MP0632, a logic-gated conditional Switch-DARPin T cell engager with CD2 co-stimulation enabling selective activity against solid tumors co-expressing MSLN and EpCAM

Poster #1072

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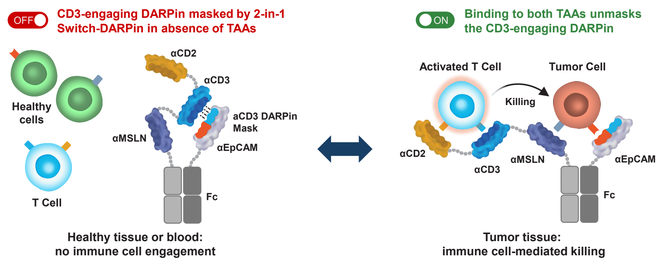
Introduction

Developing T cell engagers (TCEs) against solid tumors is often hampered by a scarcity of specific tumor-associated antigens (TAAs), which limits selectivity and increases the risk of on-target/off-tumor toxicity.

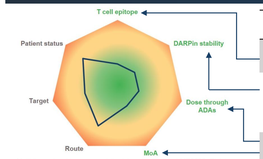
MP0632 aims to deliver durable antitumor activity, while sparing healthy cells expressing only a single TAA and thus limiting systemic toxicity:

- MP0632 is designed for **AND-gated** dual-targeting of mesothelin (MSLN) and EpCAM. Both TAAs are co-expressed in multiple solid tumor indications such as ovarian and endometrial cancer, lung and pancreatic adenocarcinoma, while showing low co-expression in healthy tissues.
- Through its **conditional** mode of action, MP0632 selectively engages CD3 in the tumor while avoiding on-target T cell activity in the periphery.
- No proteolytic cleavage is required to activate MP0632 in the tumor microenvironment which ensures **reversible** CD3 masking when disengaged from tumor cells.
- The Switch-DARPin design also integrates **CD2 co-stimulation** to support sustained T cell activity in the tumor.

MP0632, a conditional Switch-DARPin T cell engager



MP0632 incorporates a de-immunized, third-generation DARPin design, informed by preclinical immunogenicity risk assessments and clinical learnings

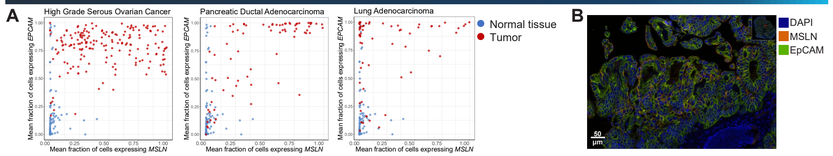


Multidimensional immunogenicity risk assessment of MP0632. Risk increases from the center outward, from green (lowest) to red (highest). DARPin-addressable factors are shown in green. For illustrative purpose only.

Protein engineering addressing key risk factors to achieve a low probability of ADA incidence*	
T cell epitopes	• Several T cell epitopes identified and successfully removed from DARPin sequence
Stability, aggregation, expression, post-translational modifications	• DARPin-Fc fusion retains beneficial properties of DARPins such as high stability and low aggregation potential • No post-translational modifications of DARPin sequence with mammalian expression
Mode of action	• Masked CD3 domain reduces systemic T cell activation and cytokine release, and allows to dose through in case of ADAs

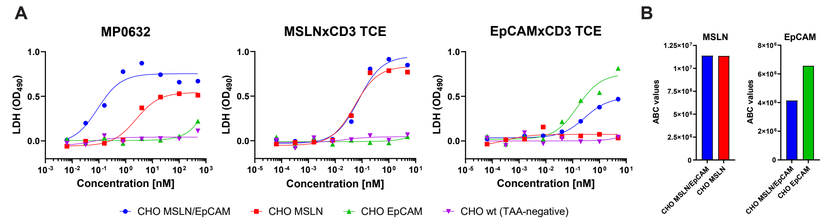
* Hu et al. The AAPS Journal (2025) 27:33, Agnihotri S. et al. Front. Immunol. 17:1816949 (2026)

Single-cell data show high MSLN/EPCAM co-expression in solid tumors and minimal co-expression in healthy tissues

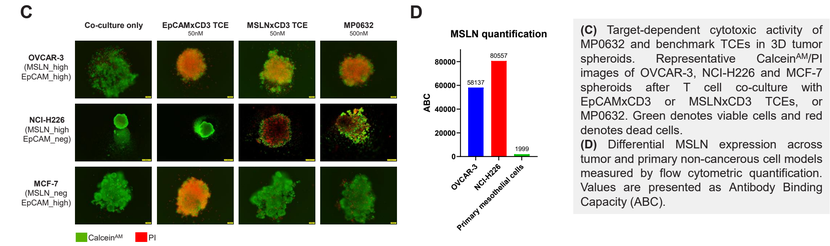


(A) *EPCAM* and *MSLN* gene expression at the single cell level in tumor and normal tissues. Plots depict mean fraction of cells expressing *EPCAM* and *MSLN*, respectively. For normal tissue (in blue) the mean is computed over all cell types for each donor and tissue type. For malignant cells (in red) the mean is computed for each sample. Normal data is from Tabula Sapiens v2 (Jones R, Krasnow M, Oliveira Pisco A et al. Cell 2026). Tumor data is from DARPin compass, an internally curated collection of public single cell datasets and target exploration tools (Toska et al, AACR Annual Meeting 2026).
(B) Representative multiplex IF staining of ovarian cancer tissue.

MP0632 enables preferential targeting of MSLN+/EpCAM+ cells

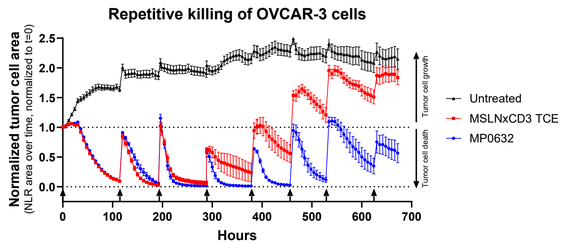


Pan T cells co-cultured with target cells (CHO) expressing both MSLN and EpCAM, or either MSLN or EpCAM alone, in presence of MP0632, MSLNxCD3, or EpCAMxCD3 TCEs. **(A)** After 48 h, cytotoxicity was assessed by LDH release. **(B)** MSLN and EpCAM expression on transduced CHO cells was quantified by quantitative flow cytometry and is shown as Antibody Binding Capacity (ABC). MSLNxCD3 and EpCAMxCD3 TCEs were reproduced based on ZW171 and Solitomab sequences, respectively.



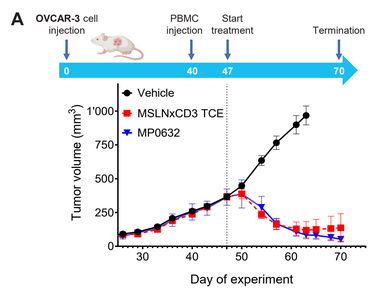
(C) Target-dependent cytotoxic activity of MP0632 and benchmark TCEs in 3D tumor spheroids. Representative Calcein^{AM}/PI images of OVCAR-3, NCI-H226 and MCF-7 spheroids after T cell co-culture with EpCAMxCD3 or MSLNxCD3 TCEs, or MP0632. Green denotes viable cells and red denotes dead cells.
(D) Differential MSLN expression across tumor and primary non-cancerous cell models measured by flow cytometric quantification. Values are presented as Antibody Binding Capacity (ABC).

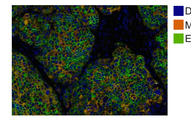
MP0632 maintains T cell mediated tumor cell killing upon repeated challenge



Pan T cells from healthy human donors co-cultured with OVCAR-3 NucLight Red (NLR) cells (at initial effector to tumor ratio of 1:1) in presence of MP0632 or MSLNxCD3 TCE at concentrations representing 100-fold EC50 values (in a 6-day killing assay) to reach saturation. Every 3 to 4 days (arrows), new OVCAR-3 NLR cells and TCEs were added to the wells to initiate a new round of killing. Cytotoxicity was assessed by IncuCyte.

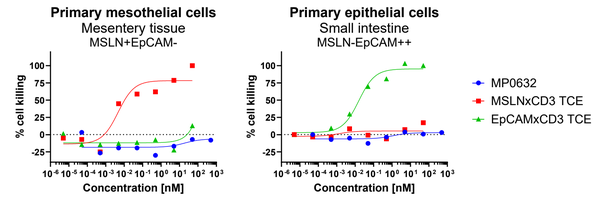
MP0632 shows potent antitumor activity against OVCAR-3 tumors





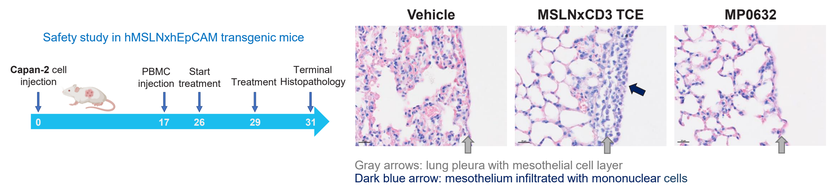
(A) OVCAR-3 (MSLN+EpCAM+) ovarian tumor cells were subcutaneously engrafted into immune-deficient NXG mice and humanized with PBMC on day 40 post tumor-cell engraftment. Treatment started 7 days after PBMC injection. MP0632 was injected at 3 mg/kg (i.v.) two times a week for 3 weeks, while the MSLNxCD3 TCE was dosed weekly at 3 mg/kg (i.v.). Tumor volumes are shown as mean +/- SEM, N=10 per group, 2 PBMC donors.
(B) MSLN and EpCAM co-staining of OVCAR-3 xenografts.

MP0632 spares primary mesothelial and epithelial cells from healthy human tissues *ex vivo*



Pan T cells co-cultured with primary healthy mesothelial and epithelial cells in presence of MP0632, MSLNxCD3, or EpCAMxCD3 TCEs. After 48 h, cytotoxicity was assessed by LDH release.

MP0632 shows no evidence of mononuclear cell infiltration in healthy lung pleura



In vivo safety assessment of MP0632. Capan-2 PDAC cells were engrafted into immune-deficient NDG mice genetically engineered to express human MSLN and human EpCAM. Mice were humanized with human PBMC and treated with either MSLNxCD3 TCE (3 mg/kg) or MP0632 (3 mg/kg) on day 26 and 29. Tissues were collected after 5 days of treatment and histopathological analysis was performed on H&E-stained tissue sections. MP0632 did not induce mononuclear cell infiltration of the lung pleura, unlike MSLNxCD3 TCE (blue arrow).

Conclusions

Our results provide preclinical proof-of-concept for MP0632's logic-gated de-immunized Switch-DARPin CD3 TCE design with a favorable therapeutic window to reduce on-target off-tumor toxicities:

- MP0632 achieved dual-target-selective cytotoxicity and *in vivo* efficacy comparable to a clinical MSLNxCD3 TCE benchmark
- CD2 co-stimulation allows for sustained T cell cytotoxicity across repeated tumor-cell challenges compared with a MSLNxCD3 TCE benchmark
- MP0632 has a favorable safety window *vs* standard CD3 TCEs: neither killing of healthy human mesothelial and epithelial cells *ex vivo* nor lung pleural mononuclear cell infiltration in hMSLNxhEpCAM transgenic mice was observed

Together, these data demonstrate the potential of the Switch-DARPin to successfully target TAAs considered undruggable for TCEs: MP0632 turns MSLN and EpCAM into a 'clean' target pair—two targets whose single-TAA CD3 engagers failed because of tolerability issues in the clinic—thereby providing a differentiated strategy and supporting the advancement of MP0632 into IND-enabling studies in MSLN+EpCAM+ solid tumors.

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