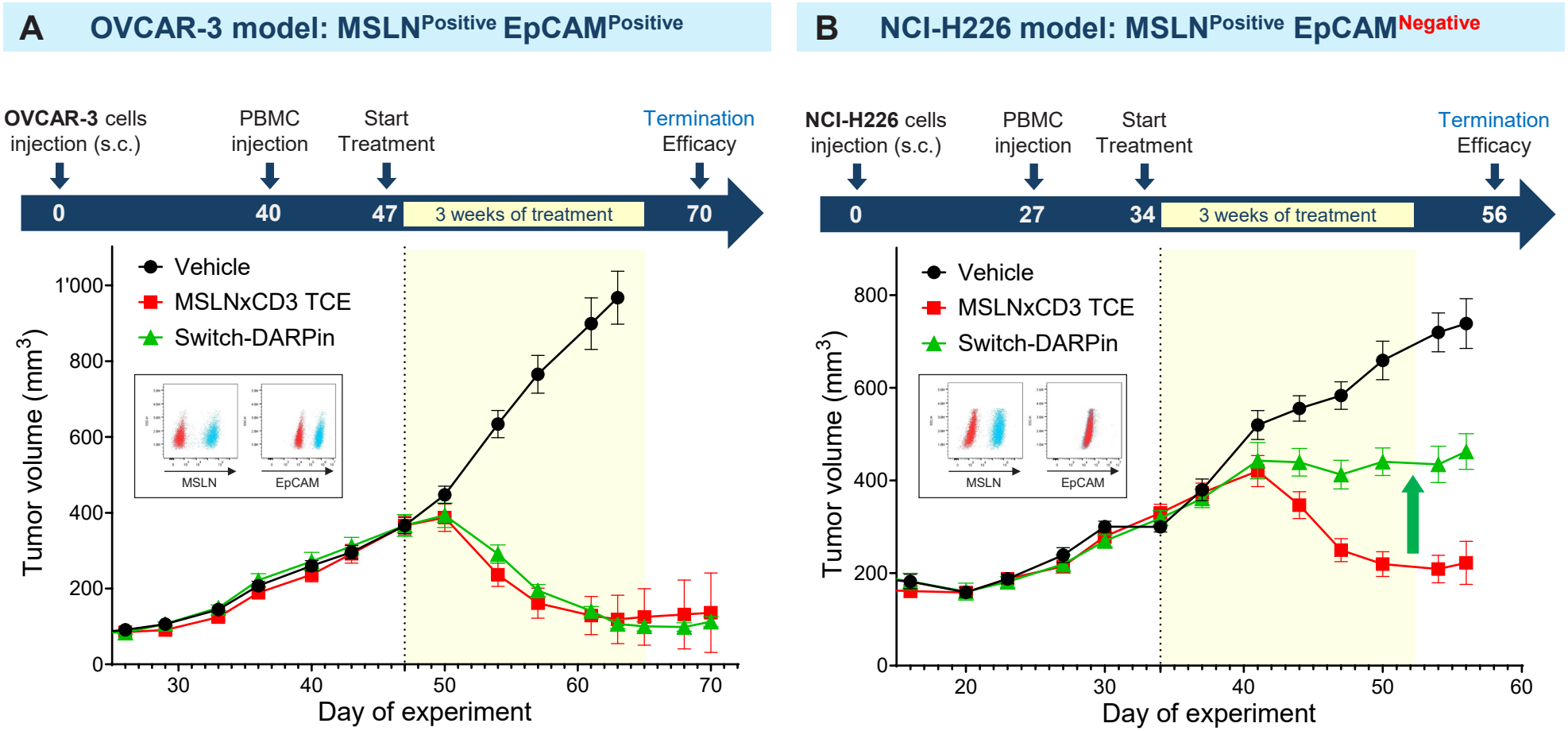
*In vitro* / *ex vivo* T cell activation, killing, and cytokine release assays. (A-C) Pan T cells co-cultured 72 h with OVCAR-3 cells (E:T = 2:1) and indicated TCEs. (A) Killing of OVCAR-3 was measured by LDH release, (B) T cell activation by CD25 upregulation on CD8 T cells using flow cytometry, (C) and cytokines released in supernatants by MSD U-plex. (D) Whole blood from healthy human donors was incubated for 24 h with indicated TCEs. Cytokines in the supernatants were measured by MSD U-plex. N of donors = 2 for both assays. MSLNxCD3 and EpCAMxCD3 TCEs based on ZW171 and Solitomab sequences, respectively. Control DARPin: EpCAMxMSLNxCD3xCD2 without Switch.

## CD2 co-engagement further improves T cell activity

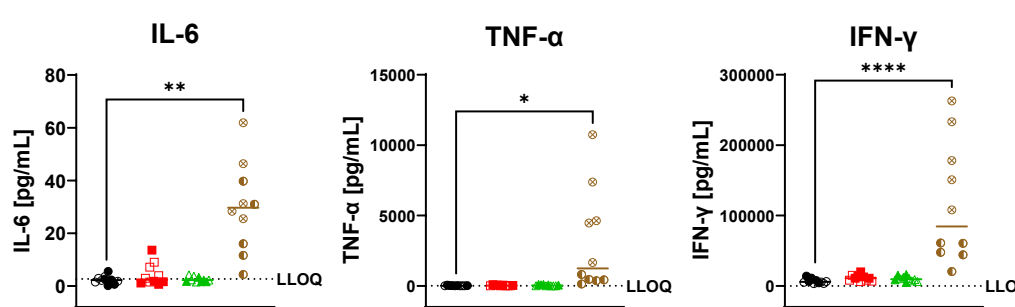


*In vitro* activity of Switch-DARPin with vs without CD2 co-engagement. Pan T cells co-cultured with OVCAR-3 target cells and Switch-DARPins +/- anti-CD2 domain. After 48 h, (A) cytotoxicity was measured by LDH release, and (B) T cell activation by measuring CD69 upregulation on CD8 T cells using flow cytometry. Open symbols show incubation of Switch-DARPins with T cells only.

## In vivo, MP0632 leads to killing of MSLN/EpCAM co-expressing OC tumors, while sparing MSLN single-expressing tumors



## No TAA-independent systemic cytokine release with Switch



*In vivo* anti-tumor activity and specificity. (A) OVCAR-3 (MSLN+EpCAM+) or (B) NCI-H226 (MSLN+EpCAM-) cells were subcutaneously (s.c.) engrafted into immune-deficient NXG mice and humanized with PBMC (2 donors) on day 40 and 27 post tumor cell engraftment, respectively. Treatment started 7 days after PBMC injection. The Switch-DARPin was injected at 3 mg/kg (i.v.) two times a week for 3 weeks, while the MSLNxCD3 TCE was dosed weekly at 3 mg/kg (i.v.). Tumor volumes are shown as mean +/- SEM, N=10 per group. MSLN and EpCAM expression on cell lines (cyan) vs FMO controls (red) is shown. (C) Cytokines measured in serum 2 h post first-injection (OVCAR-3 model). Median and significance by Kruskal-Wallis test are shown. (D) Human CD4 and CD8 T cell count at study termination (OVCAR-3 model). Open and closed symbols represent PBMC donors A and B, respectively. MSLNxCD3 TCE based on ZW171 sequence. Control DARPin: with non-functional Switch.

## Conclusions

Preclinical proof of concept for MP0632's AND-gated Switch-DARPin design and its favorable therapeutic window:

- Selective T cell cytotoxicity against cells co-expressing MSLN and EpCAM *in vitro*, with attenuated to no activity against single-TAA-expressing cancer cell lines and primary healthy mesothelial cells.
- Robust regression of established MSLN+EpCAM+ OC tumors *in vivo*, with low activity in EpCAM-negative lung cancer model.
- Safe incorporation of a CD2 co-stimulatory domain for efficient tumor cell killing while maintaining a favorable low cytokine release profile.

Together, these data establish MP0632 as our clinical development candidate and support advancement into IND-enabling studies for OC and other MSLN+EpCAM+ solid tumors.

For any questions, please contact: info@molecularpartners.com / attention of A. Link

References: 1. <https://seer.cancer.gov/statfacts/html/ovary.html> 2. Ghisoni et al., Nat Rev Clin Oncol. 2024; 3. Gupta et al. Trends Immunol. 2025; 4. Toska et al., AACR2026, Abstract #2691

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