

A next-generation conditional Switch-DARPin T cell engager with CD2 co-stimulation enabling selective activity against solid tumors which co-express mesothelin (MSLN) and EpCAM

Abstract # 829

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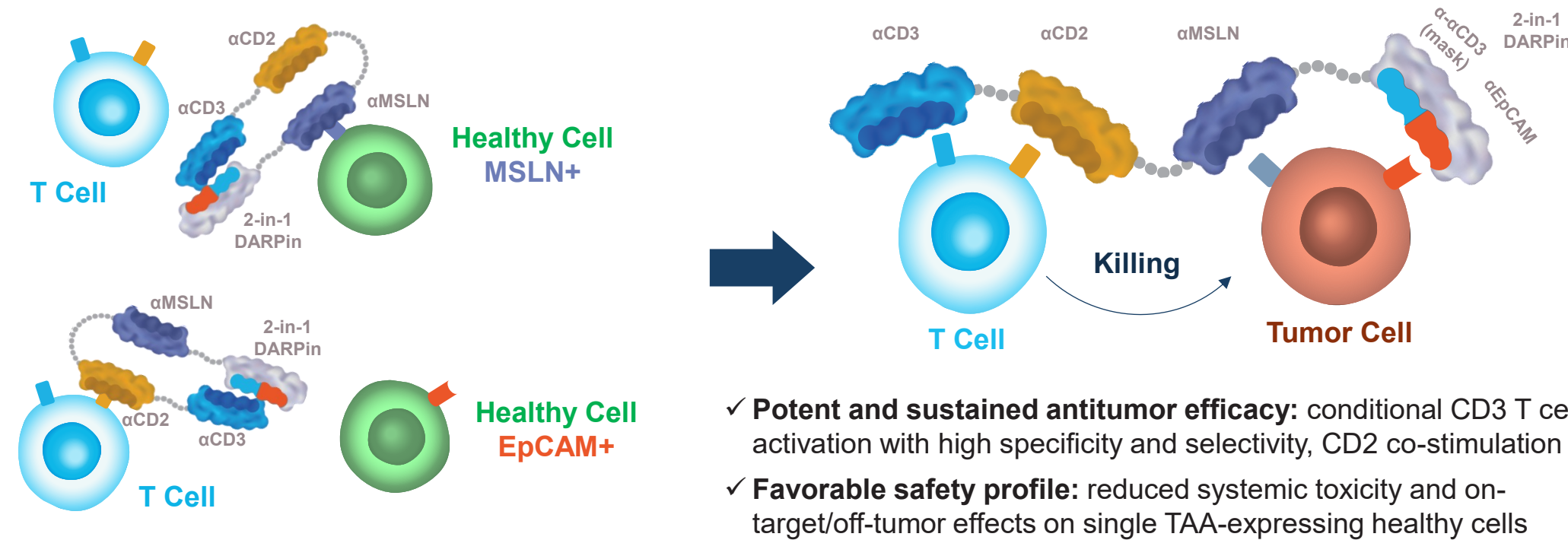
Matteo Bianchi, Joanna Robinson, Sarah Jetzer, Simon Häberle, Anja Schlegel, Marco Franchini, Tamara Lekishvili, Marcela Guzman Ayala, Alexander Link
Molecular Partners AG, Zürich-Schlieren, Switzerland

Introduction

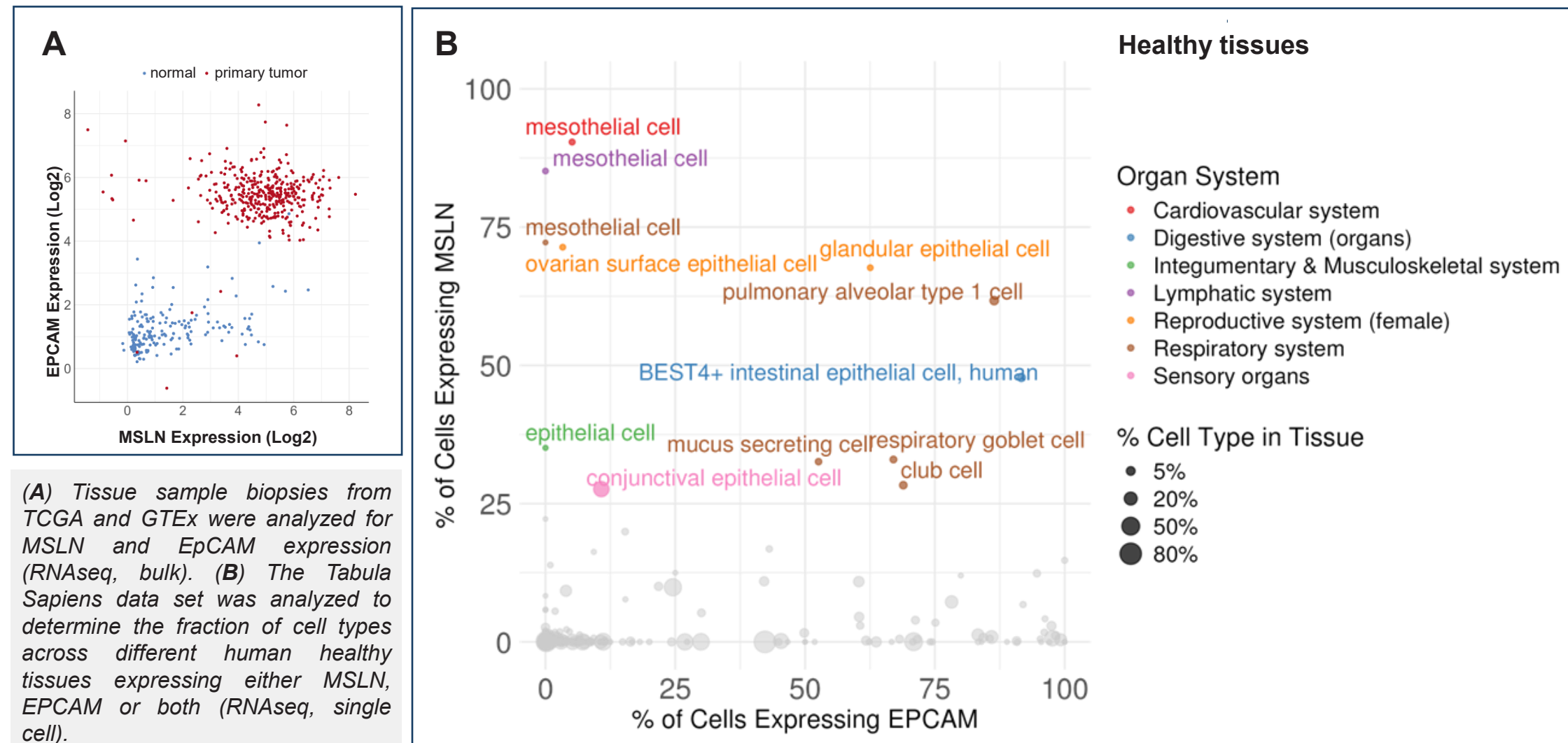
Development of T cell engagers (TCEs) for solid tumors is hampered by limited availability of specific tumor-associated antigens (TAAs), resulting in reduced TCE selectivity and increased risk of on-target/off-tumor toxicity due to antigen-expression in healthy tissues. Particularly in ovarian cancer (OC) immunotherapy has had limited success due to the absence of 'clean' TAAs, the presence of dysfunctional T cells and an immunosuppressive tumor microenvironment.^{1,2} 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.³ To address this unmet need, we developed a MSLN and EpCAM-targeting multispecific, logic-gated CD3 TCE with a CD2 co-stimulatory effector function.

Switch-DARPin T cell engager: TAA-dependent activation (AND-gate)

OFF CD3-engaging DARPin is masked by a 2-in-1 Switch-DARPin (single TAA-expressing cells) **ON** CD3-engaging DARPin released in presence of both TAAs (MSLN x EpCAM co-expression)

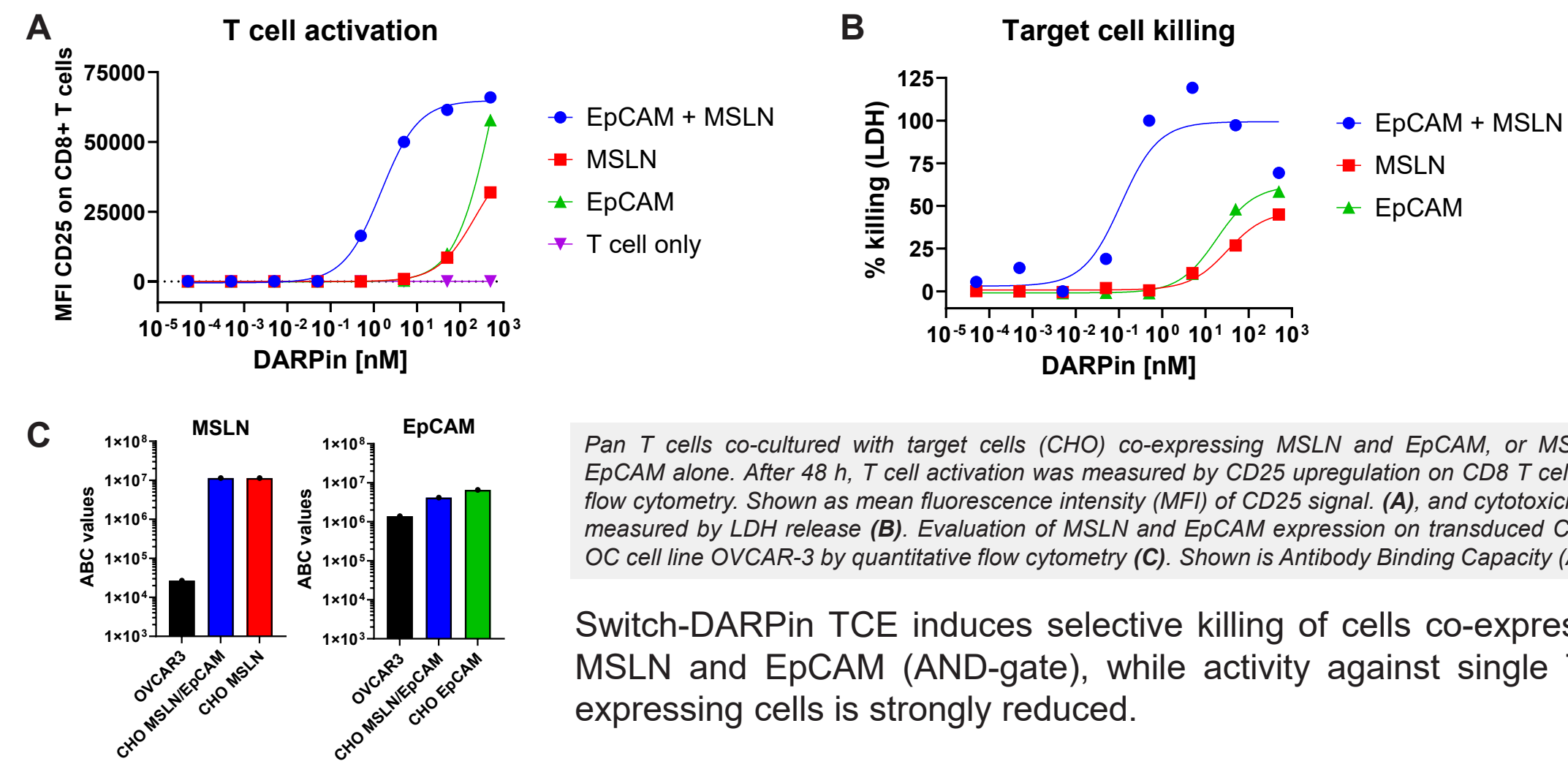


MSLN & EpCAM are highly co-expressed in OC, with minimal expression in healthy tissues

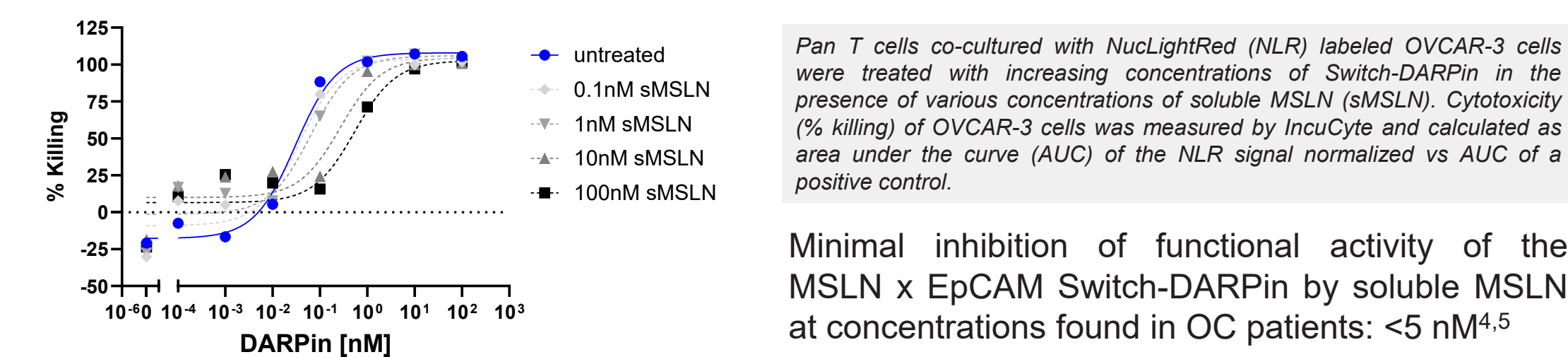


MSLN and EpCAM exhibit high co-expression in OC, while co-expression is low in healthy tissues. Analysis of normal tissues and cell types revealed that EpCAM alone is highly expressed on epithelial cells (grey dots >25% EpCAM+, not labelled), while MSLN is expressed at high levels on mesothelial cells (see cell type labels). Co-expression of both MSLN and EpCAM is rare (<10%) and only found in a small proportion of cell types of the lung, intestines and the female reproductive system.

Switch-DARPin enables preferential targeting of tumor cells

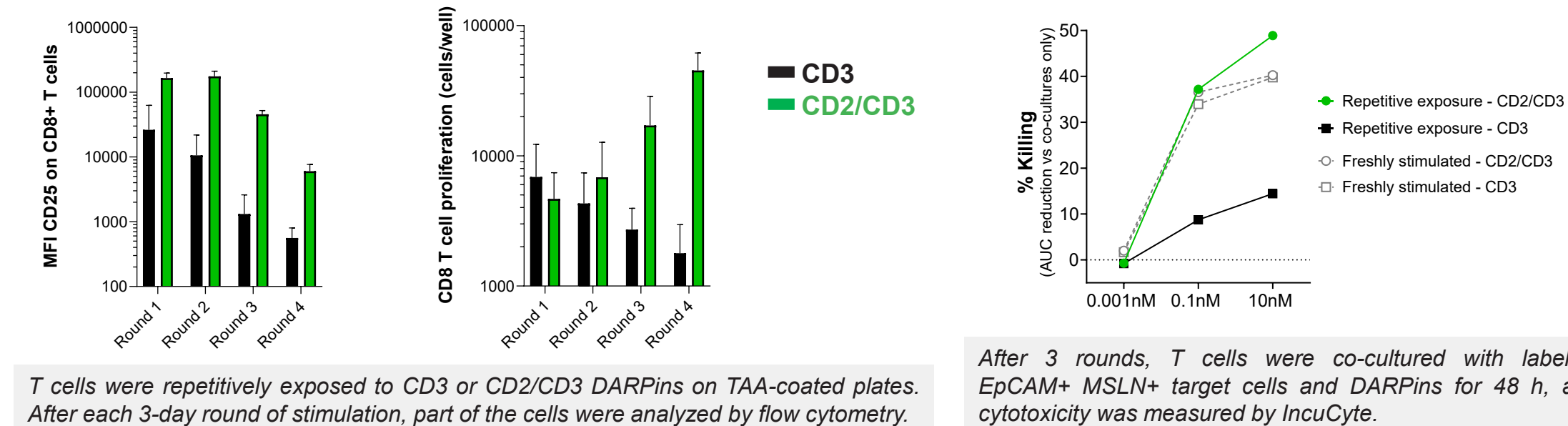


Activity of Switch-DARPin is minimally impacted by soluble MSLN

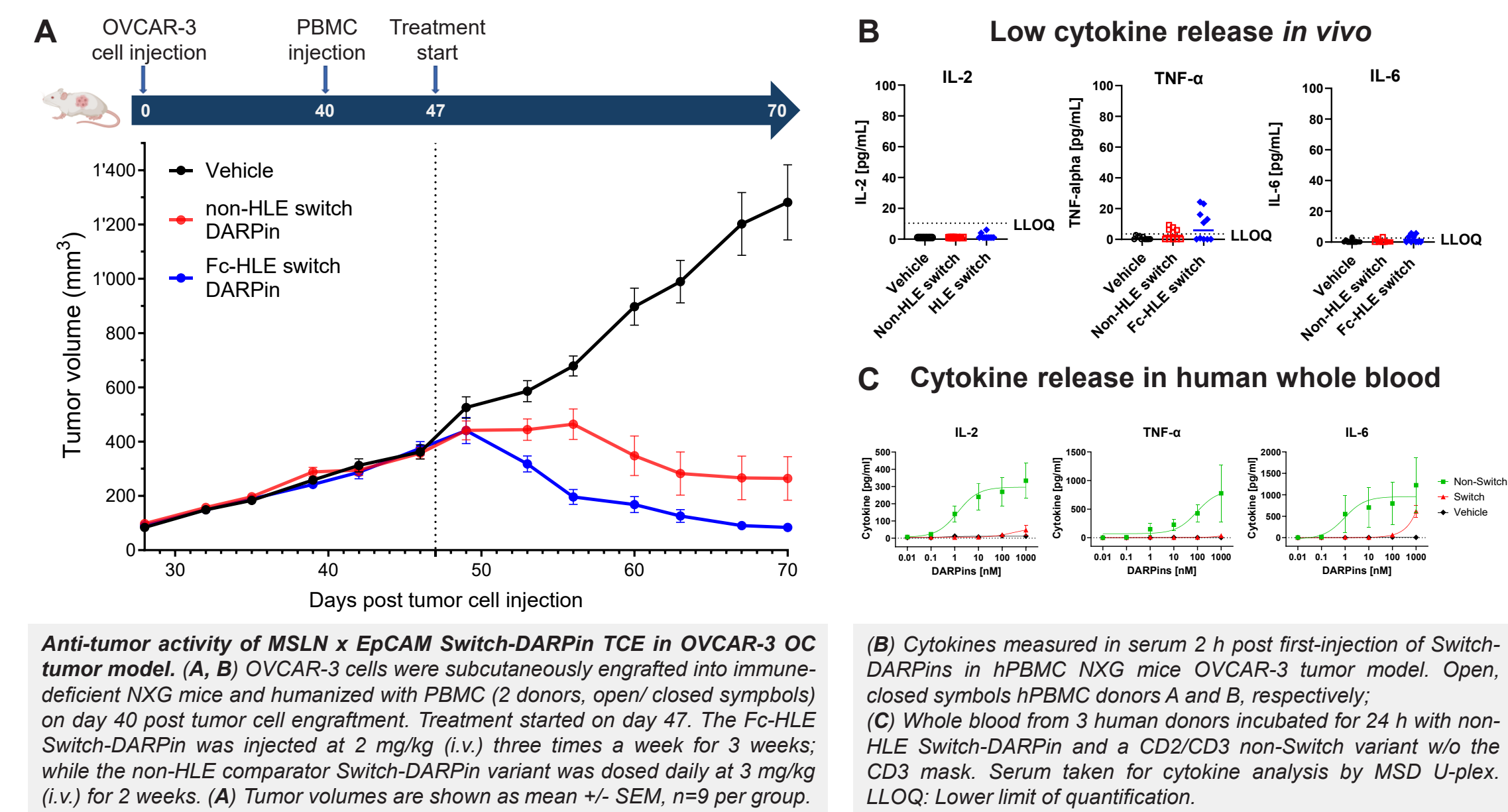


CD2 co-stimulation enables sustained T cell function

T cells repetitively exposed to CD2/CD3 Switch-DARPin show superior activation and proliferation profiles... and a higher cytotoxic activity compared to T cells exposed to CD3-only DARPin

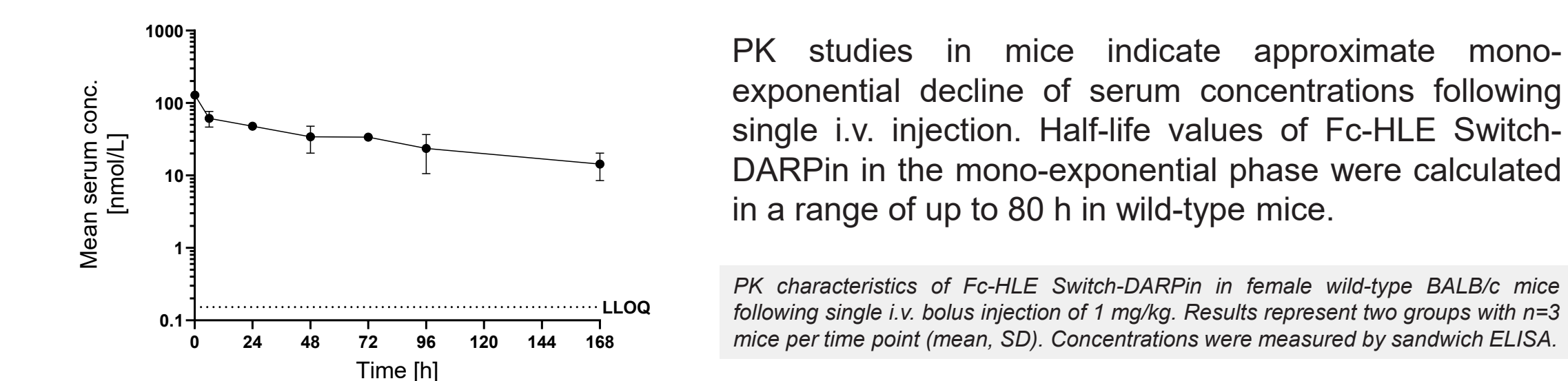


Anti-tumor activity in vivo with a favorable systemic safety profile



Treatment with the MSLN x EpCAM Switch-DARPin induced significant tumor regression in PBMC-humanized OVCAR-3 xenograft model with low systemic cytokine release in serum. In human whole blood assay, low non-TAA-specific cytokine release is detected with the Switch-DARPin in contrast to a CD2/CD3 non-Switch variant.

Pharmacokinetics (PK) of half-life extended (HLE) Switch-DARPin in mice



Conclusions

- Clinical development of TCEs for solid tumors is often limited by systemic toxicity in the absence of single tumor-specific antigens, and impaired efficacy due to T cell exhaustion.
- We designed a logic-gated Switch-DARPin TCE (AND-gate) for tumor-localized immune activation targeting MSLN & EpCAM which are highly co-expressed in OC and other solid tumors.
- Our preclinical findings demonstrate selective T cell cytotoxicity of the Switch-DARPin against cells co-expressing both TAAs, with attenuated activity against cells expressing only MSLN or EpCAM.
- CD2 co-engagement induced sustained T cell proliferation and activity.
- The Switch-DARPin induced significant tumor regression in a MSLN+ EpCAM+ xenograft model without causing systemic cytokine release, indicating a favorable safety profile.
- This approach provides an opportunity for novel cancer treatments through logic-gated tumor-directed immune activation with increased efficacy & safety over single MSLN-targeting modalities.

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

References: 1. Ghisoni et al., Nat Rev Clin Oncol. 2024; 2. Gupta et al. Trends Immunol. 2025; 3. seer.cancer.gov/staffacts/html/ovary; 4. Hassan et al., Clin Cancer Res 2006; 5. Hanaoka et al. Mol Diagn Ther. 2017.

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