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Appropriate Targets for RLT:
"High Selectivity vs. High Expression"

GRC "Radionuclide Theranostics for the Management of Cancer" Sunday River, 15th July 2026

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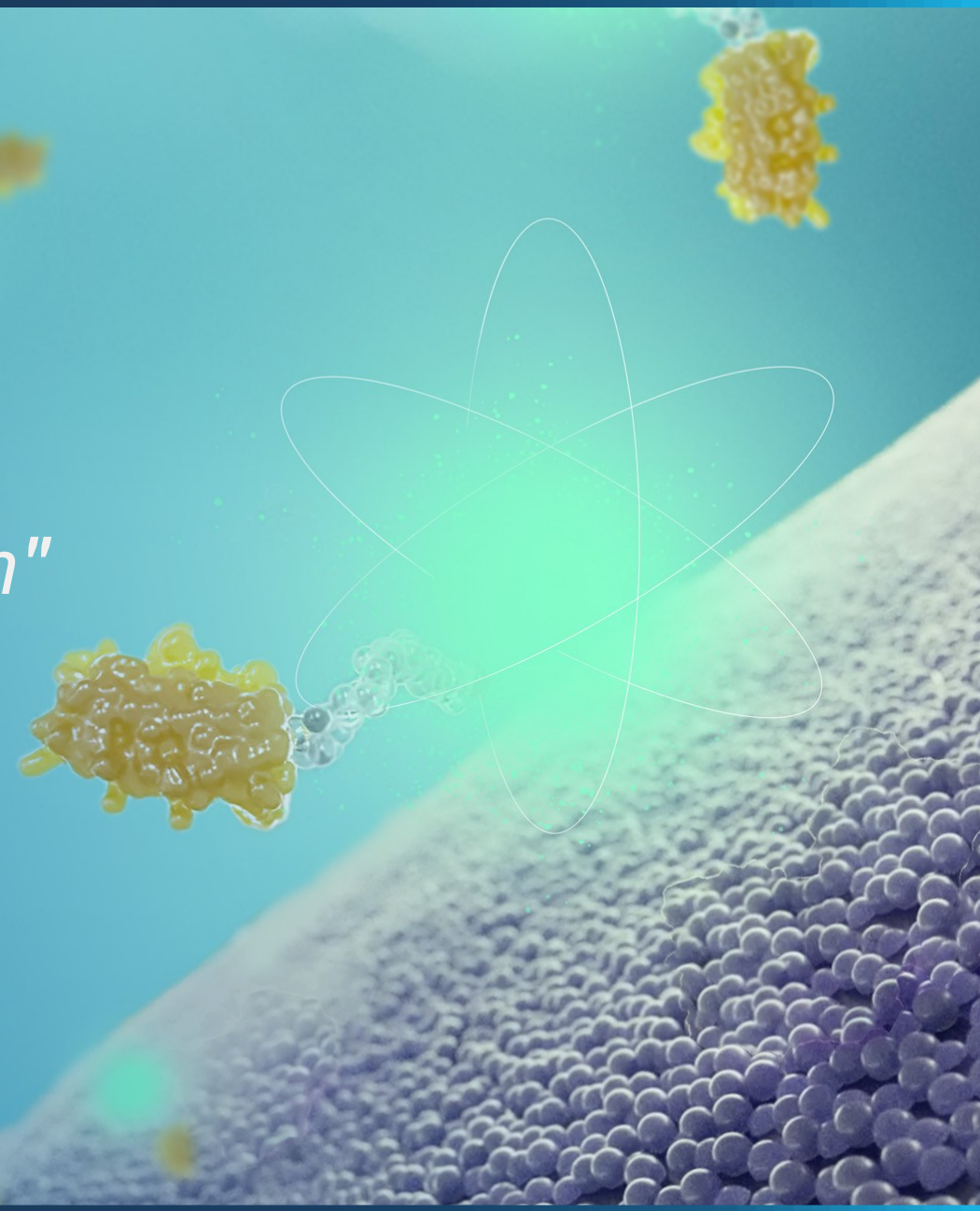

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Dissecting the Components of High Selectivity and High Expression

High Selectivity *(low off-tumor expression)*

Low target density or accessibility off-tumor
a) **Critical organs** (macro-distribution – visible by imaging)
b) **Critical cells** (micro-distribution – not visible by imaging)

Low levels of shed (soluble) target in circulation and within the tumor

No indistinguishable variants (paralogues, isoforms, glycoforms…) on healthy cells

High Expression *(high on-tumor expression)*

"Evaluation for specific indication & target patient"

High target density and accessibility on tumor cells (may also extend to TME, vasculature, CSCs…)

High target homogeneity
a) **Intra-tumor**: uniform target distribution within tumor mass
b) **Inter-lesion**: maintained expression across lesions
c) **Inter-patient**: high prevalence across patient population

Maintained target expression
a) Throughout **disease course**
b) Under **treatment pressure**

Clinical validation with other modalities (TCEs / ADCs proven safe and efficacious) as surrogate for target drugability

ADC, antibody-drug conjugate; CSCs, cancer stem cells; TCE, T cell engager; TME, tumor microenvironment.

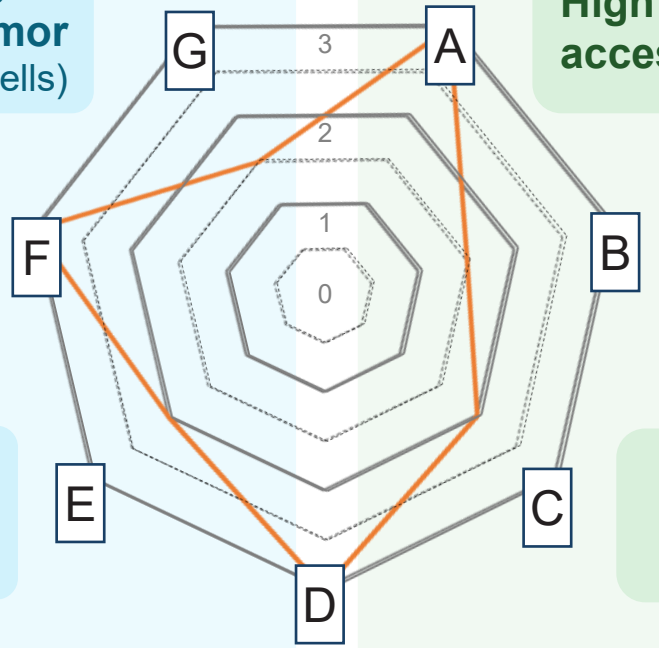
High Selectivity & Expression as Key RLT Target Selection Criteria

High Selectivity *(off-tumor expression)*

Low target density or accessibility off-tumor
(critical organs / cells)

Low levels of shed target

No indistinguishable variants



Clinical validation

High Expression *(on-tumor expression)*

High target density and accessibility on tumor

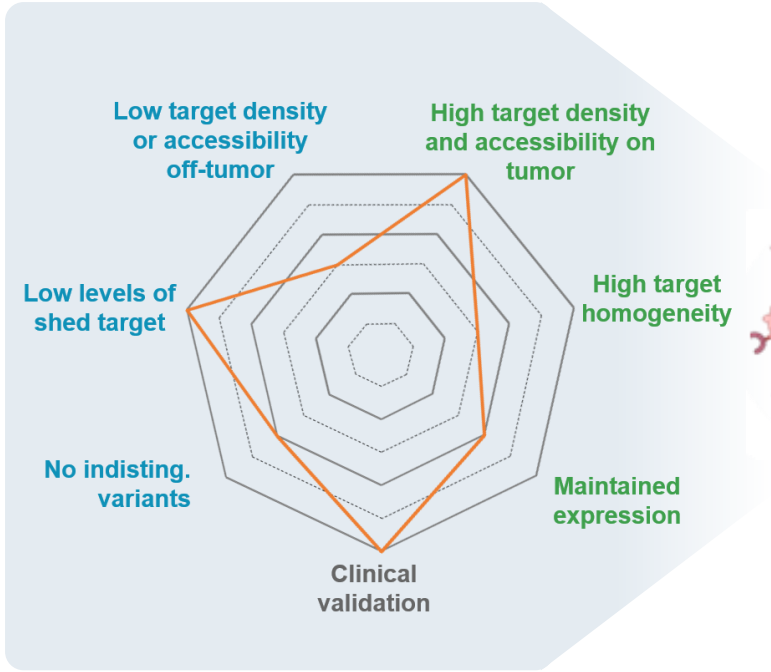
High target homogeneity
(intra-tumor / inter-lesion / inter-patient)

Maintained expression
(disease course / treatment pressure)

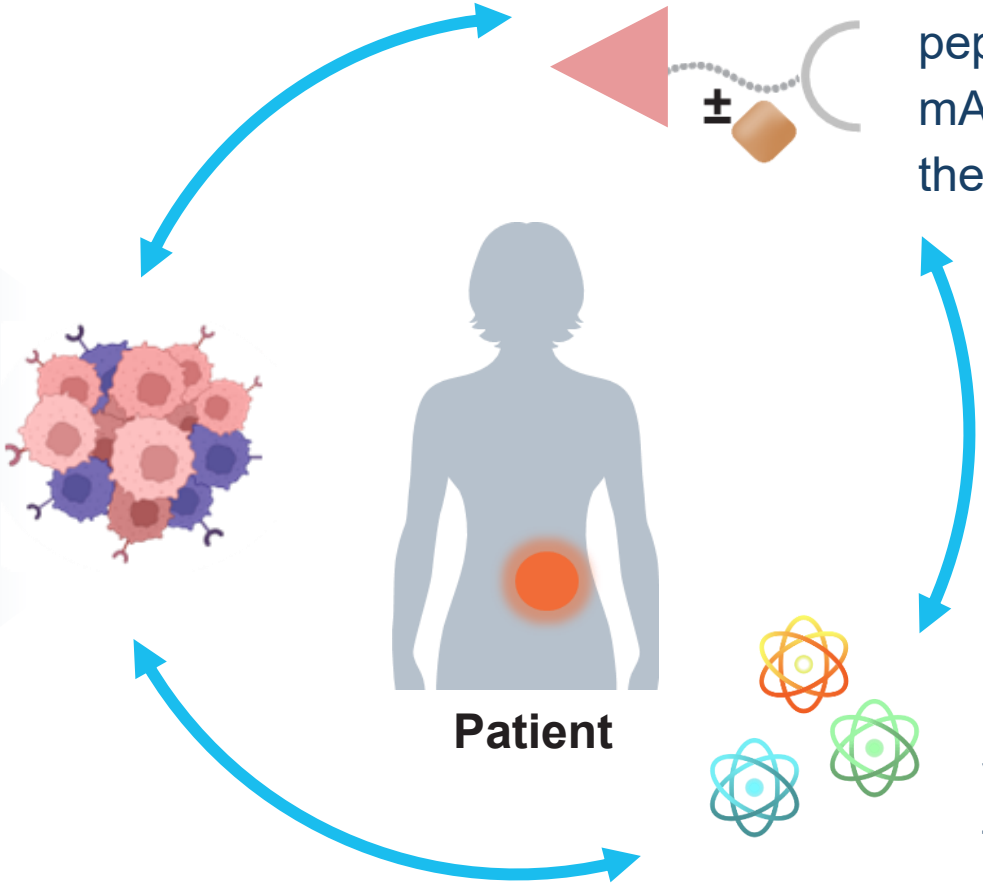
Our assessment of PSMA in Prostate Cancer

Addressing Target-Specific Challenges Through Molecular Design

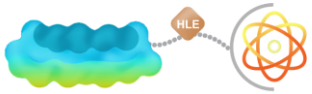
Target & Disease Biology:



"There are no perfect targets!"



Vector & Modifiers*: LMWs, peptides, mini-proteins and mAbs, designed to address the biology of the target

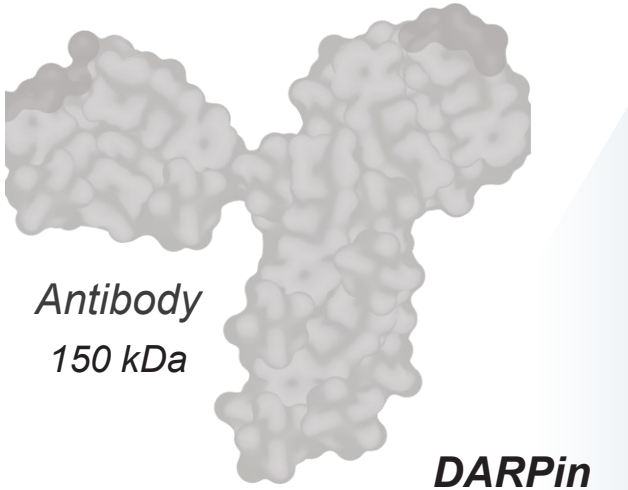


RADIO-DARPin Therapeutics

Isotope: matching the vector's characteristics and the biology of the target

LMW, low molecular weight; mAb, monoclonal antibody.
*Modifiers: cleavable linkers and pharmacokinetic modifiers.

DARPin Features for Tumor Targeting of Radionuclides



DARPins[1] are small binding proteins derived from natural ankyrin repeat proteins

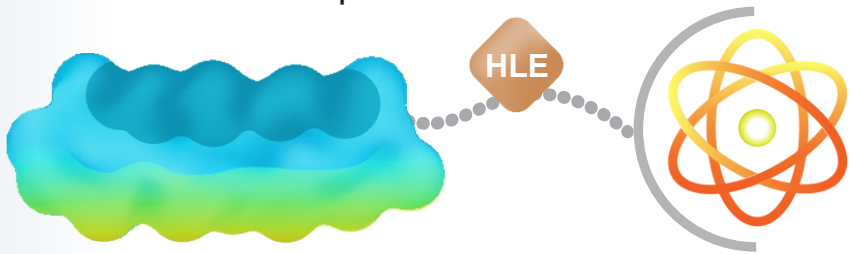
DARPin key features

- ✓ **Small size** (~15 kDa)
  → *Deep tumor penetration*
- ✓ **Broad target range** (100's)
  → *Opening indications*
- ✓ **High affinity** (low pM range)
  → *Long tumor retention*
- ✓ **High selectivity**
  → *Low normal tissue*
- ✓ **High stability**
  → *Surface engineering for low kidney*
- ✓ **Clinical Validation**
  → *8 clinical compounds, > 2500 patients treated*

HALF-LIFE EXTENDER

- Tailored exposure
- Promote tumor uptake

LINKER & CHELATOR



SURFACE ENGINEERING

- Enabled by high stability
- Reduce kidney accumulation

α-EMITTING ISOTOPE

- Proven clinical efficacy
- High energy deposition
- ^{212}Pb and ^{225}Ac

RADIO-DARPin

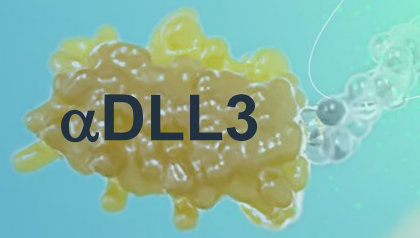
"Isotope-agnostic" consistent BioD profiles across isotopes and chelators[2]

DARPin, designed ankyrin repeat protein.
1. Binz et al., J Mol Biol 2003; 2. Steiner, RDS 2026.

Case Example: Tumor Expression Challenge

DLL3's Low Receptor Density

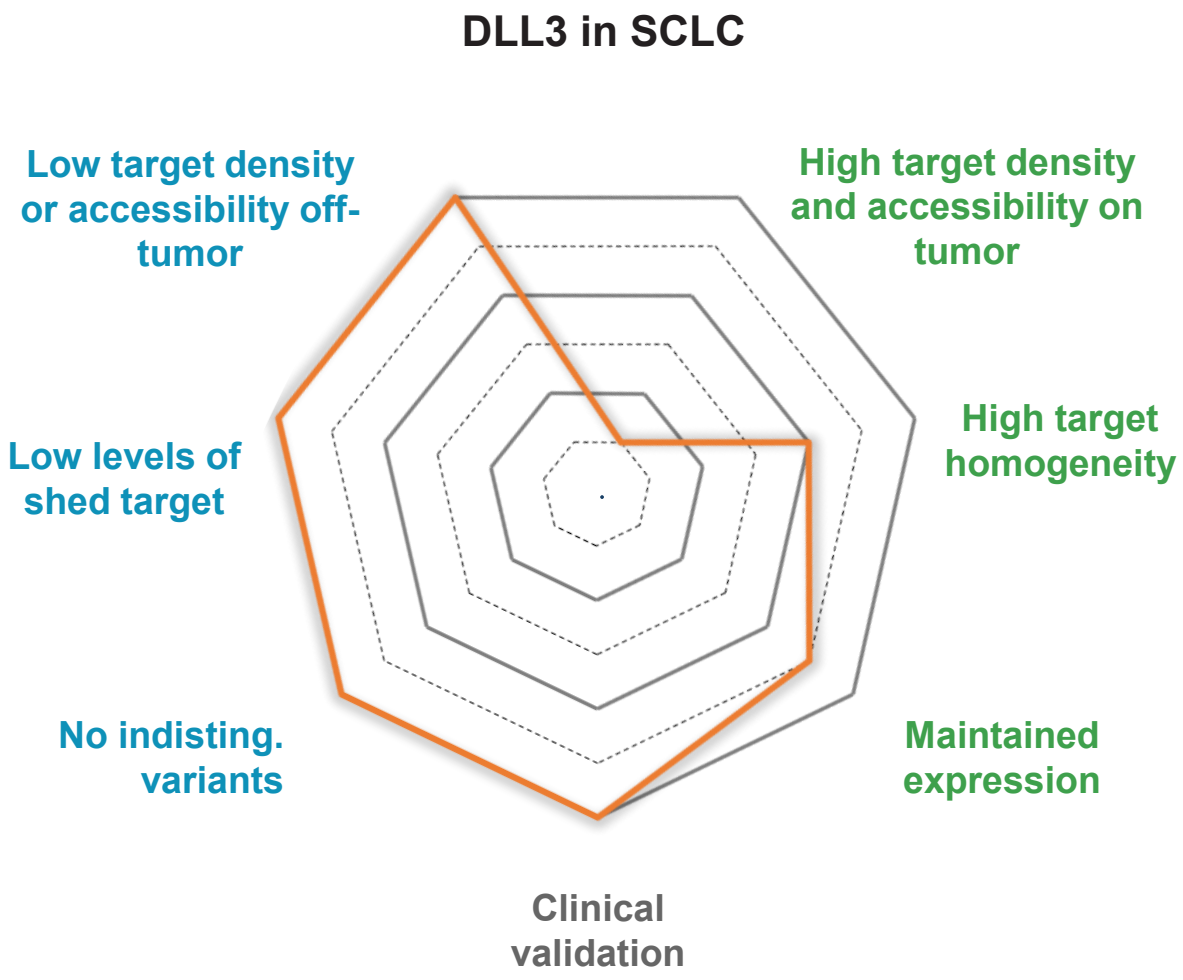
MP0712 targeting DLL3 for SCLC –
Our first clinical Radio-DARPin



^{212}Pb

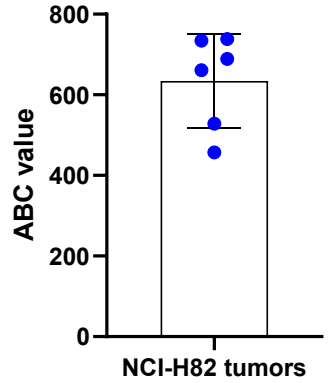
DLL3 is a Highly Selective Target, fit for Radioligand Therapy

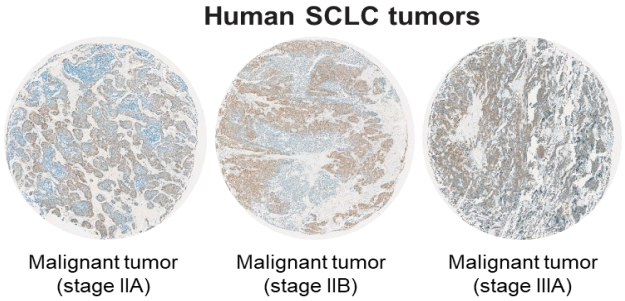
However, low cell surface density on tumor cells is a challenge



Very low DLL3 density confirmed in clinically relevant models[1]

(of <1000 receptors/cell)



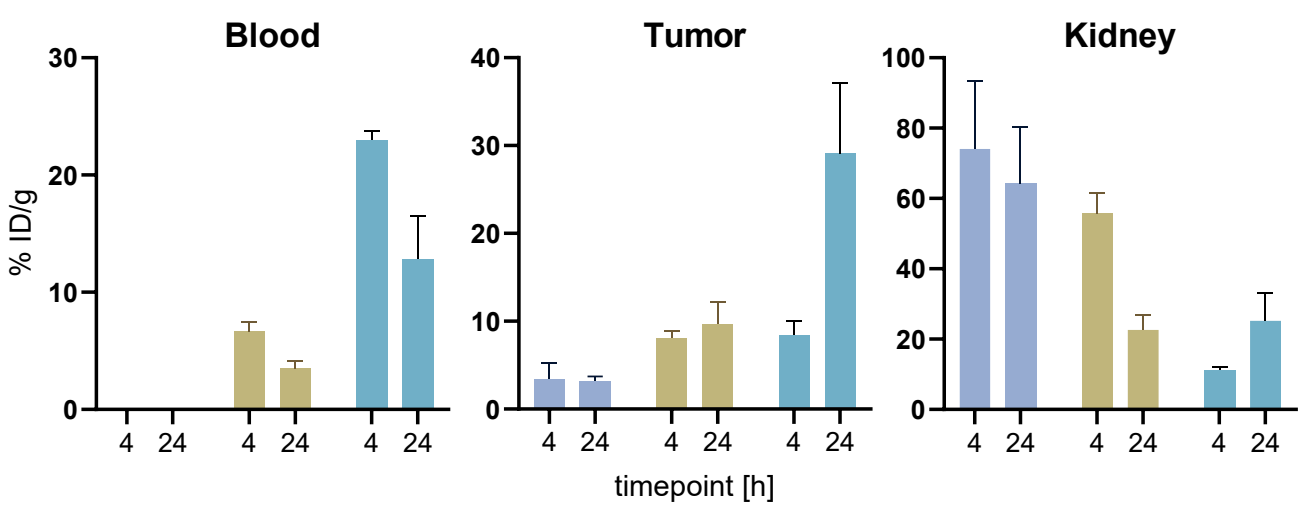


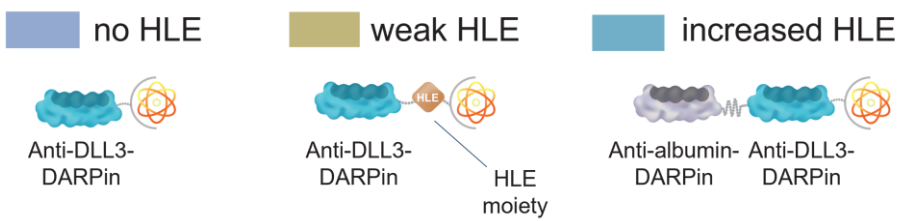
1. Croset et al., AACR 2025.

ABC, antibody binding capacity; DLL3, delta-like ligand 3; SCLC, small cell lung cancer.

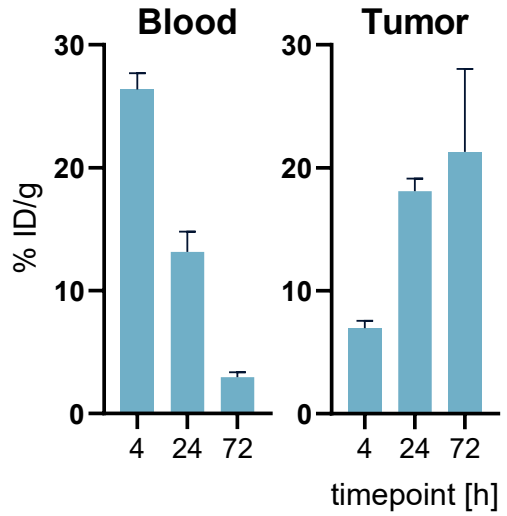
MP0712: a DLL3 DARPin with a Target-Tailored Design

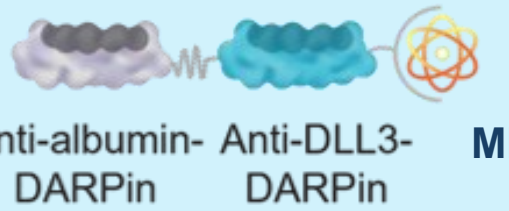
Impact of half-life on biodistribution





MP0712 time course



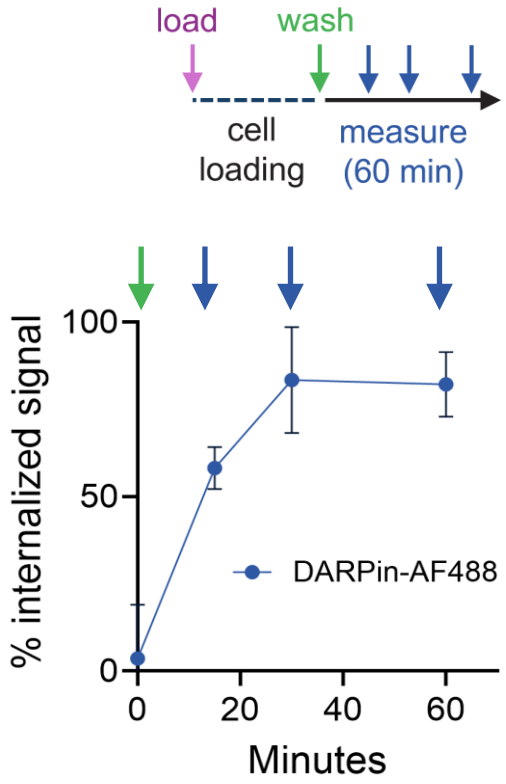


Final MP0712 design

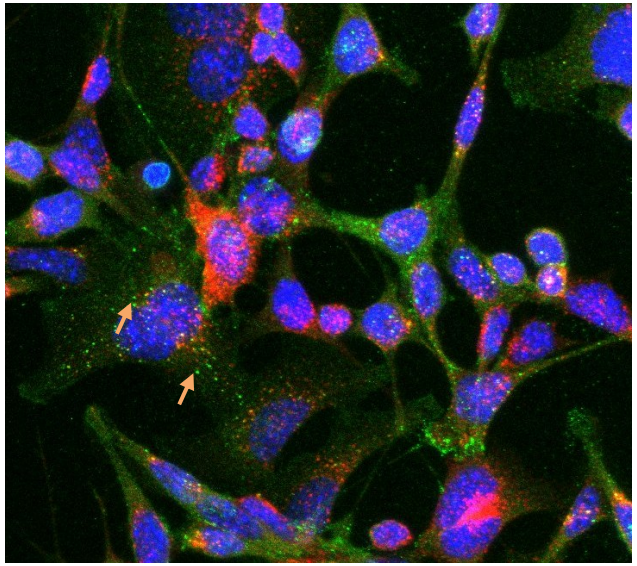
Riesenberg, et al., AACR 2026.

HLE, half-life extension; ID, injected dose.

MP0712-DLL3 DARPin is Rapidly Internalized and Accumulates Intracellularly in DLL3-Expressing Cells *in vitro*

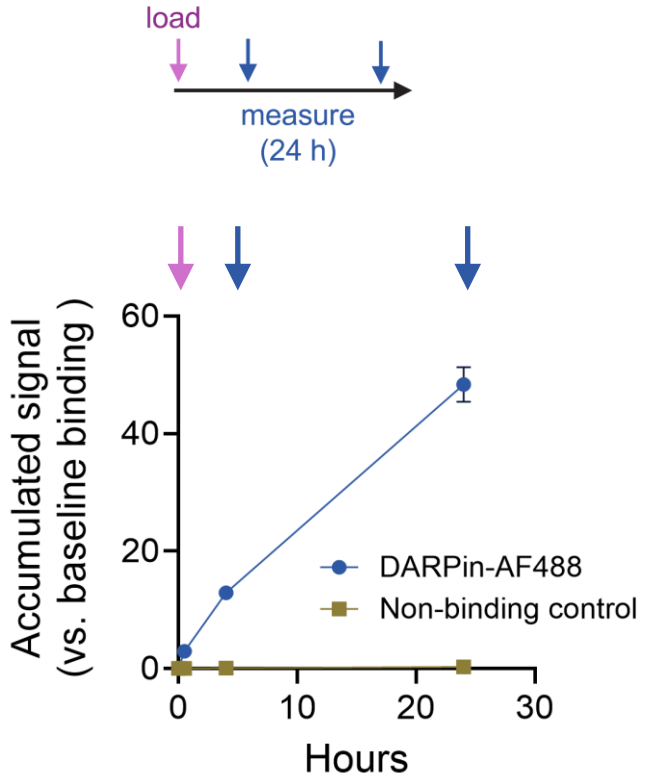


Surface-bound DLL3-DARPin is rapidly internalized into SHP-77 human SCLC cells*



DAPI DARPin EEA1

Internalized DLL3-DARPin shows significant co-localization to the endosomal compartment in HEK-hDLL3 cells**

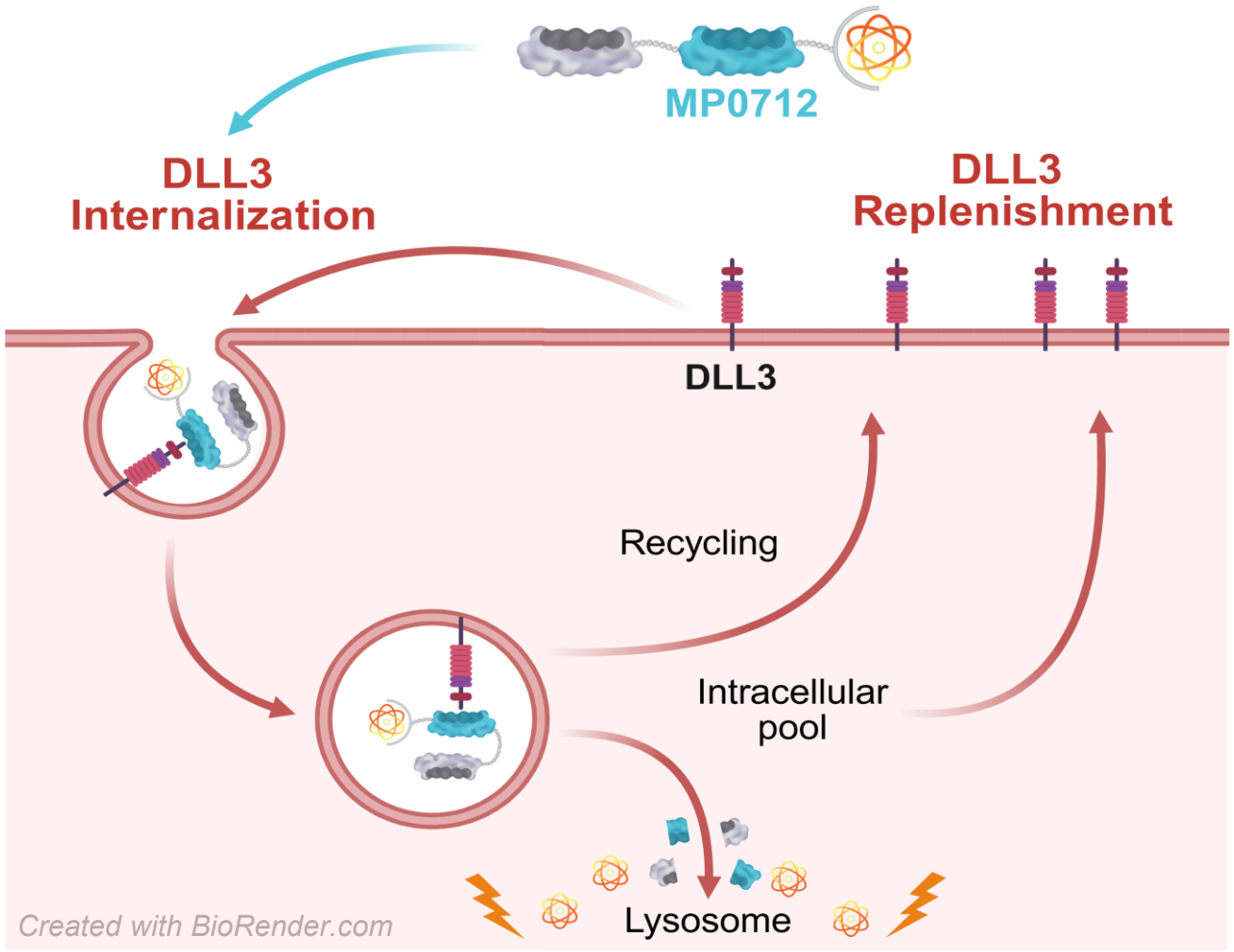


DLL3-DARPin accumulates in HEK-hDLL3 cells over time (beyond the bound fraction at saturation)*

Riesenberg, et al., AACR 2026.

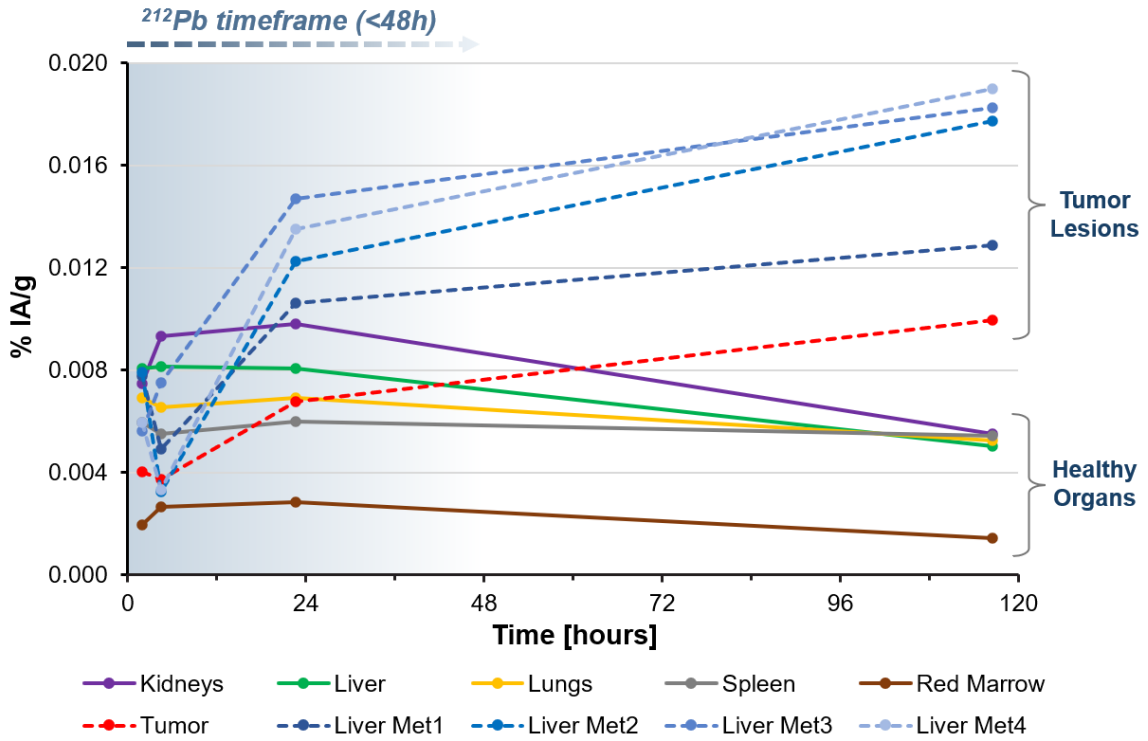
* Internalization of DARPins labelled with anti-DARPin Fab-Alexa 488 conjugate.
** Immunofluorescence co-staining of anti-DARPin antibody, an early endosomal marker (EEA1) and cell nucleus marker (DAPI) after 3 h incubation.

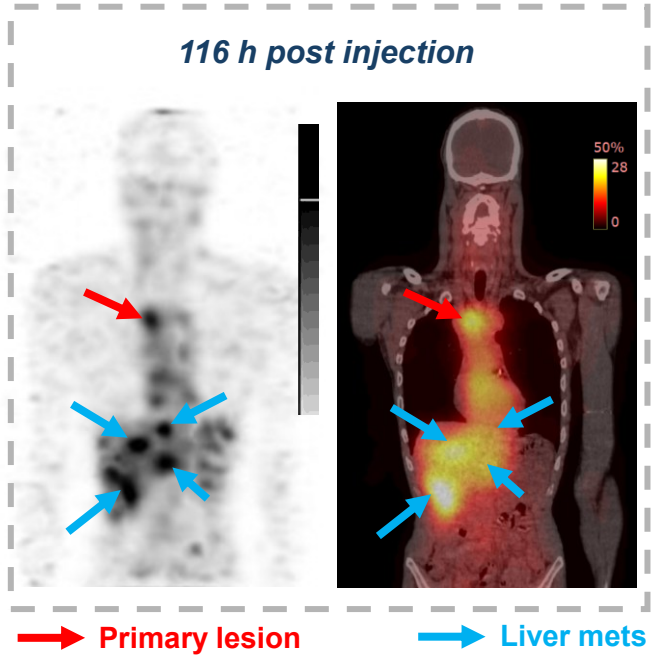
Hypothesis: Free Surface DLL3 is Continually Replenished for Binding and Internalization of MP0712



DARPin binding properties and extended systemic half-life to exploit the rapid internalization & replenishment of DLL3 "dynamic receptor density" for radioisotope accumulation in SCLC cells

First MP0712 SPECT/CT Imaging with ^{203}Pb Confirms Sustained Tumor Uptake[1]





- Continued tumor uptake up to 116 h imaging period; healthy organ washout from 24 h onwards[1]
- Phase 1 study of ^{212}Pb-MP0712 for treatment of SCLC and other DLL3+ tumors ongoing (NCT07278479)
- ^{203}Pb imaging suggest MP0712 potentially compatible also with longer-lived isotopes[1]
- DARPins amenable to different isotopes → NuMeRI initiated compassionate use of ^{177}Lu/^{225}Ac x DLL3

1. Patient with mSCLC imaged as part of a Named Patient Access Program at NuMeRI, Pretoria, ZA. Example of patient case series presented with courtesy of Prof. Dr. M. Sathekge. Complete SPECT/CT imaging data set presented at TWC 2026 (Kabunda et al.).

Lizak et al. TWC 2026. Quantitative image analysis performed by RAPID, LLC.
mSCLC, metastatic small cell lung cancer.

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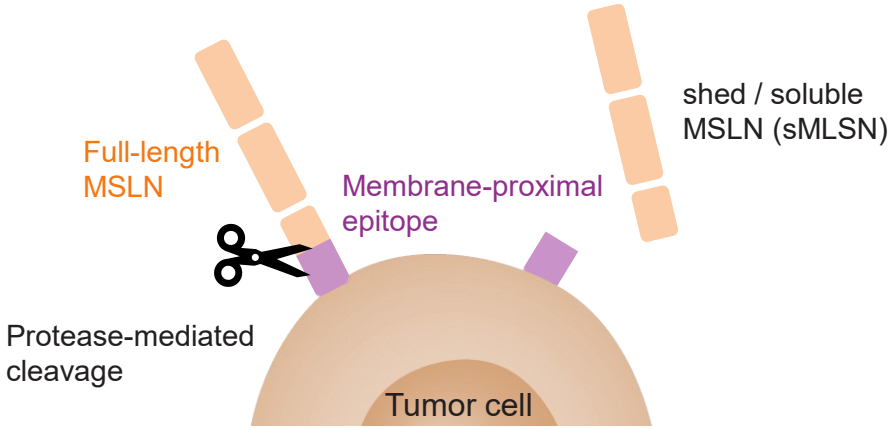
Case Example: Target Selectivity Challenge
MSLN's High Shedding

MP0726 targeting MSLN for OC

MSLN is an Attractive Target for Ovarian Cancer

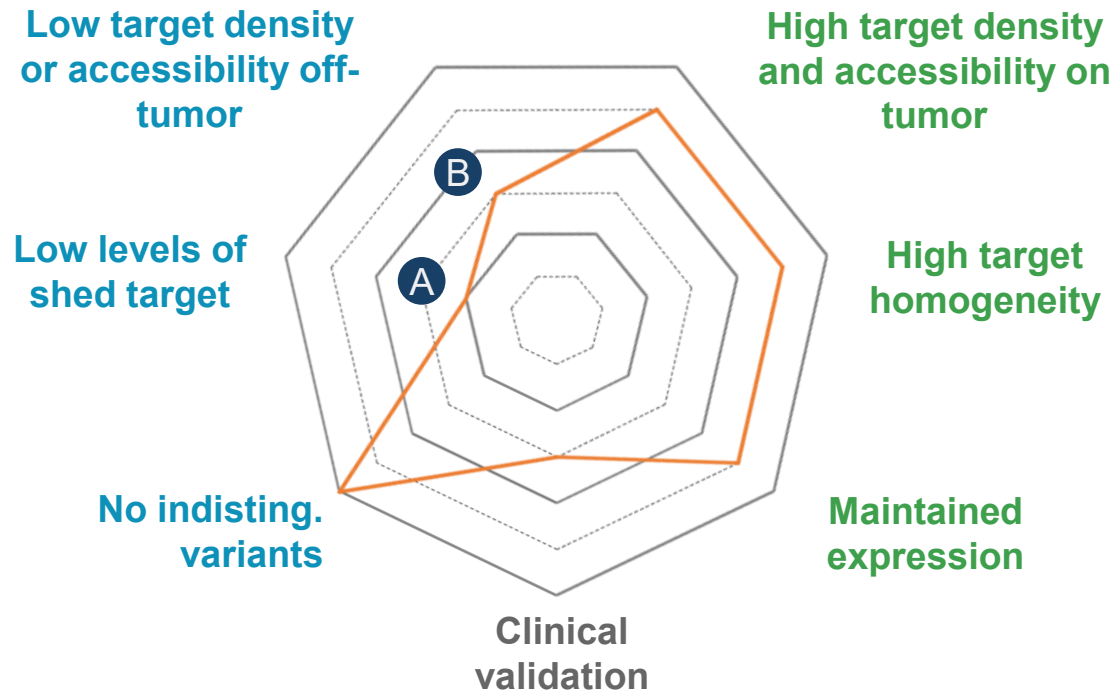
MSLN biology and shedding



A
- Systemic sMSLN up to 160 ng/ml (4 nM) reported for OC patients[1,2] and potentially higher in ascites and TME → sink risk especially when aiming at micro-dosing
- High sMSLN reported to limit the efficacy of the combo anetumab ravtansine + pembrolizumab in a Ph1/2 study[3]

B
- MSLN is expressed on mesothelial cell layer lining the lungs, heart and abdomen → on-target tox risks

MSLN in OC



- MSLN is expressed in ovarian cancer with high prevalence (> 80%) and high level of intra-tumoral homogeneity[4]
- Expression is maintained in lymph node and peritoneal metastases[4]

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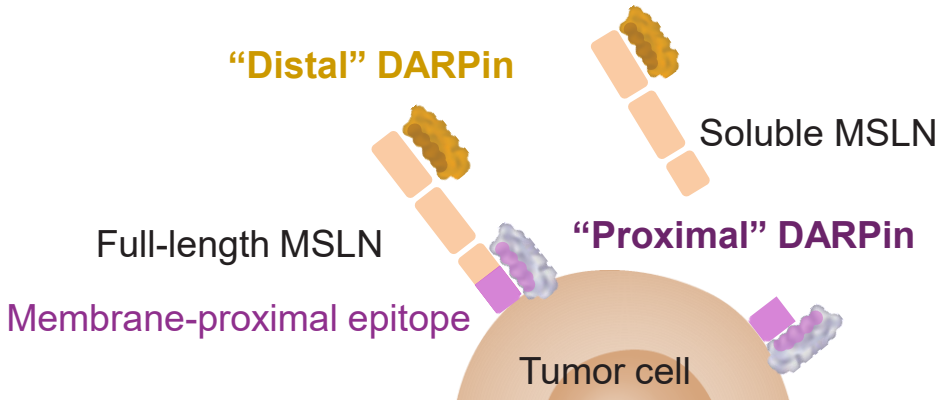
MSLN, mesothelin; OC, ovarian cancer; TME, tumor microenvironment.
1. Beyer et al., Clin Chem 2007;53,666–72; 2. Hassan et al., Clin Cancer Res 2006;12;447–53;
3. Mansfield et al., Lung Cancer 2024;195:1079284; 4. Weidemann et al., Appl Immunohistochem Mol Morphol 2023;31:77–83.

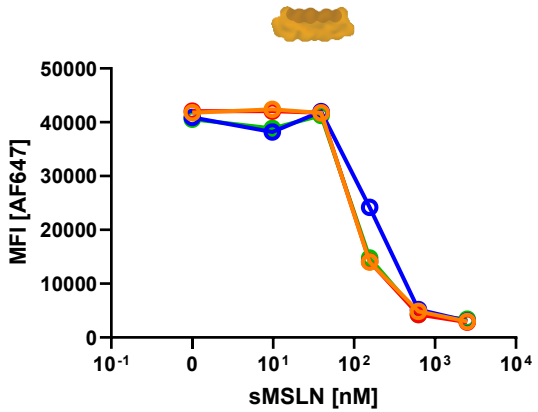
DARPin Design Overcoming Binding to Shed Target



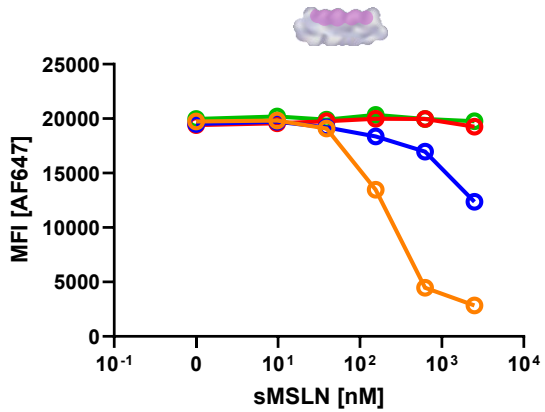
sMSLN versions

- 296 - 597 — Full length 296–597
- 296 - 591 — 296–591
- 296 - 586 — 296–586
- 296 - 580 — 296–580

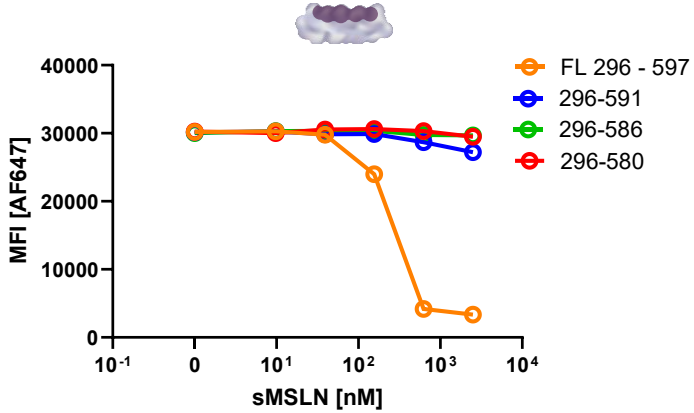
Distal MSLN DARPin



Proximal MSLN DARPin-1



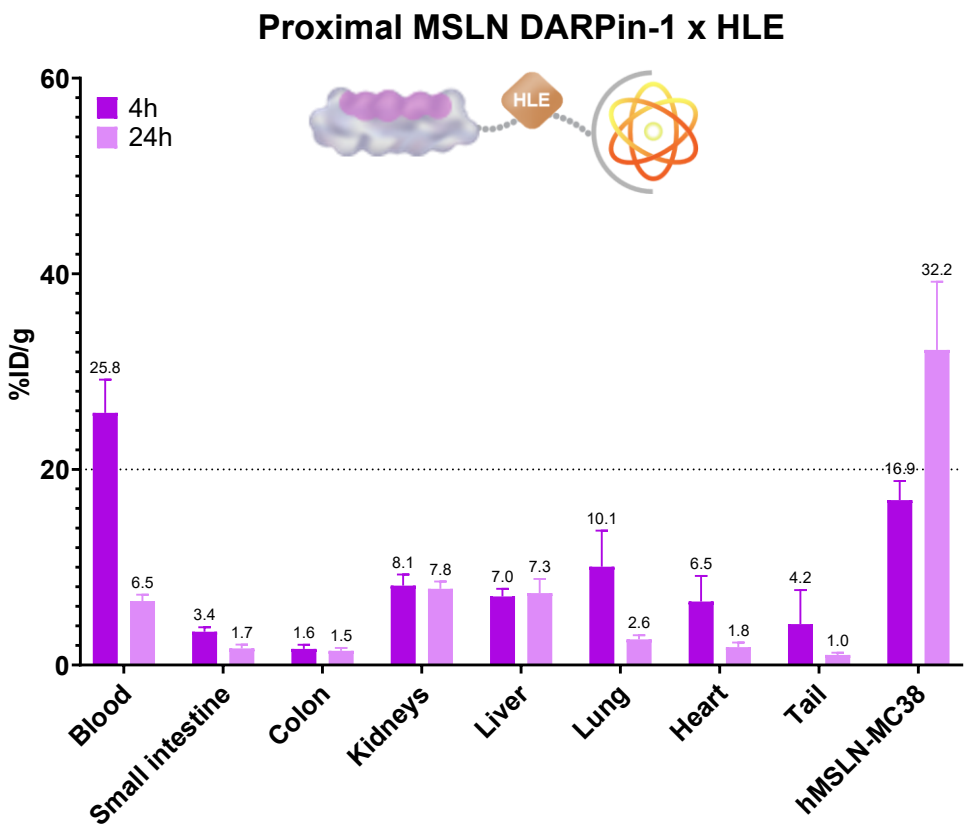
Proximal MSLN DARPin-2

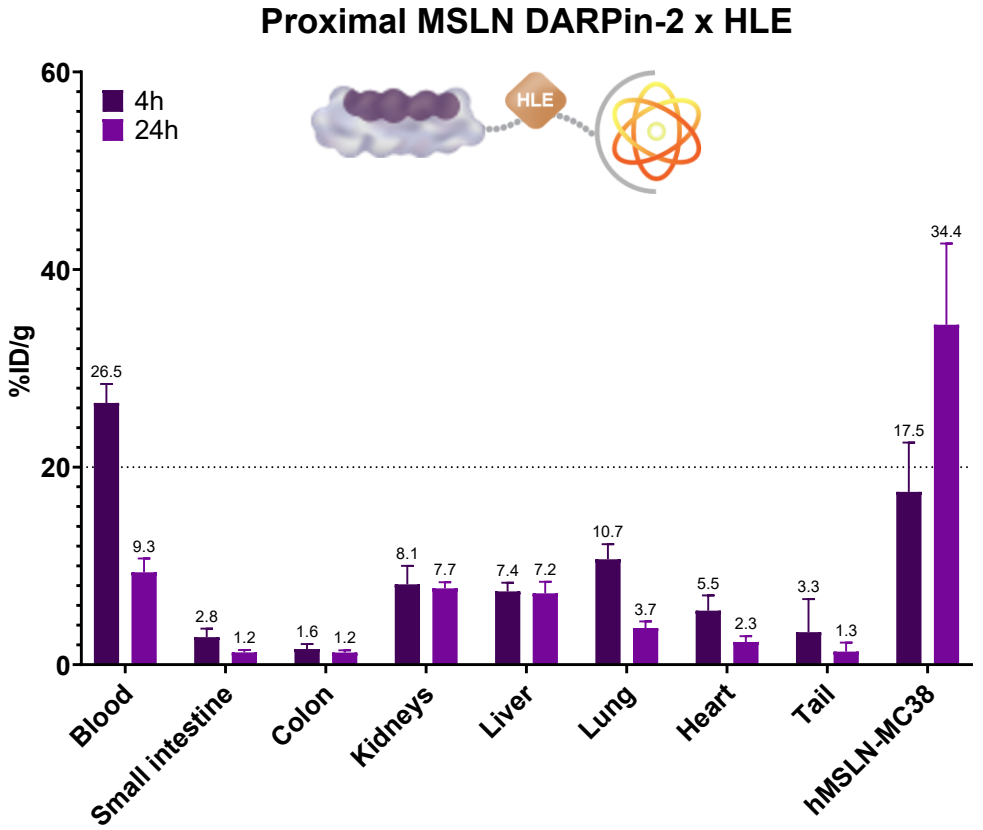


Wullschleger, et al., AACR 2025.

OVCAR-8 Cell binding competition assay (100nM DARPin with increasing concentration of shed MSLN).

Proximal MSLN DARPins Show Attractive BioD Profile





Outlook: Progressing MP0726 to FIH imaging in 2026 and exploring Compassionate Care / IIT studies for early derisking of potential on-target off-tumor toxicity

Wullschleger, et al., AACR 2025.

Mice xenografted s.c. with hMSLN-MC38 (Biocytogen).
Dose: 10 µCi of ^{212}Pb at 0.01 mg/kg of MSLN DARPin.
BioD, biodistribution; FIH, first in human; IIT, investigator-initiated trial; HLE, half-life extension.

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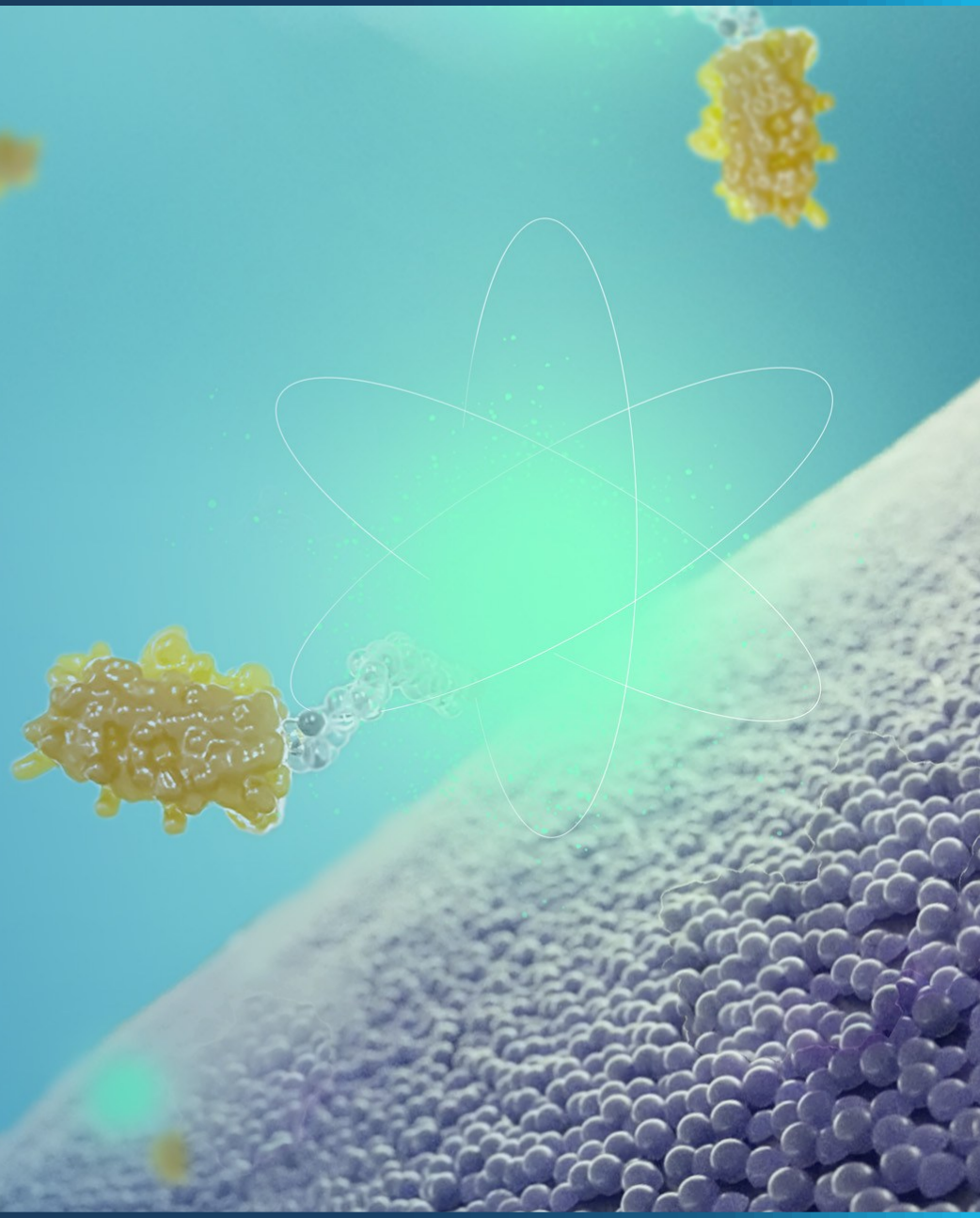
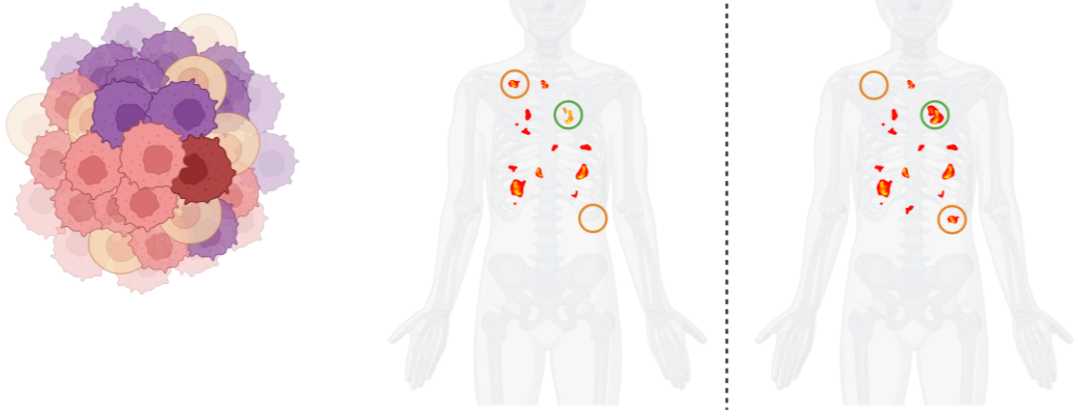
Heterogeneity and Loss of Expression Challenges

Multi-specific Radio-DARPin approaches



Mono-Specific RLTs do not Cover Tumor Complexity

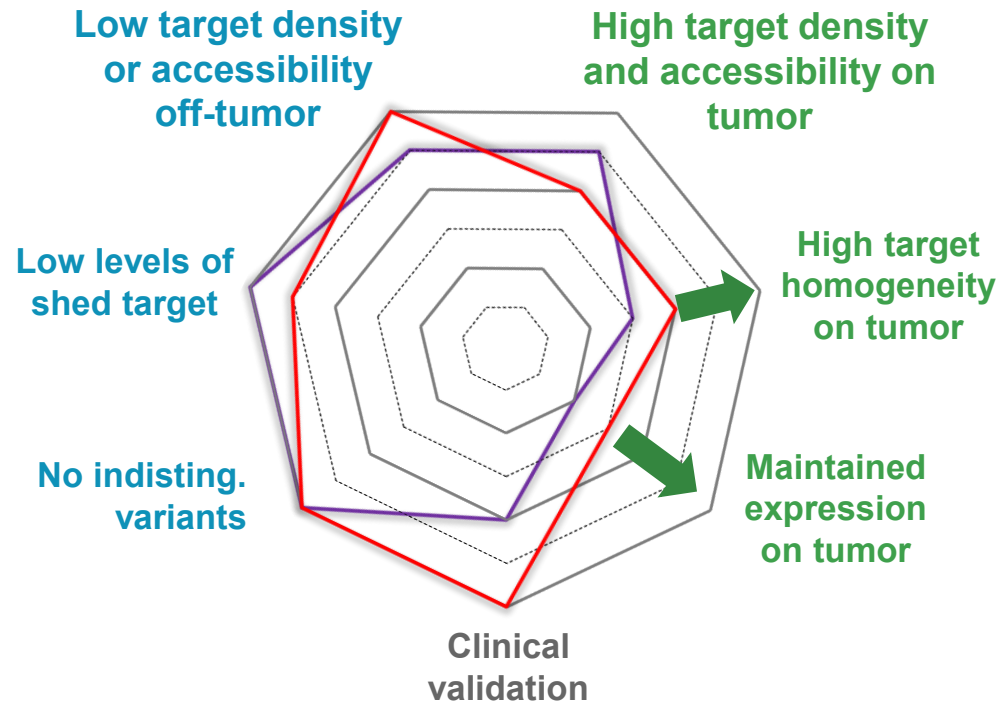
Tumors are highly heterogeneous



Tumor Heterogeneity
- Intra-tumor
- Inter-lesion
- Inter-patient

Loss of Target Expression
- Disease evolution
- Therapies-induced

Are there strategies to improve the lack of perfectly homogeneous & stable targets?

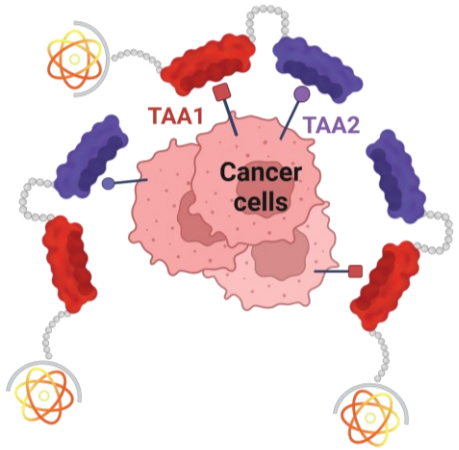


RLT, radioligand therapy; TAA, tumor-associated antigen.

Multi-Specific DARPins as a Solution to Improve Therapeutic Index

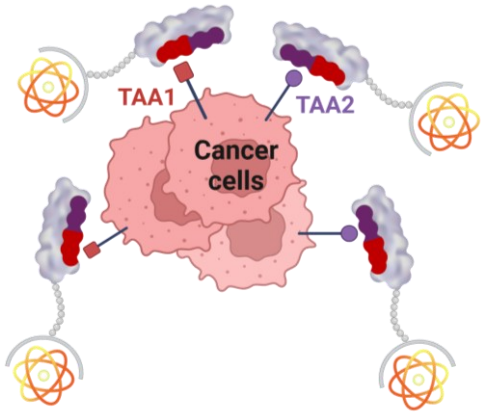
Our molecular designs

Classical bi-specific DARPins



Can either bind target A or B, or both A and B simultaneously

Small 2-in-1 DuoDARPins



Can either bind target A or B, but not both simultaneously

Multi-specifics for better therapeutic index

Enhancing efficacy and decreasing escape:

- **Broader** coverage of **tumor cells** and **lesions**
  - Within a tumor lesion
  - Across tumor lesions
  - Across patients
- Potential for **higher absorbed dose to tumor**
  - Increase in effective antigen density
  - Longer tumor retention and increased internalization

Avoiding cumulative toxicity:

- **No additive tox** from receiving **consecutive** or **mixtures** of RLTs

Our ambition: Multi-specific Radio-DARPin therapeutic candidate selection in 2027; multiple research projects ongoing enabled by our expertise from 6 clinical-stage multi-specific DARPins

Images created in part with BioRender.com

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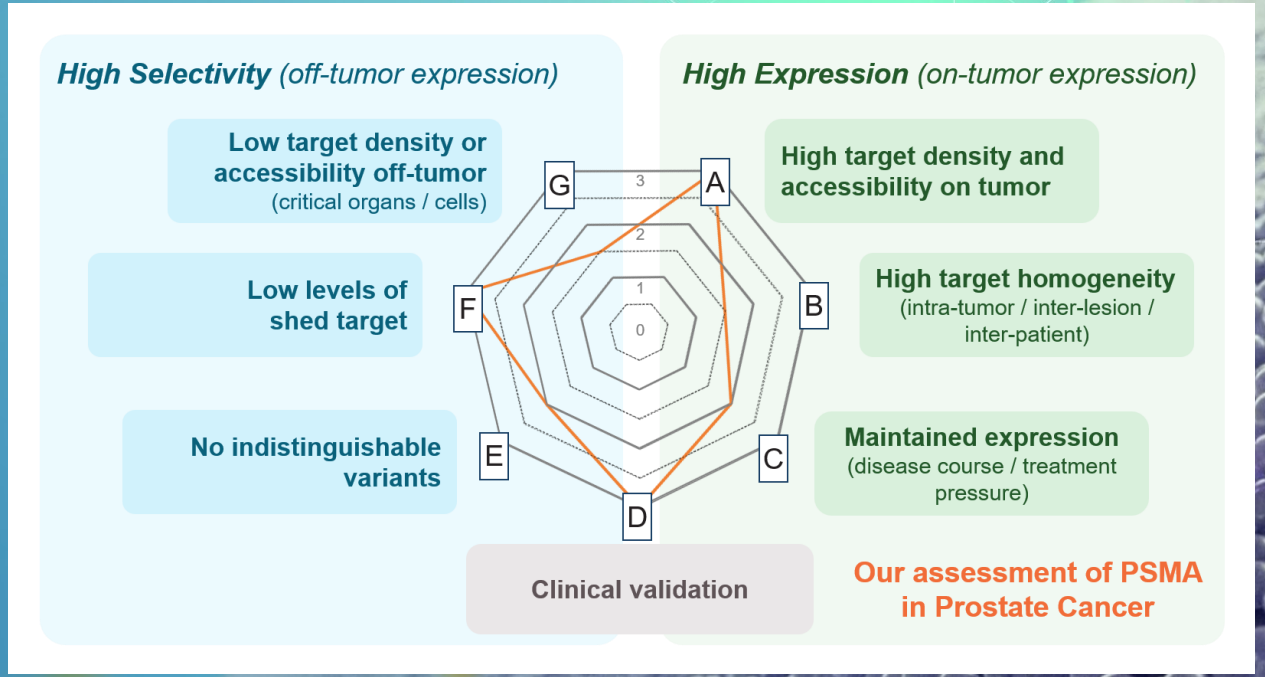
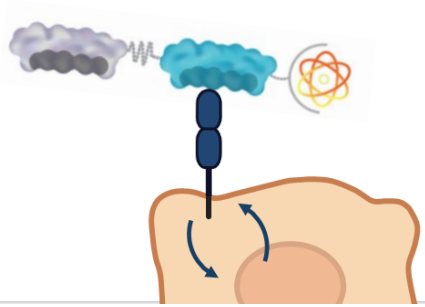
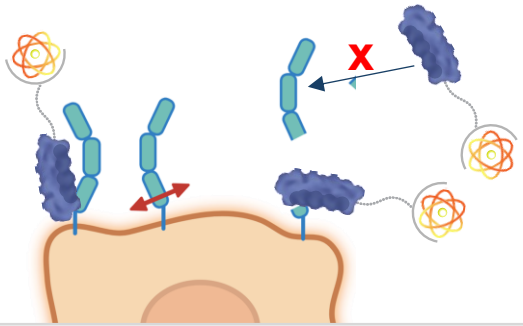
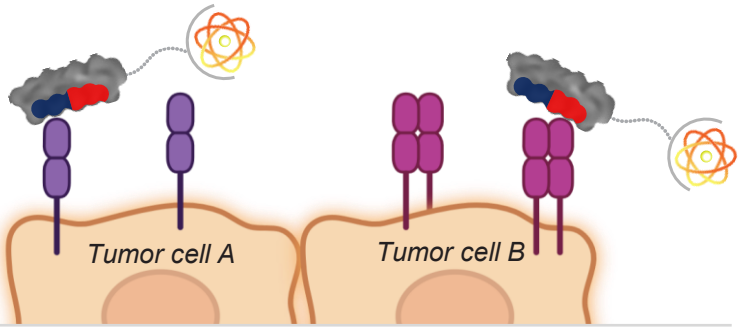
Conclusions, Outlook and Stimulus for Discussion



Summary & Outlook

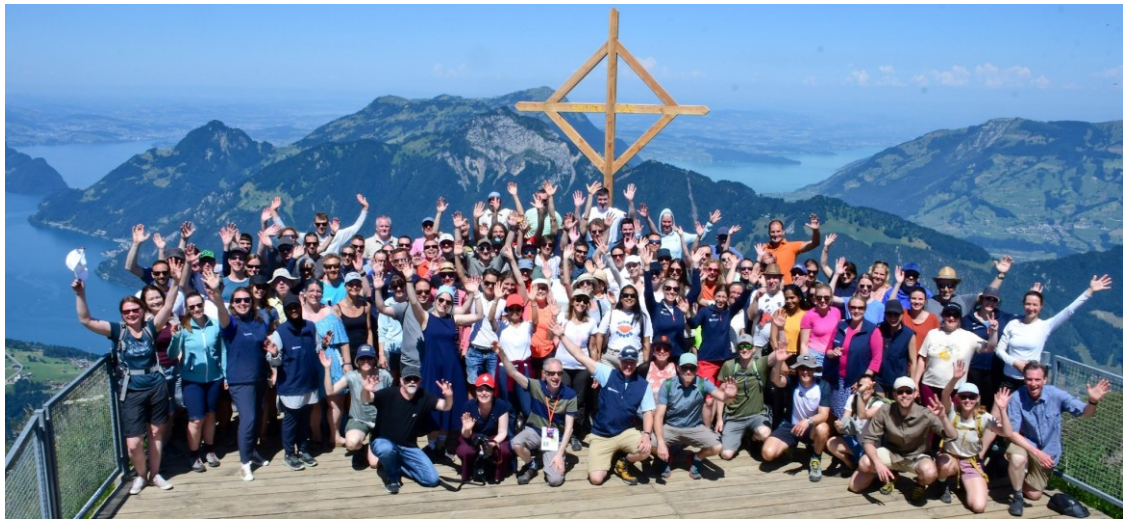
	DLL3	MSLN	Multiple Targets
Challenge	**"Low target density"**	**"Shed target"**	**"Target heterogeneity"**
DARPin Design	**Design to leverage rapid internalization & replenishment** of DLL3 	**Selectivity for membrane-bound** MSLN vs shed MSLN 	**Bi-specifics** to address tumor heterogeneity 
Status	**MP0712** (^{212}Pb x DLL3): Dosing patients in US Phase 1 Compassionate care initiated in ZA with **^{225}Ac x DLL3** DARPin	**MP0726**: FIH imaging expected to start in H2 2026	**Multiple early programs** with ambition of candidate selection in 2027

Images created in part with BioRender.com

FIH, first in human.

Acknowledgments

The entire team at Molecular Partners AG



Orano Med Team

oranomed
^{212}Pb for Targeted Alpha Therapy

NuMeRI Team

NUCLEAR MEDICINE RESEARCH INFRASTRUCTURE
NuMeRI

Patients & their Families

There are Many Exciting but no Perfect Targets

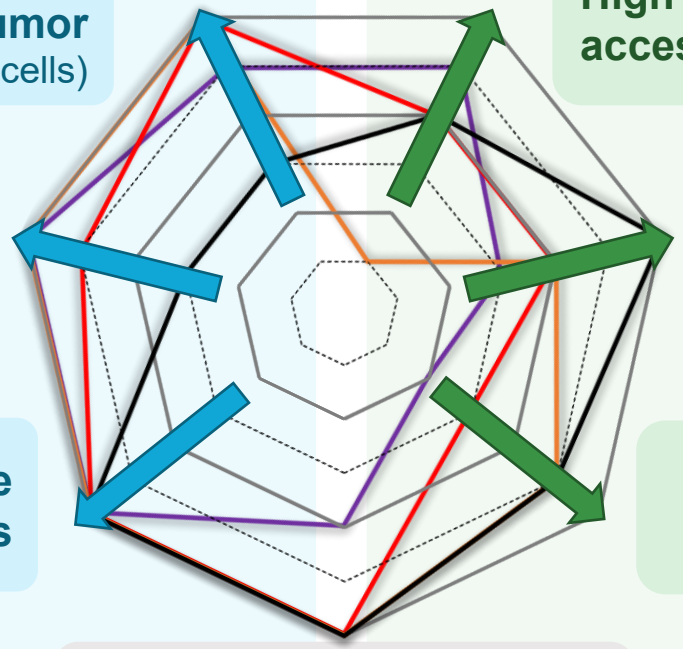
RLT success lies as much in smart molecular design as in target selection

High Selectivity *(off-tumor expression)*

Low target density or accessibility off-tumor
(critical organs / cells)

Low levels of shed target

No indistinguishable variants



High Expression *(on-tumor expression)*

High target density and accessibility on tumor

High target homogeneity
(intra-tumor / inter-lesion / inter-patient)

Maintained expression
(disease course / treatment pressure)

Clinical validation

MOLECULAR partners

Looking forward to the discussion!

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