Logic-gated Switch-DARPin-based immune-cell engagers guided by data-driven tumor-antigen profiling: A computational workflow for the development of cancer immunotherapies

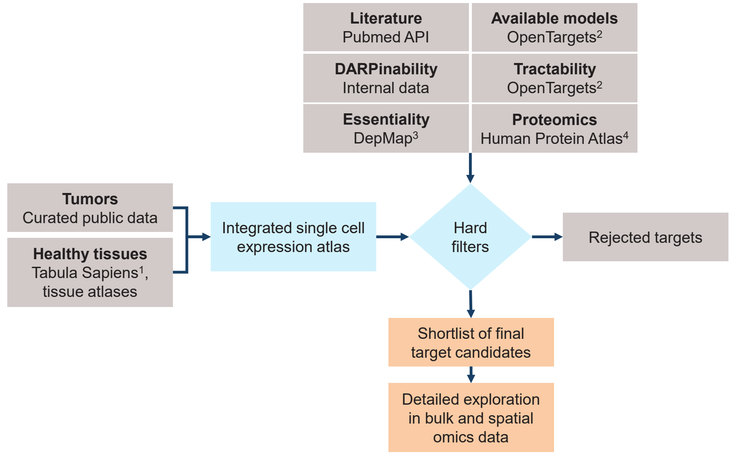
Albulena Toska, Ana Maria Florescu, Eleni Tselempi, Alexander Link, Martin Steegmaier, Marcela Guzman Ayala
Molecular Partners AG, Schlieren-Zurich, Switzerland

Poster #2691
2026 AACR

Introduction

- The lack of highly specific tumor-associated antigens (TAAs) is a major safety challenge for immune-engaging treatment approaches in solid tumors.
- Our Switch-DARPin design enables conditional immune activation through logic-gated recognition of co-expressed TAAs.
- To enable systematic development of Switch-DARPins, we built the DARPin Compass, a data-driven workflow that ranks TAA genes and gene pairs based on expression and tumor selectivity to guide experimental candidate selection.
- Here, we show how the DARPin Compass was built and applied to guide rational TAA pair selection for MP0632, the first Switch-DARPin T cell engager (TCE) candidate for ovarian cancer.

DARPin Compass: identify best target pairs based on multiple data sources



Curated single-cell tumor and healthy tissue datasets are integrated into a unified atlas across 11 tumor indications. Selected targets are ranked by expression, refined using biological and technical criteria, and validated using bulk and spatial omics data.

A scoring system to rank targets and pairs of targets

Expression levels in cancer tissue

Median expression (% positive cells) in:

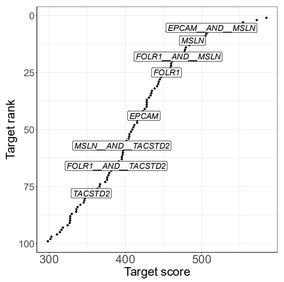
- Cancer cells
- Stromal cells
- Metastases and across subpopulations

Comparison to healthy tissues

- Ratio to off-tumor tissue or individual vital organs such as lung, kidney or bone marrow
- All ratios are computed from the fraction of single-positive or double-positive cells and scaled to a maximum of 100
- Scores are computed as the sum of expression and ratios

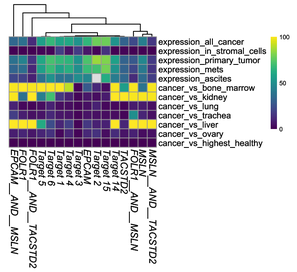
Ranking identifies *EPCAM* and *MSLN* pair as highest-value target

Top 100 targets and pairs for ovarian tumors



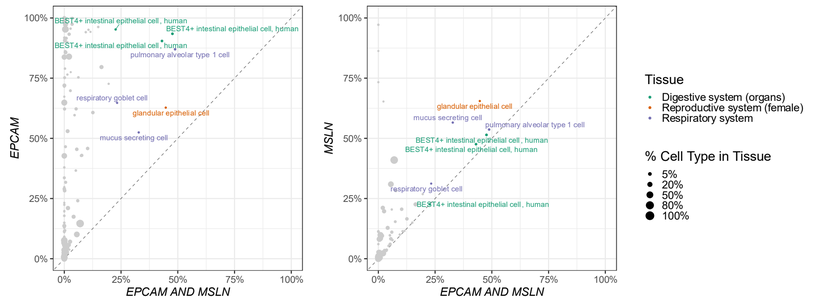
Best targets accumulate in the upper right corner with high score and low ranking. *FOLR1,* as positive control with high value, validates our method. TROP2 (encoded by *TACSTD2),* another validated clinical target, ranks lower.

Scoring details



Individual scores for all parameters and all targets, with higher values meaning higher expression or safety margin, respectively. *EPCAM* and *MSLN* show the highest scores overall followed by *MSLN* alone.

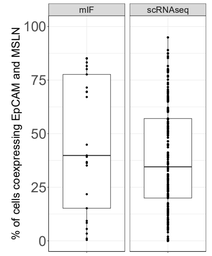
EPCAM and *MSLN* co-expression creates a safer therapeutic window



Percentages of cells expressing targets in normal tissues: The dots falling above the diagonal line suggest that the *EPCAM*/*MSLN* combination would provide a safety advantage above both *MSLN* and *EPCAM* as individual targets. Tissues highlighted with colored font show highest *EPCAM/MSLN* co-expression.

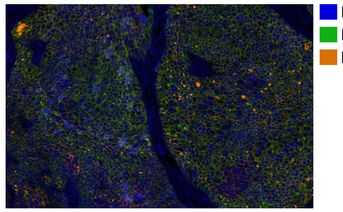
Co-expression prevalence of EpCAM and MSLN in OC is confirmed by mIF

Comparison between scRNAseq and mIF



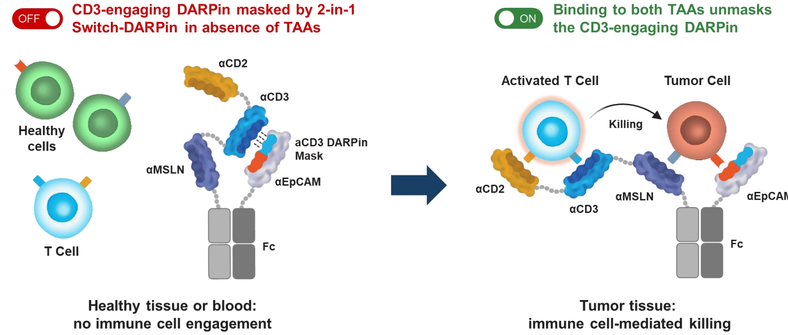
Co-expression of EpCAM and MSLN in ovarian tumor measured internally using multiplex immunofluorescence (mIF) and compared to public single-cell RNAseq (scRNAseq). The mIF analysis includes all cells in the slide, while the scRNAseq includes only tumor cells.

EpCAM/MSLN staining in an ovarian tumor



Representative staining example

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



- Favorable safety profile: reduced systemic toxicity and on-target/off-tumor effects on single TAA-expressing healthy cells.
- Potent and sustained antitumor efficacy: conditional CD3 activation with high specificity and selectivity, CD2 co-stimulation.
- For further details, see also the AACR 2026 MP0632 preclinical poster #1624 (Bianchi et al.).

Conclusions

- The DARPin Compass is a scalable, data-driven platform for identifying and prioritizing tumor associated antigen pairs with improved tumor selectivity and safety.
- By enabling logic-gated targeting concepts, it expands the addressable target space beyond single-antigen approaches in solid tumors.
- Application to ovarian cancer demonstrates how the platform translates complex expression data into actionable target pairs for conditional immune activation.
- More broadly, the DARPin Compass is disease-agnostic and readily extendable, providing a strong foundation for discovery and partnering of next-generation Switch-DARPin immunotherapies.

Acknowledgments: We would like to acknowledge Daniel Greenwood and Hoda Sharifian for contributing to early stages of this work and the Elucidata team for support with single cell data curation.

Conflict of interest disclosures: All authors are employees and stock owners of Molecular Partners AG.

References: 1. The Tabula Sapiens Consortium, Science, 2025; 2. Buniello et al., Nucleic Acids Research 2025; 3. Arafeh, R., Shibue, T., Dempster, J.M. et al., Nat. Rev. Cancer 2025 4. Ulhen et al, Science 2015.