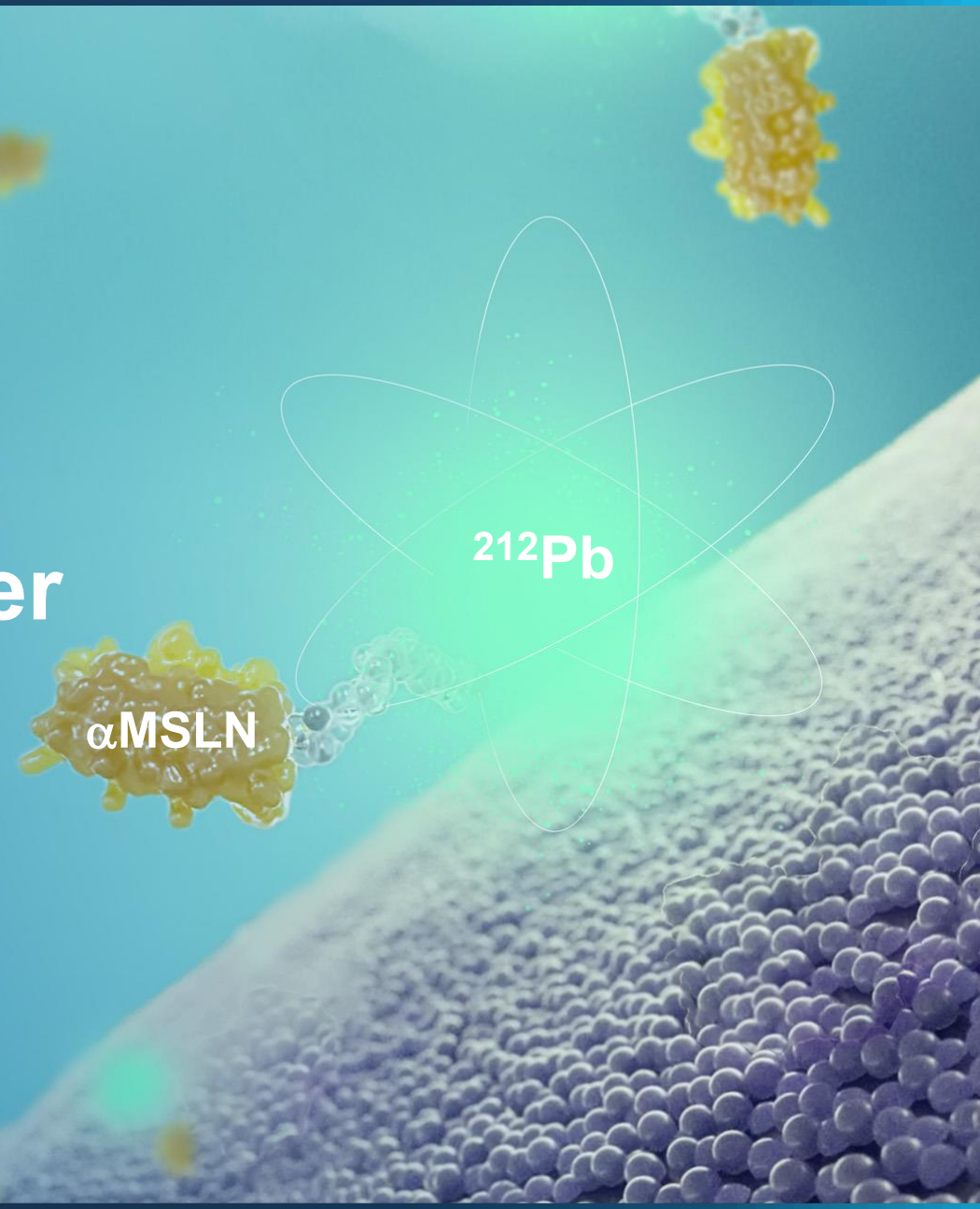
Preclinical characterization of ^{212}Pb x MSLN Radio-DARPin Therapeutic for Ovarian Cancer



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SNMMI, June 24th, 2025

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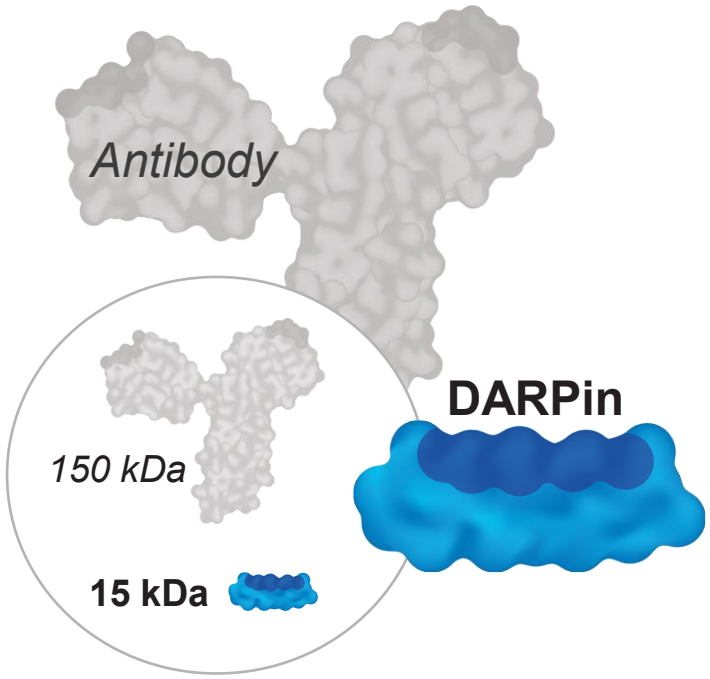
- All authors are employees of Molecular Partners and Orano Med
- Christian Lizak has ownership of stocks in Molecular Partners

Leverage DARPin Features to Address Biological Problems

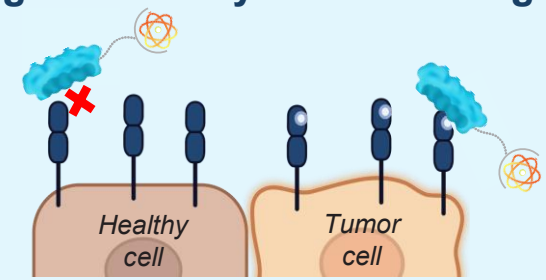


DARPins are binding proteins derived from natural ankyrin repeat proteins

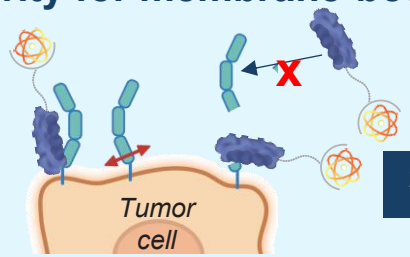
DARPin key features

- ✓ **Small size** (~15 kDa)
  - → *Deep tumor penetration*
  - → *Short systemic half-life*
- ✓ **High affinity** (pM range)
  - → *Long tumor retention*
- ✓ **High selectivity**
  - → *Low accumulation in other tissues*
- ✓ **High stability**
  - → *Kidney engineering*
- ✓ **Clinical Validation**
  - *7 clinical compounds*
  - *> 2500 patients treated*

High selectivity to tumor antigens

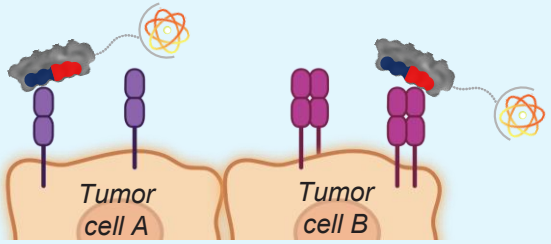


Selectivity for membrane-bound antigen



^{212}Pb x MSLN

Small bi-specific DARPins (*2in1 DARPin*)



DARPin: Designed Ankyrin Repeat Protein
Binz HK. *et al, J Mol Biol*, 2003

Created in part with BioRender.com

Radio-DARPins as Ideal Vectors for Targeted Alpha Therapy

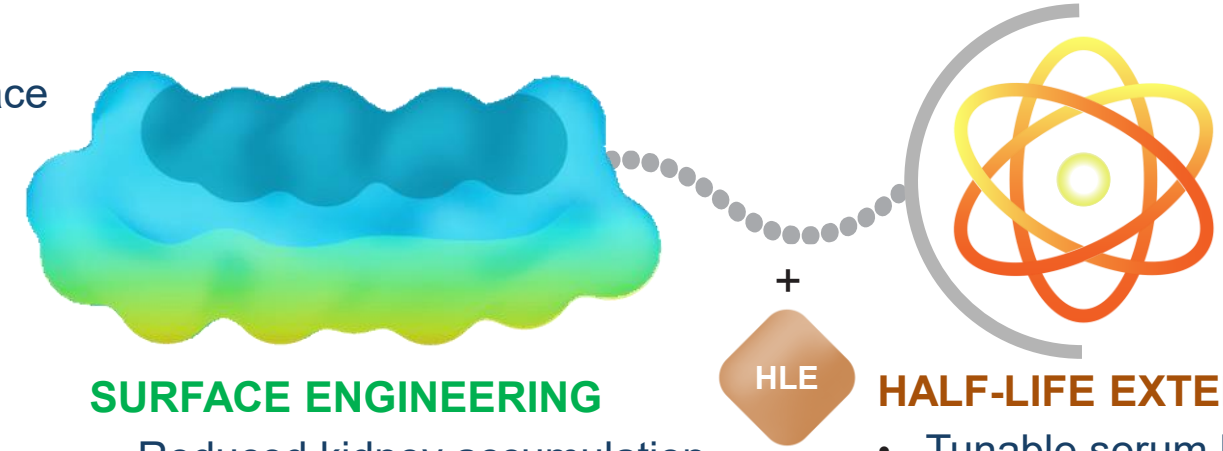
Combining versatile DARPin features with the power of ^{212}Pb

MOLECULAR PARTNERS
PIONEERS of DARPin THERAPEUTICS

ORANO MED
PIONEERS of TARGETED ALPHA THERAPY

INTRINSIC DARPin PROPERTIES

- Proven selective targeting
- High affinity
- Broad target space
- Small size
- High stability



SURFACE ENGINEERING

- Reduced kidney accumulation

^{212}Pb: ALPHA-EMITTING THERAPEUTIC ISOTOPE

- Proven clinical efficacy
- Fast & high energy deposition (10.6h half-life)
- Safe profile
- Ideal waste management

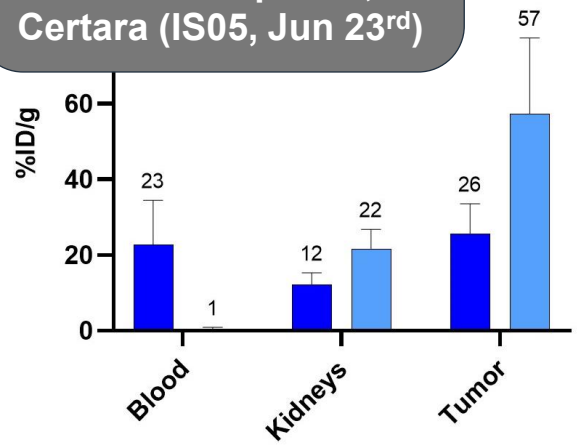
HALF-LIFE EXTENDER

- Tunable serum half-life
- Promote tumor uptake

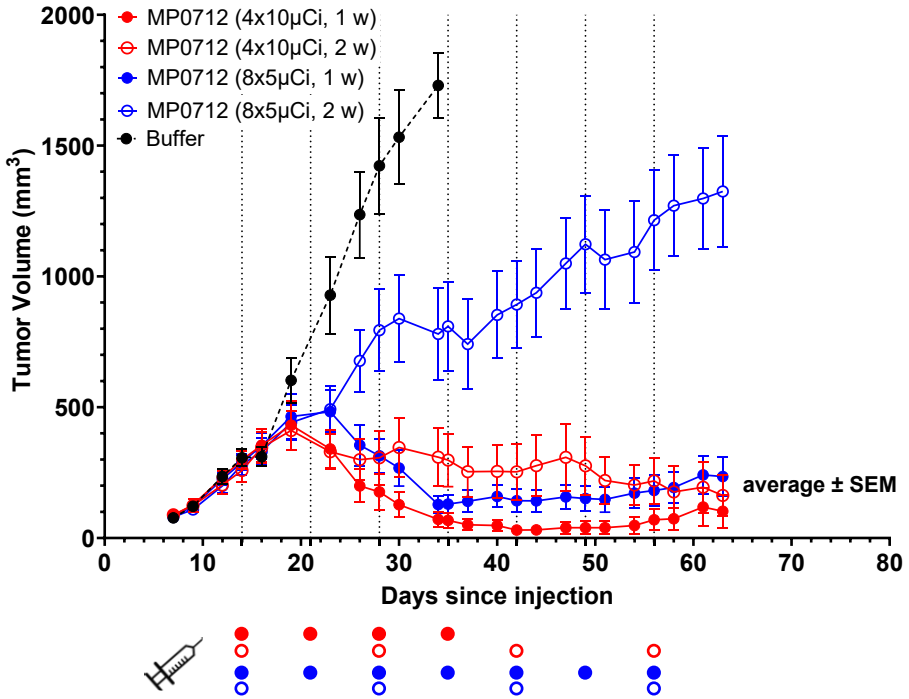
MP0712, the first ^{212}Pb-DLL3 Targeted Radiotherapeutic for SCLC

*Mice xenografted **IV** with*
NCI-H82

"Clinical Pharmacology and Model-Informed Drug Development"
Hunter Stephens, Certara (IS05, Jun 23rd)



*Mice xenografted **SQ** with*
NCI-H82



Characteristics of MP0712

- Encouraging preclinical results
  - High tumor uptake
  - T:K ratio >2 in model matching clinically relevant DLL3 expression levels (NCI-H82)
  - Complete and durable tumor regression at 4x 10 µCi*
  - Favorable safety profile up to 30 µCi /1.11 MBq (*not shown*)
- IND-enabling package completed
- Initial first-in-human clinical data expected in 2025

Croset A. et al, AACR, 2025

Efficacy study in NCI-H82 tumor model
MP0712 and negative control injected 4x 10 µCi or 8x 5 µCi at 1 HED every 1 or 2 weeks
10 µCi = 370 kBq

* At day 63, complete tumor regression was seen for ~70% of mice

^{212}Pb x MSLN Targeted Radio-DARPin for Ovarian Cancer

Overcoming biological hurdles for next-gen targeted alpha therapy

Ovarian Cancer (OC): High medical need and marginal progress

- 5-year OS < 50% (diagnosis often in late stage)
- Limited options for 2L (platinum) resistant / refractory patients who are ineligible for ADCs (~50% patients)"

Mesothelin (MSLN): A promising target for OC as 1st indication

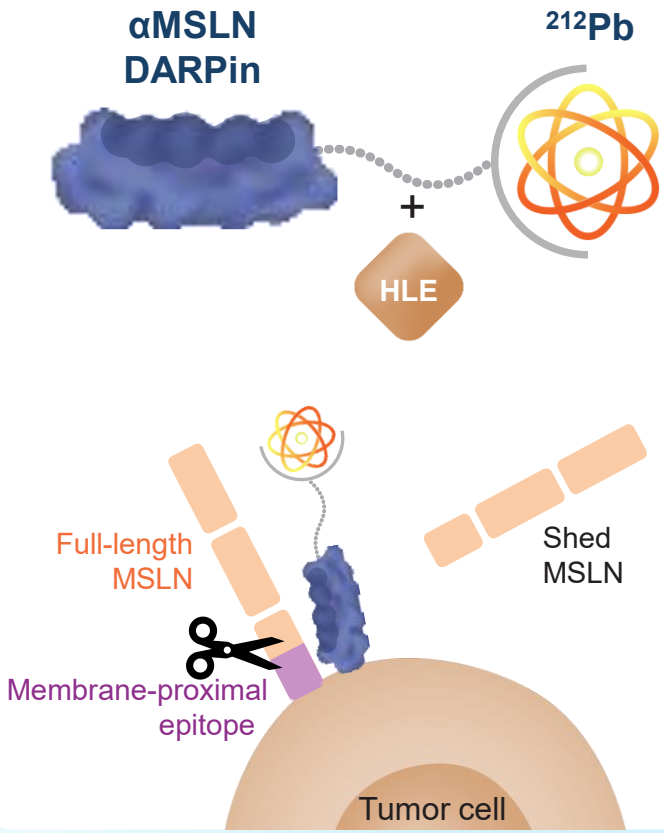
- Highly expressed in OC (>80% prevalence), expression maintained in metastases[1]
- Shed MSLN might limit efficacy of MSLN-targeted therapies[2-5]
  - Systemic sMSLN up to 160 ng/mL (4 nM) reported for OC patients[6,7]
  - High sMSLN reported to limit the efficacy of MSLN ADC in a phase 1/2 study[8]

→ **sMSLN sink might interfere with radio-therapeutics** (especially at micro-dosing)

RDT x MSLN: Targeted delivery of alpha radiation with ^{212}Pb

- MSLN DARPin targets **membrane-proximal epitope** (and not shed MSLN)
- ^{212}Pb payload: high energy alpha emissions in short time frame
- Potential for combinations with immunotherapy

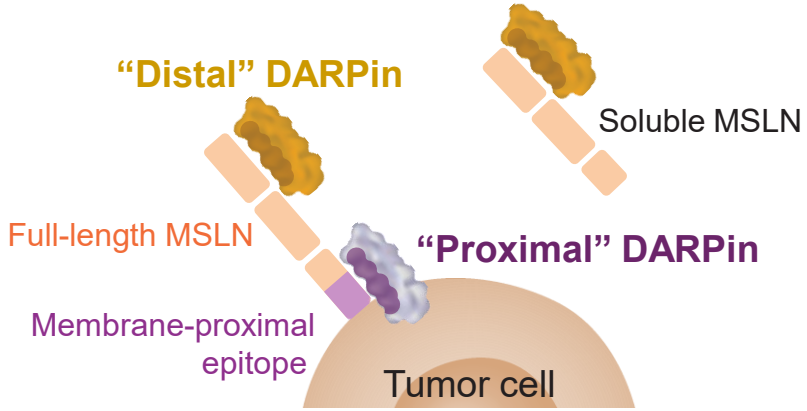
Product composition



1. Weidemann S. *et al*, *Appl Immunohistochem Mol Morphol*, 2023; **2.** Awuah et al, *Mol Cancer Ther*, 2016;
3. Liu X. *et al, Commun Biol*, 2020; **4.** Li M. *et al, Mol Cancer Ther*, 2008; **5.** Wang K. *et al, PLoS ONE*, 2012;
6. Beyer HL. *et al, Clin Chem*, 2007; **7.** Hassan R. *et al, Clin Cancer Res*, 2006; **8.** Smith KER. *et al*, 2024 (ASCO poster)

TCE: T-cell engager

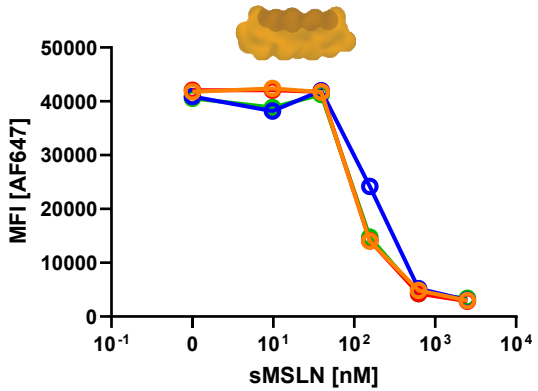
Binding of Proximal DARPin is Maintained in Presence of sMSLN



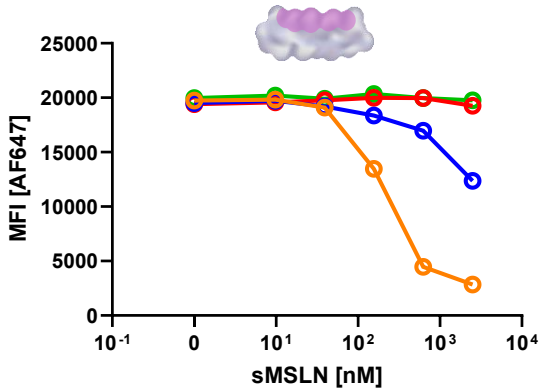
sMSLN versions

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

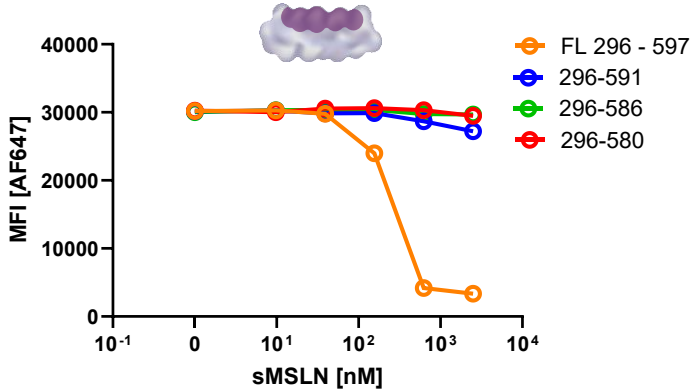
"Distal" MSLN DARPin



"Proximal" MSLN DARPin-1



"Proximal" MSLN DARPin-2



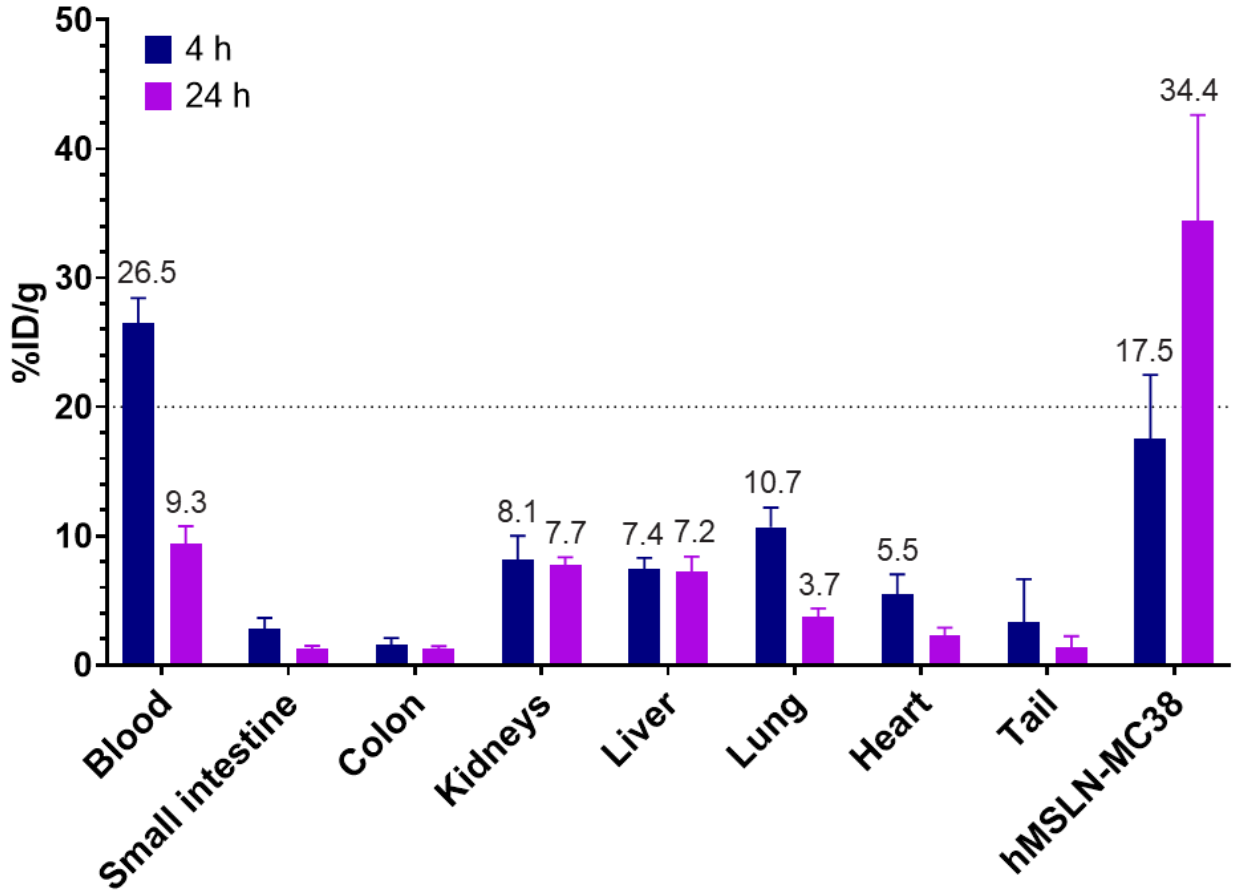
- Identified binders have picomolar affinity to membrane-proximal MSLN (K_D= 34 pM for DARPin-2, *not shown*)
- **Binding to tumor cells *in vitro* was not affected by soluble MSLN**, particularly for DARPin-2

OVCAR-8 cell binding competition assay
100nM DARPin with increasing concentration of different sMSLN versions
sMSLN: shed/soluble MSLN

Wullschleger *et al*, *AACR*, 2025

Attractive BioD Profile of ^{212}Pb x MSLN RDT Candidate

Biodistribution in hMSLN-MC38 model*



- Selected binder (DARPin-2) shows **favorable *in vivo* biodistribution**:
  - Strong tumor uptake
  - Modest accumulation in healthy organs

  → **T:K ratio of 2 (4h) and 4.5 (24h)**
- Data meet internal success criteria for continued preclinical development

→ **MP0726 nominated as MSLN x RDT development candidate**

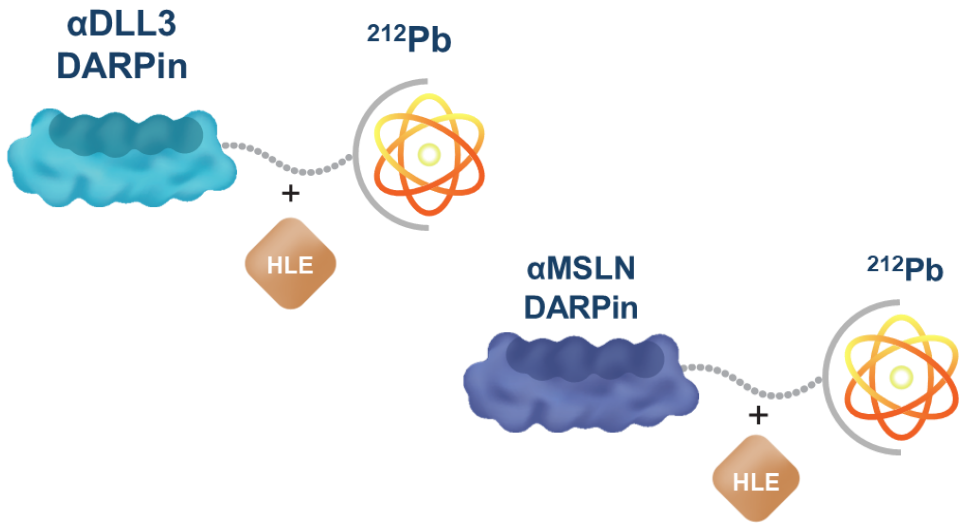
Mice xenografted s.c. with hMSLN-MC38 (Biocytogen)
Dose: 10 µCi of ^{212}Pb at 0.01 mg/kg of MSLN DARPin

* Only values >3% ID/g are shown

Wullschleger *et al, AACR* 2025

Summary & Outlook – Radio-DARPin Therapeutics

- ✓ **Successful RDT platform optimization**
  - Attractive biodistribution profiles (tumor, kidney, blood)
- ✓ **MP0712: ^{212}Pb x DLL3 RDT lead candidate for SCLC**
  - T:K > 2 in mouse models expressing low DLL3
  - Good efficacy & favorable safety profile *in vivo*
  - IND-enabling package completed
- ✓ **MP0726: ^{212}Pb x MSLN as next RDT program for OC**
  - Selectivity for membrane-bound antigen vs shed antigen
  - Attractive BioD profile with T:K > 2



MP0712 / ^{212}Pb x DLL3	• **First-in-Human studies to start in 2025** (Phase 1), IND application in Summer 2025 • Initial clinical data by end 2025 (imaging & dosimetry) • Initial efficacy and safety data in H1 2026
Radio-DARPin Therapy (RDT)	• **MP0726: Proceed with preclinical development of ^{212}Pb x MSLN program** • Additional ^{212}Pb x RDT programs nominated in collaboration with Orano Med (up to 10 products) • Continue evolving RDT platform for next differentiated RDT programs

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Entire Team at Molecular Partners AG

Orano Med Team

Julien Torgue

Amal Saidi

Aaron Schatzmann

Tania Stallons

Amy Wong

MOLECULAR partners

Thank you for your interest!

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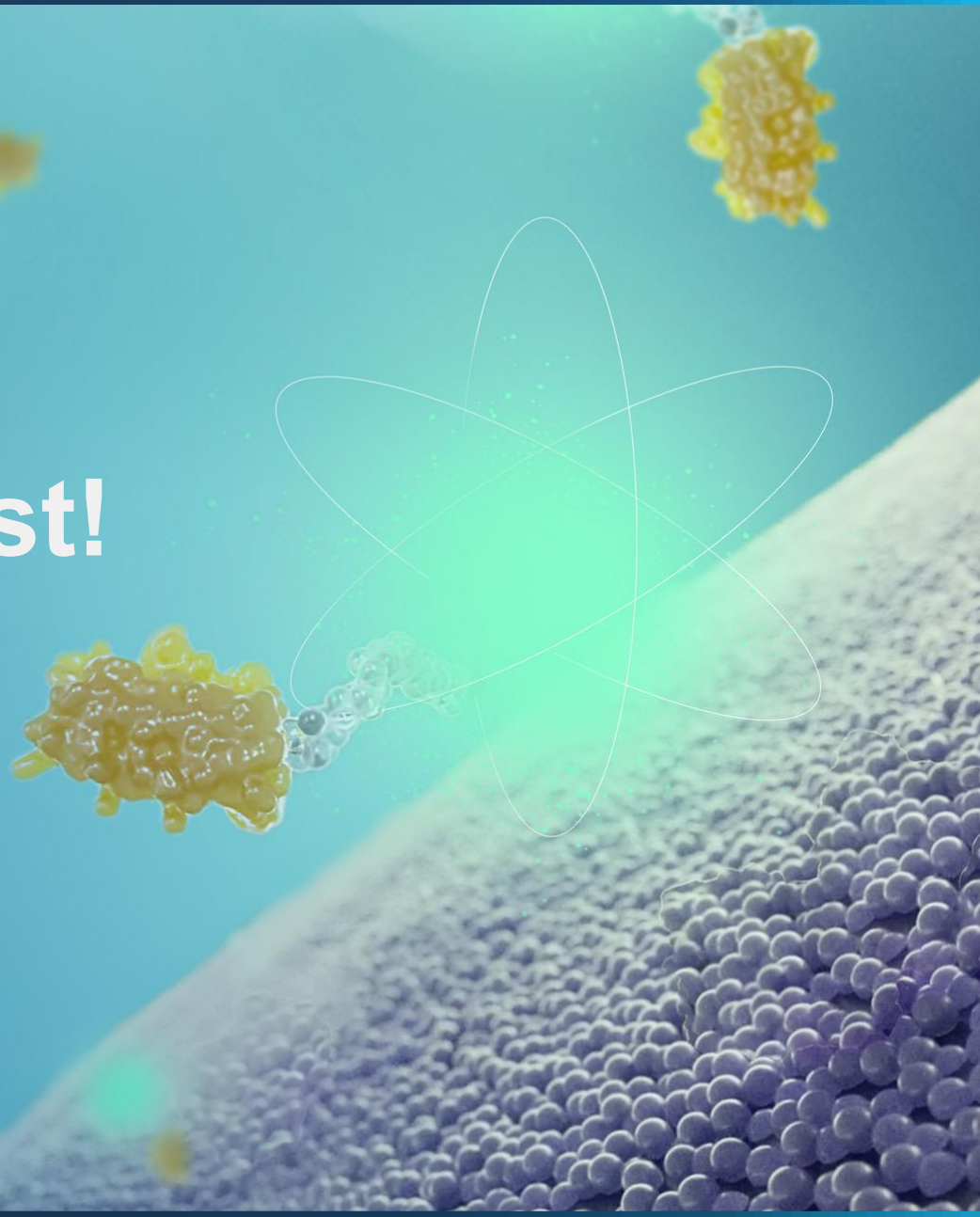

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