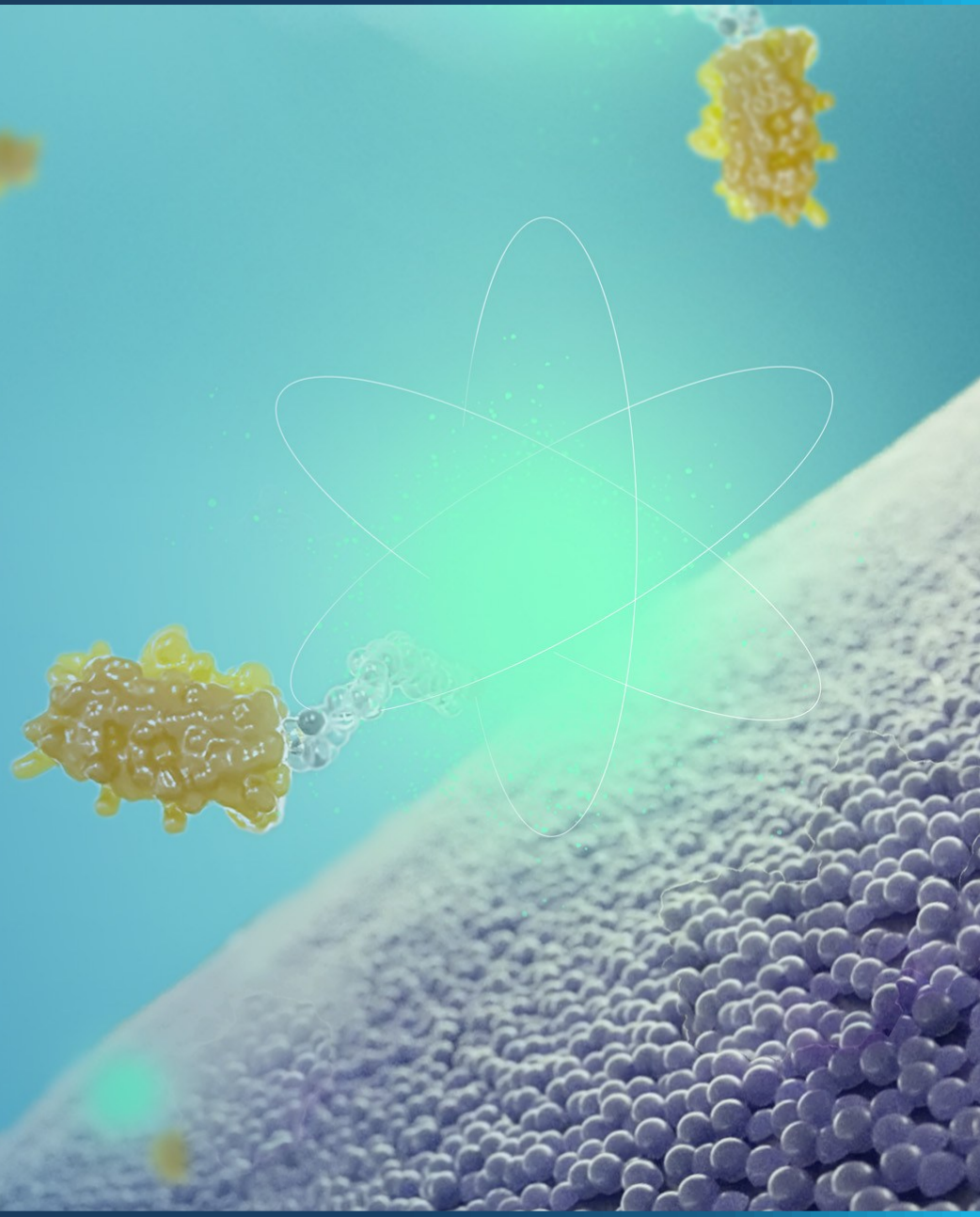
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How much Target Expression is Enough?

Learnings from advancing MP0712, a DLL3 Radio-DARPin for SCLC, into the clinic



SNMMI Theranostics Conference, 7th November 2026

Dani Steiner, PhD, SVP Targeted Radio Therapeutics

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Any forward-looking statements speak only as of the date of this presentation and are based on information available to Molecular Partners as of the date of this release, and Molecular Partners assumes no obligation to, and does not intend to, update any forward-looking statements, whether as a result of new information, future events or otherwise.

Dissecting the Components of Target Expression

Low off-tumor expression *(high selectivity)*

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 on-tumor expression *(high uptake)*

Evaluation for specific indication & "target patient"

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

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.

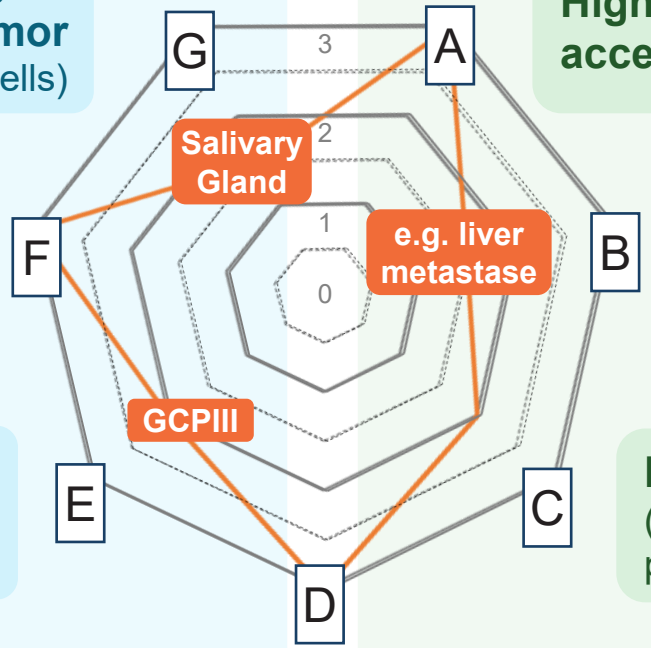
Target Expression as a Key Criterion for RLT Target Selection

Low off-tumor expression

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

Low levels of shed target

No indistinguishable variants



High 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)

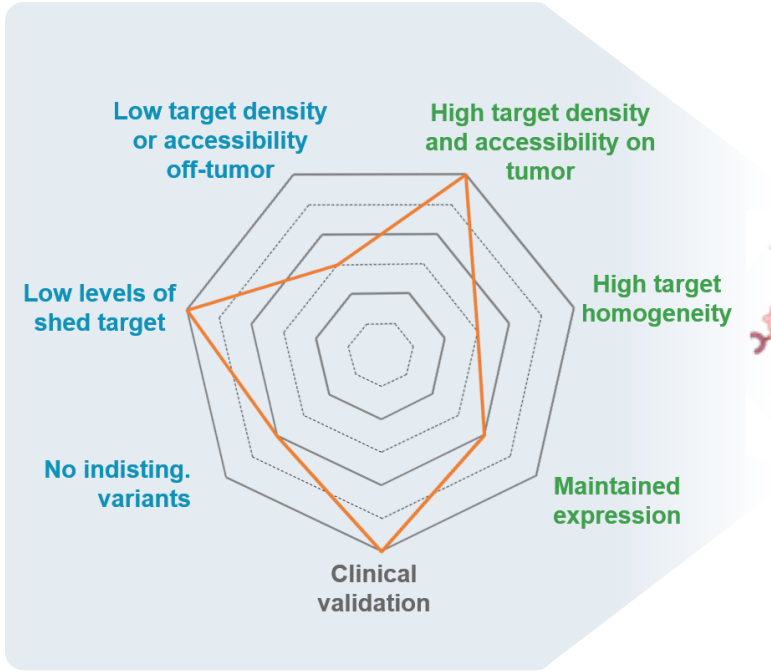
Clinical validation

Our assessment of PSMA in Prostate Cancer

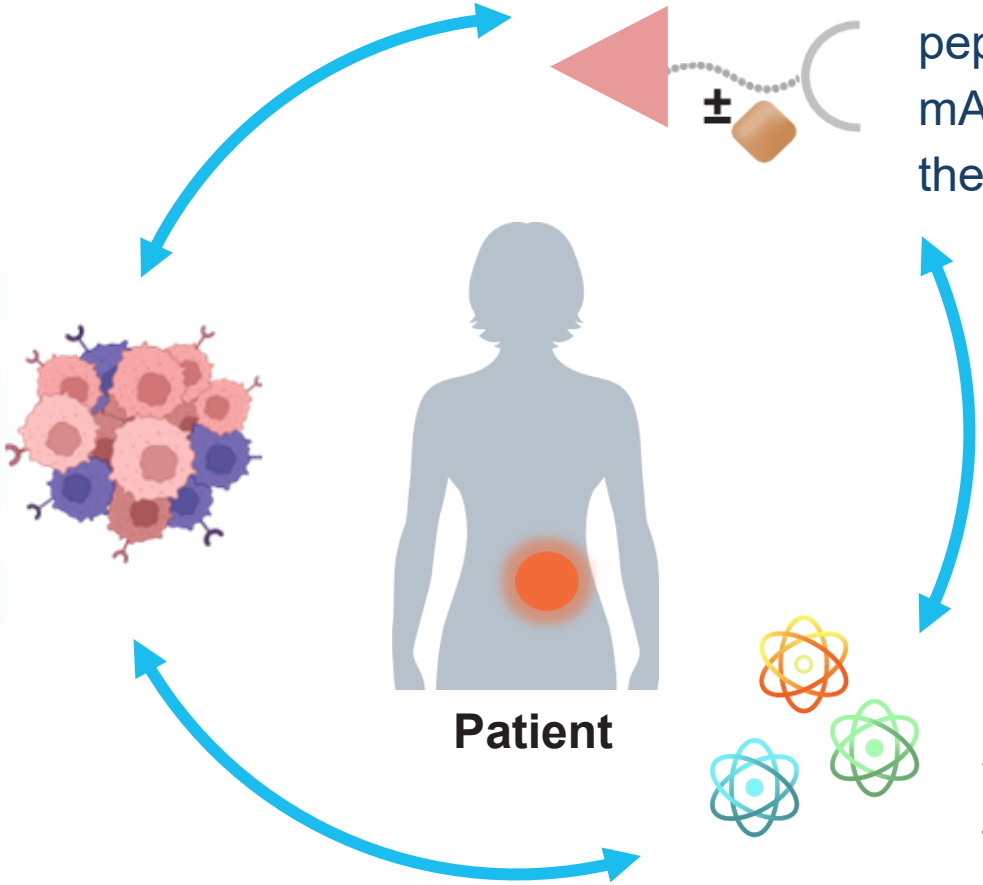
mAB,monoclonal antibody;
PSMA, prostate-specific membrane antigen.

Addressing Target-Specific Challenges Through Molecular Design

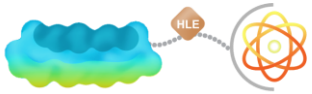
Target & Disease Biology:



"There are no perfect targets!"



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

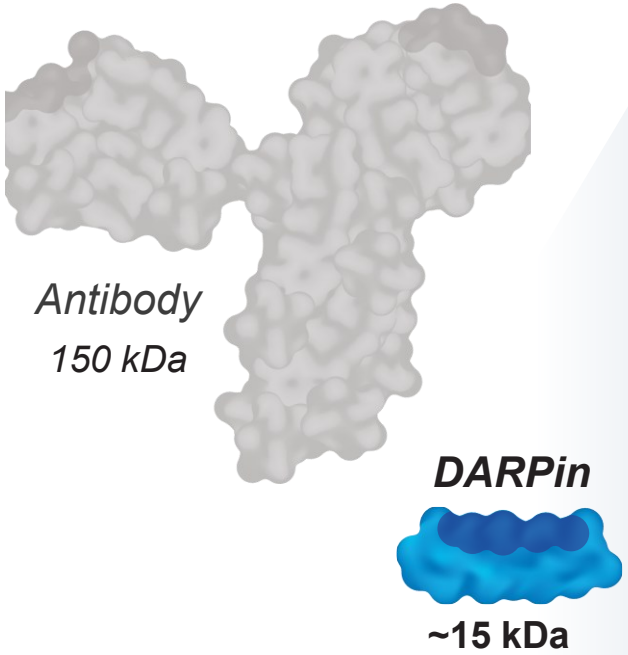


Radio-DARPin Therapeutics

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

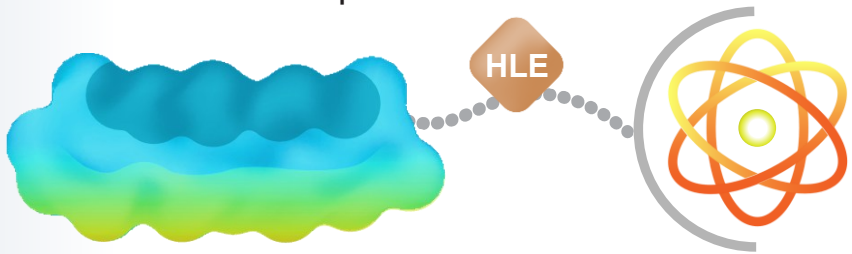
DARPin key features

- ✓ **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

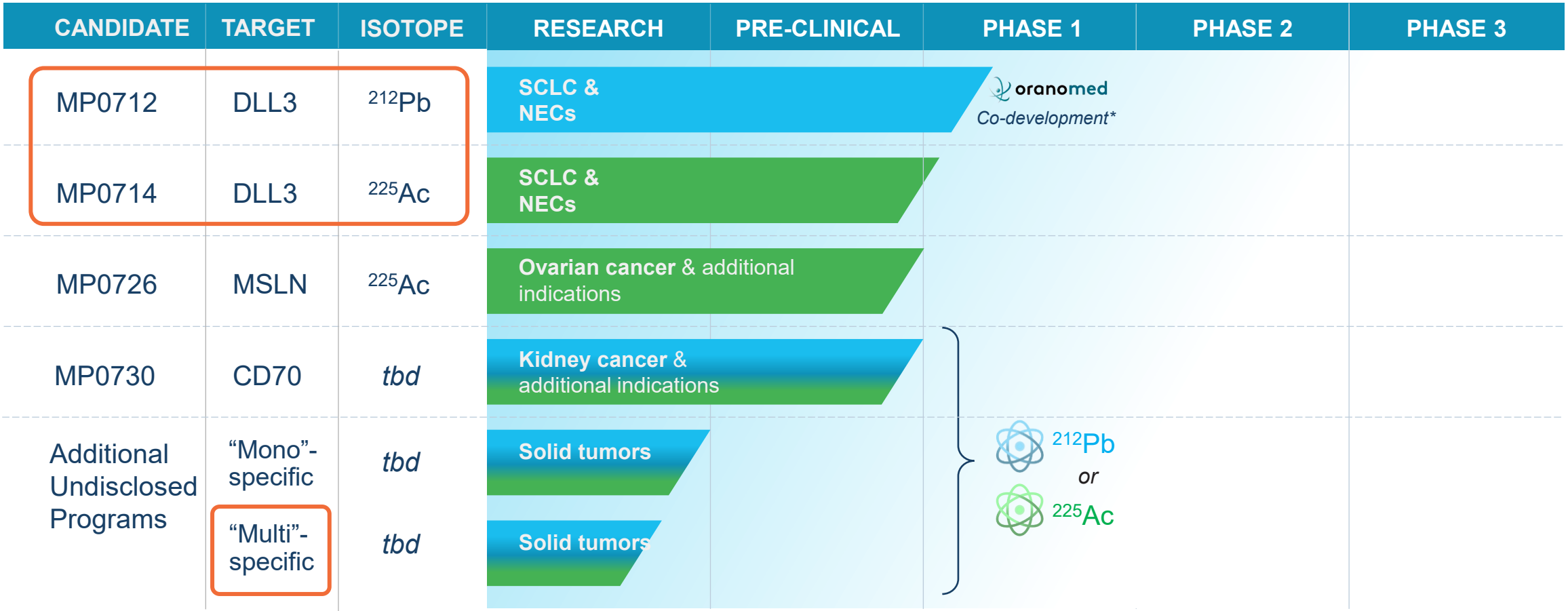
- Proven clinical efficacy
- High energy deposition
- ^{212}Pb and ^{225}Ac

RADIO-DARPin

"Isotope-agnostic": consistent BioD profiles when exchanging isotopes and chelators[2]

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

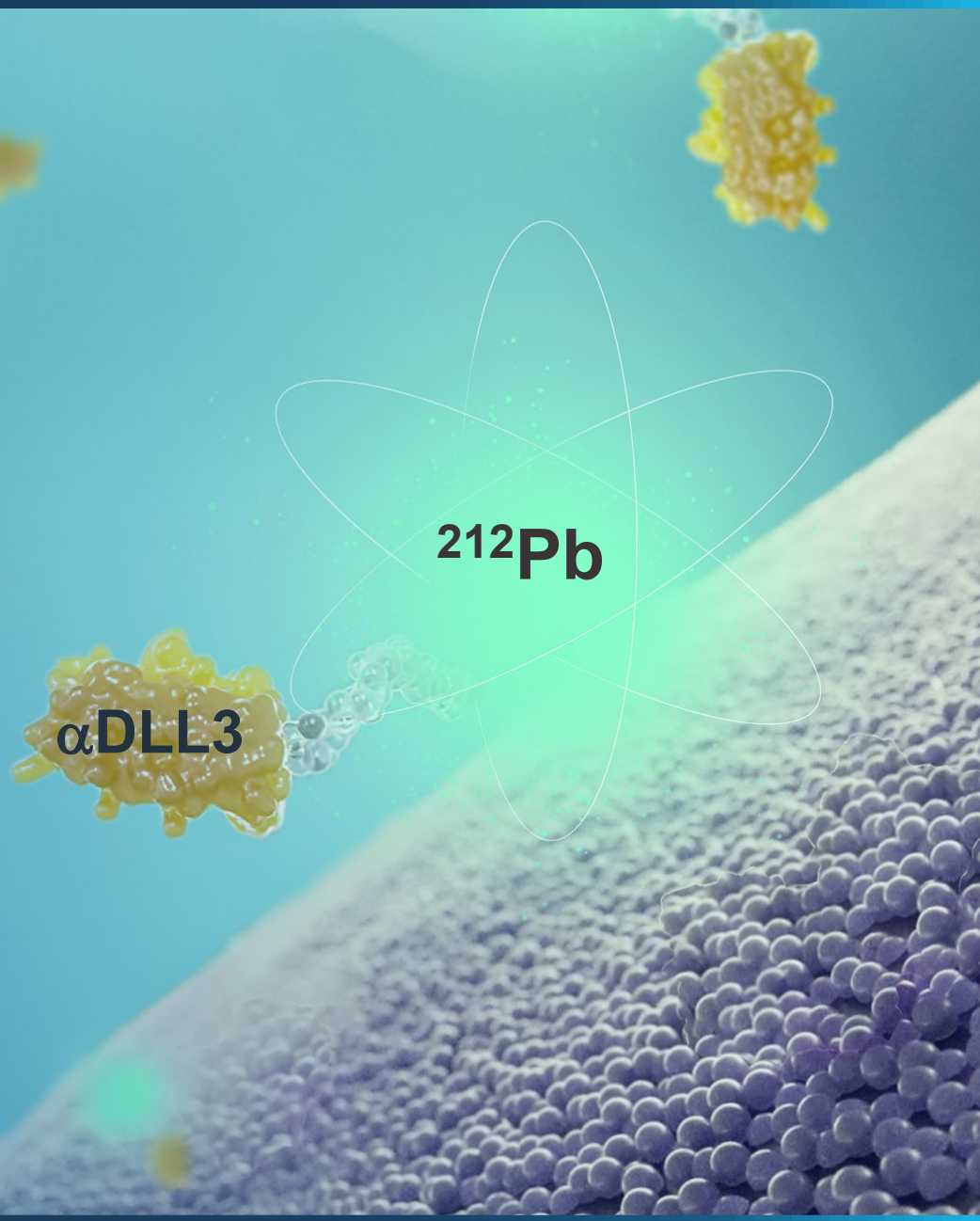
Our Radio DARPin Pipeline



* The strategic collaboration with Orano Med includes DLL3, with the option to extend it to additional programs, either as co-development or as supply. DLL3, Delta-like ligand 3; FIH, first in human; IND, investigational new drug; MSLN, mesothelin; NEC, neuroendocrine cancer; SCLC, small cell lung cancer.

Tackling Low On-Tumor Receptor Density

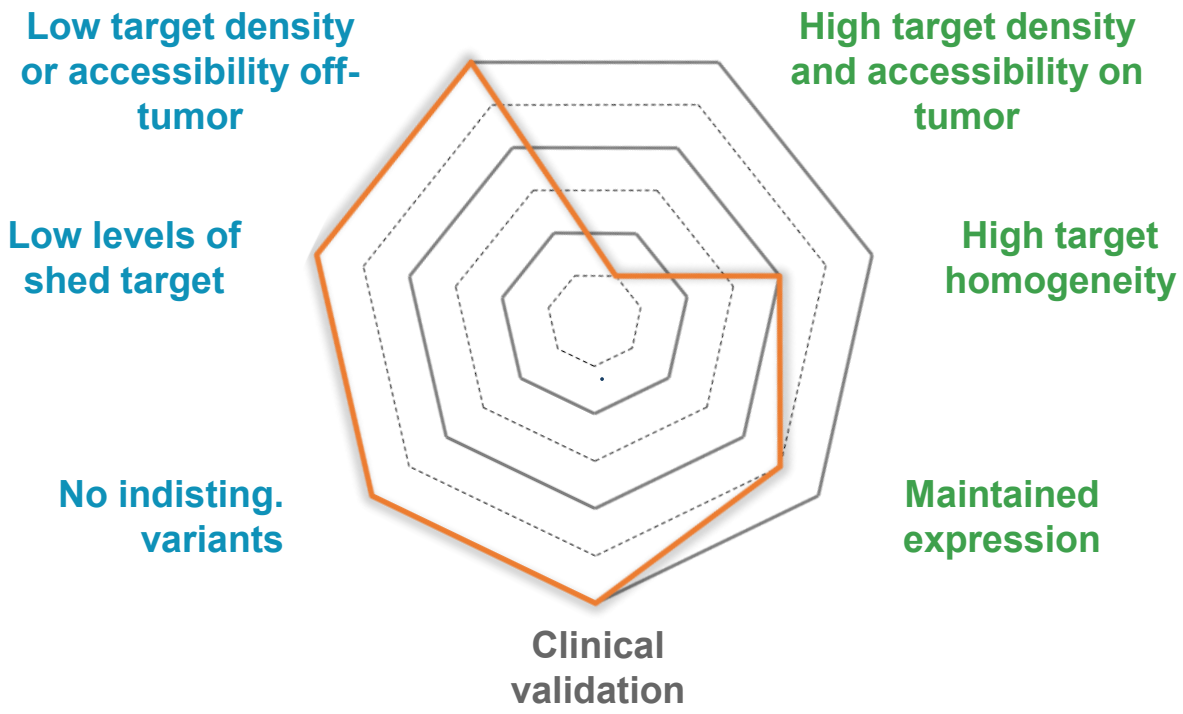
MP0712 targeting DLL3 for SCLC –
Our first clinical Radio-DARPin



DLL3 is a Highly Selective Target, fit for Radioligand Therapy

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

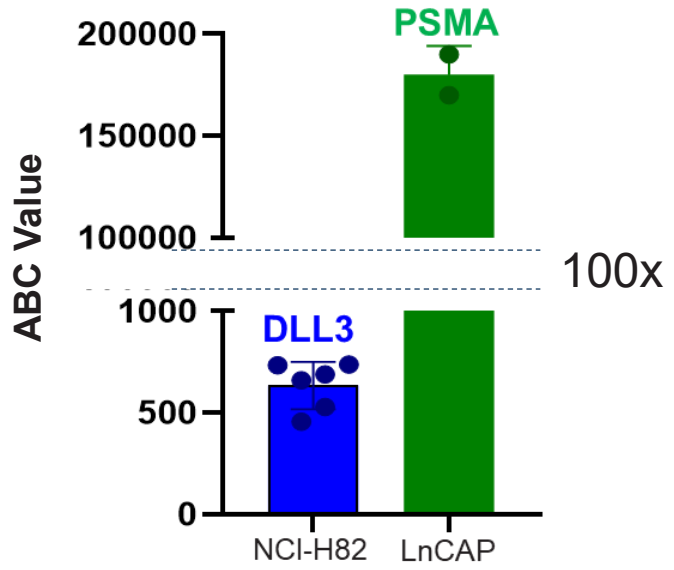
DLL3 in SCLC



Very low DLL3 copy number

DLL3: <1000 receptors/cell

PSMA: >100'000 receptors/cell



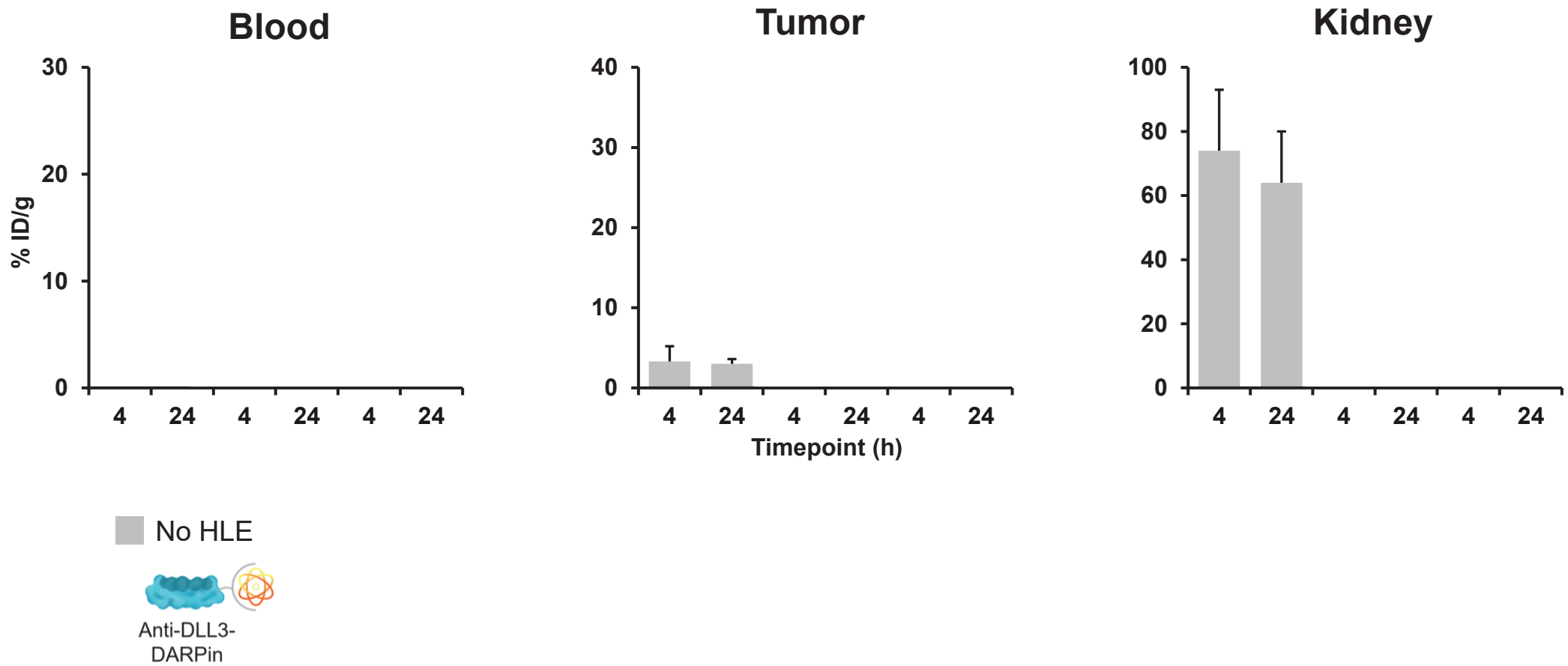
For PSMA & other targets, radioligand uptake in tumor lesions often correlates with target expression levels.

Can DLL3 achieve meaningful tumor uptake despite much lower expression levels?

ABC, antibody binding capacity; DLL3, delta-like ligand 3; SCLC, small cell lung cancer. PSMA: Lückerath et al., JNM 2018; Kwon et al, Journal of Biomedical Optics 2023. DLL3 quantification carried out in-house on NCI-H82 tumors (n=6).

MP0712: a DLL3 DARPin with a Target-Tailored Design

Systemic half-life as one key driver to boost tumor uptake for DLL3

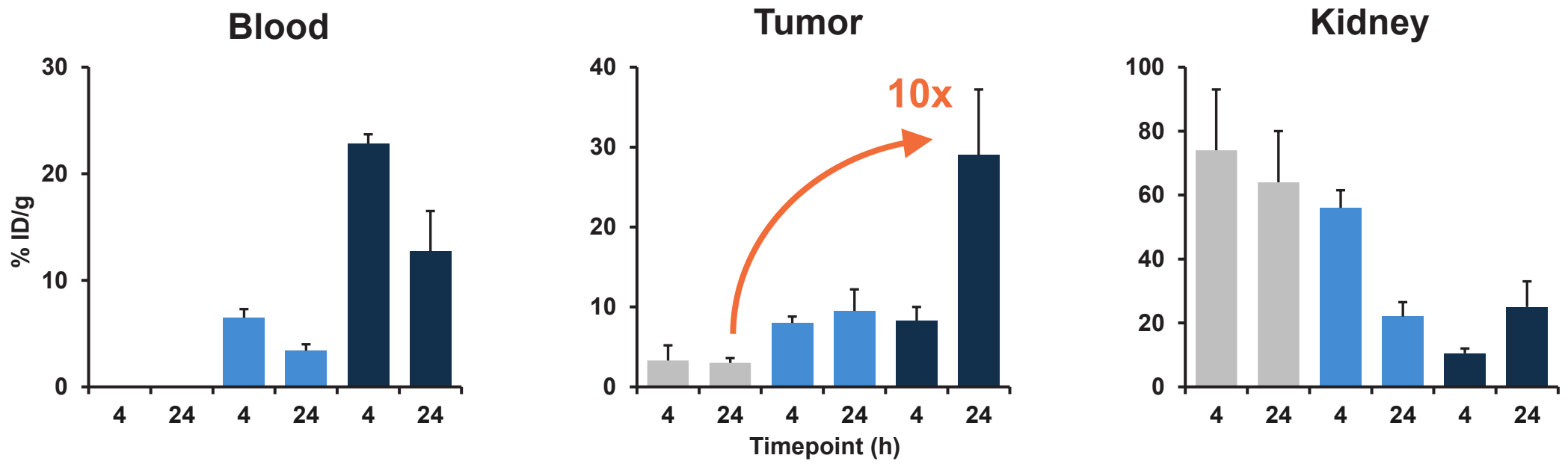


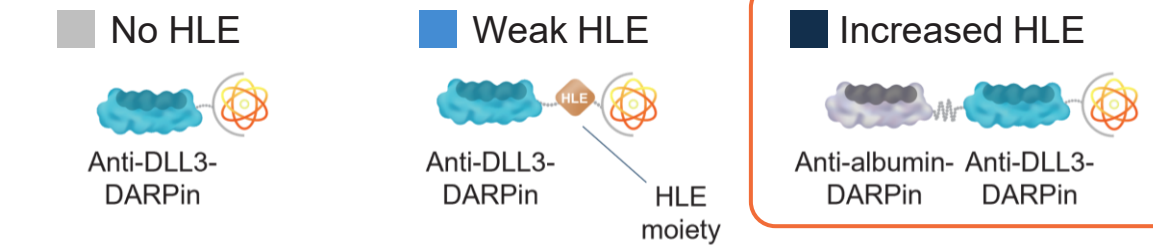
Riesenberg, et al., AACR 2026.

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

MP0712: a DLL3 DARPin with a Target-Tailored Design

Systemic half-life as one key driver to boost tumor uptake for DLL3





Final MP0712 design with increased HLE achieves 10× higher tumor uptake despite very low DLL3 target density

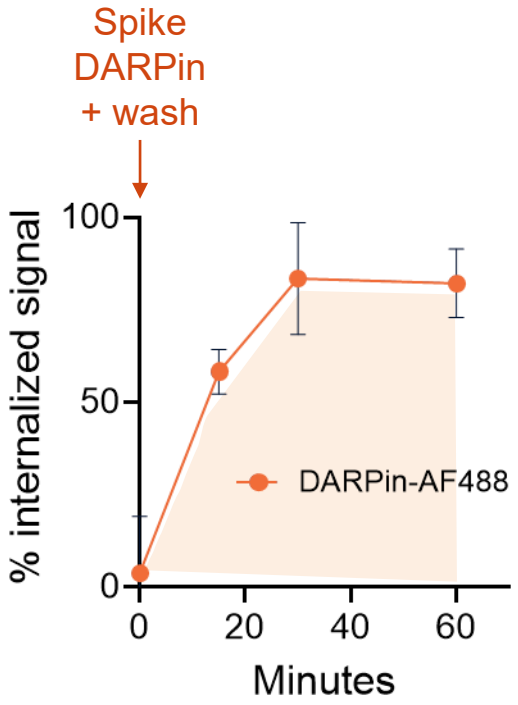
HLE-dependent blood exposure

Riesenberg, et al., AACR 2026.

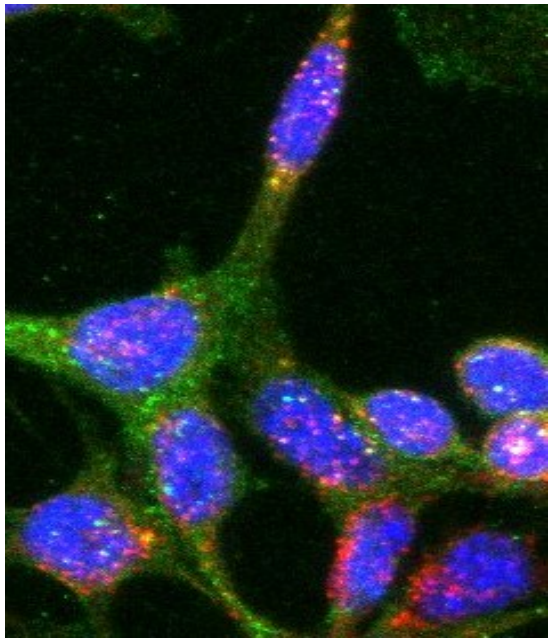
HLE, half-life extension; ID, injected dose.

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

DLL3 DARPin is rapidly internalized*…

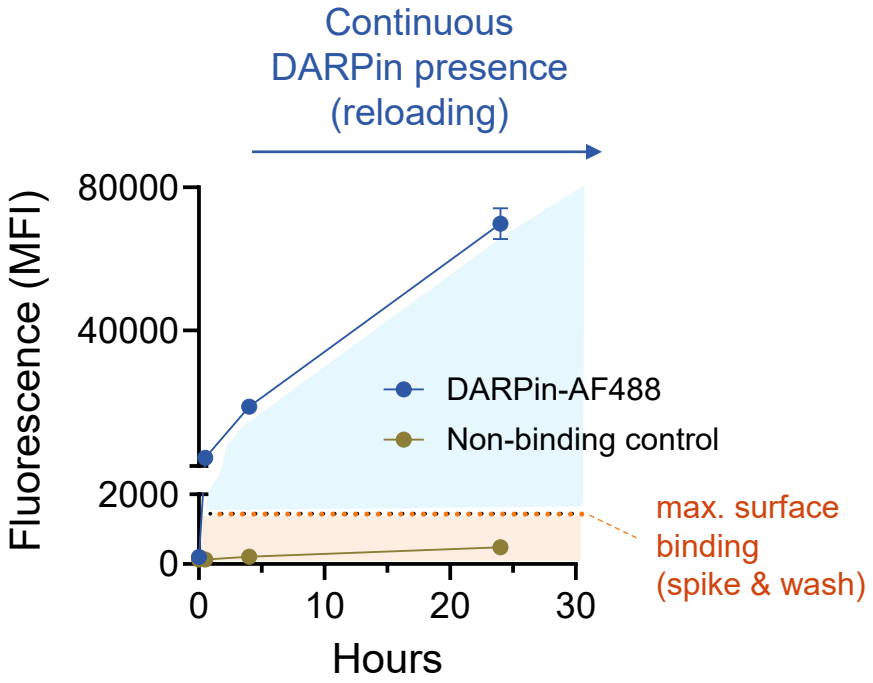


… co-localizes to the endosome…**



DARPin
Nucleus (DAPI)
Endosome (EEA1)

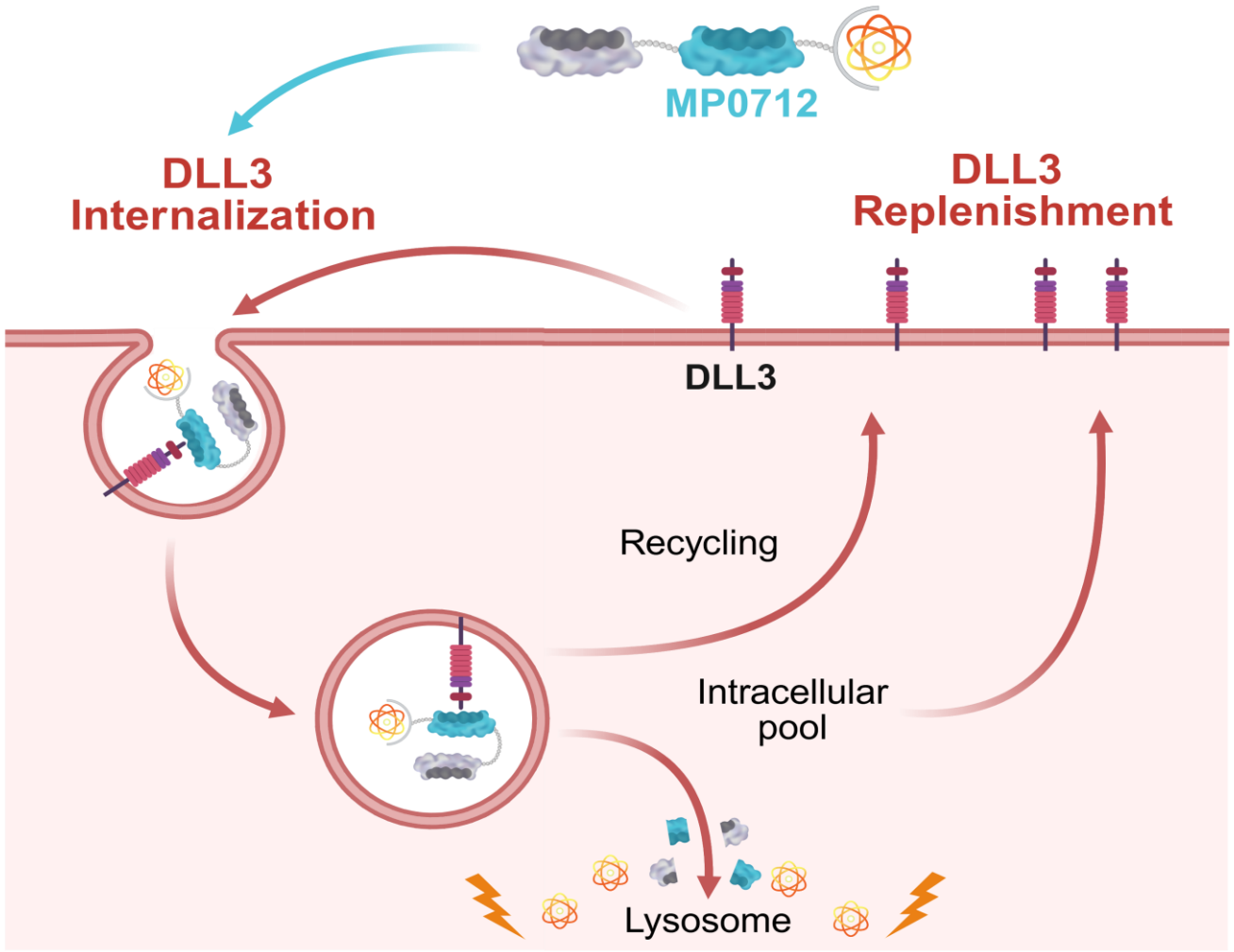
… and accumulates over time in cells**



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Internalization of DARPins labelled with anti-DARPin Fab-Alexa 488 conjugate into *SHP-77 human SCLC cells, into ***hDLL3-HEK cells.
** Immunofluorescence co-staining of anti-DARPin antibody, an early endosomal marker (EEA1) and cell nucleus marker (DAPI) after 3 h incubation in HEK-hDLL3 cells.
MFI, Mean Fluorescence Intensity.

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

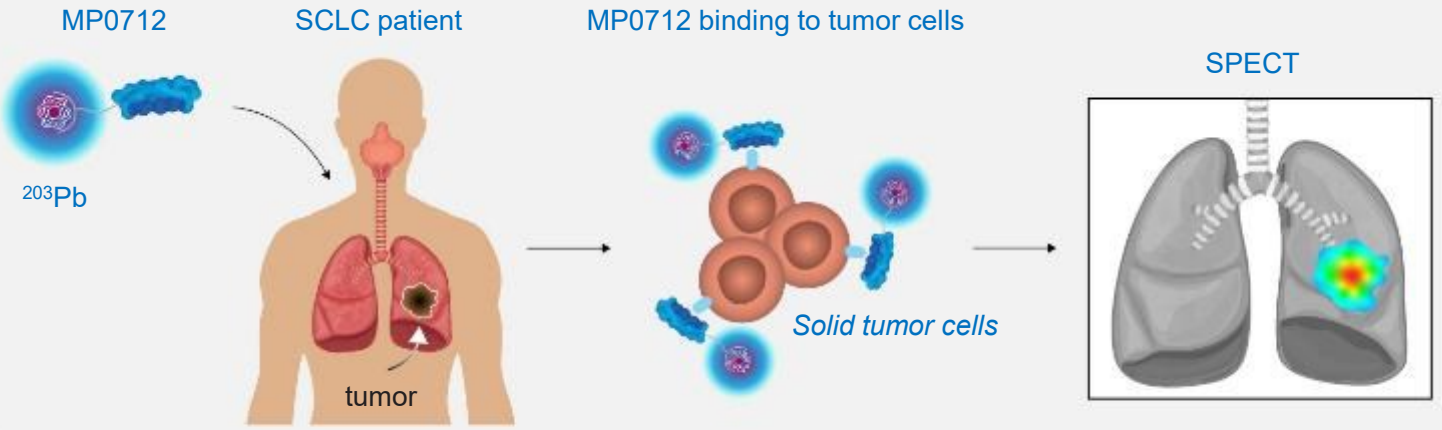


DARPin binding properties and extended systemic half-life allows to exploit the rapid internalization & replenishment of DLL3 for radioisotope accumulation in SCLC cells

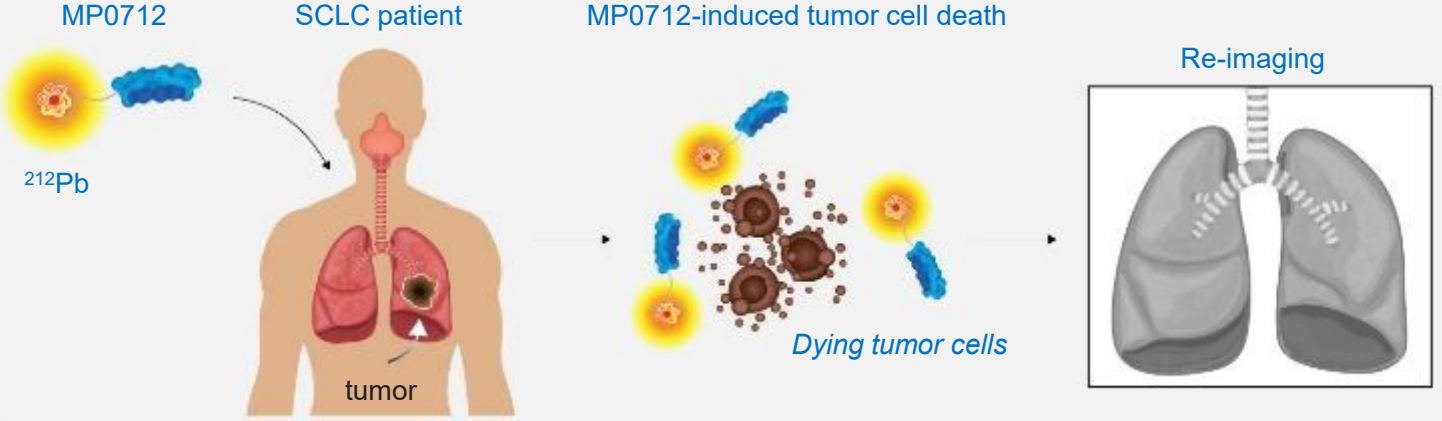
"Leveraging dynamic receptor density for optimal targeting"

MP0712 Development Pathway

1. Imaging



2. Treatment



Named Patient Access Program:

- Imaging and dosimetry with ^{203}Pb
- Option for treatment with ^{212}Pb

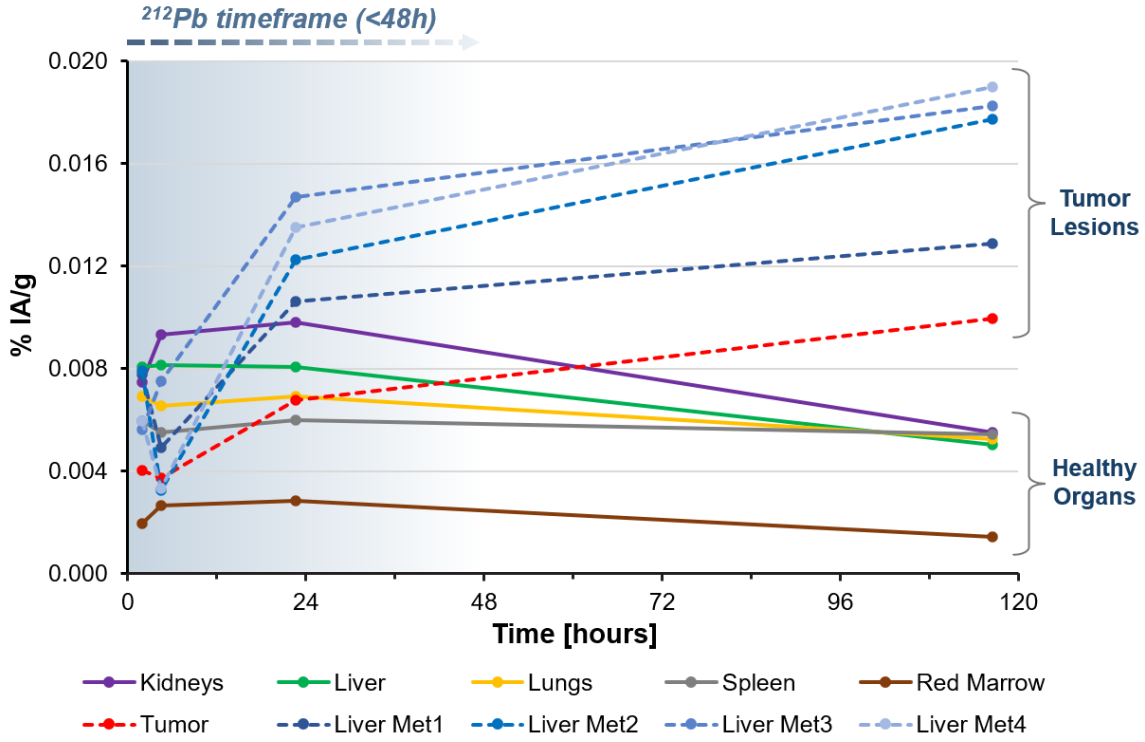
Request from NuMeRI, Pretoria, South Africa

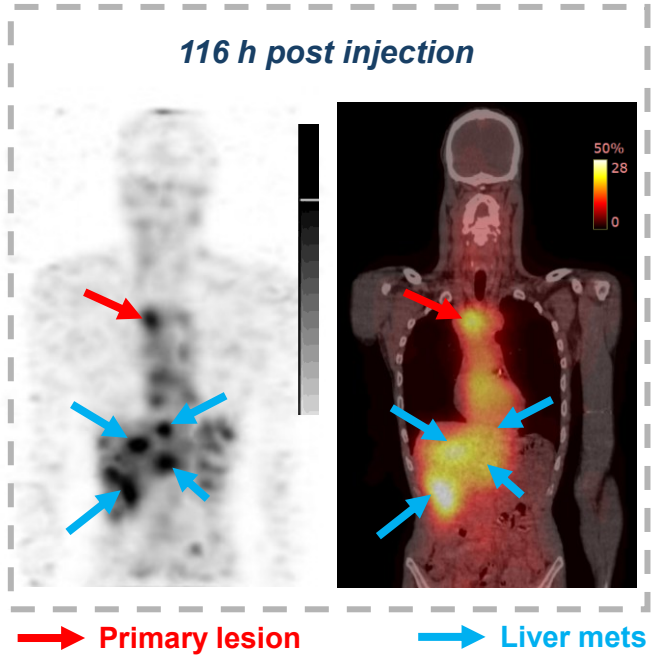
Phase 1/2a Study:

- Safety of ^{212}Pb
- Efficacy signals
- Includes an imaging and dosimetry step with ^{203}Pb

NuMeRI, Nuclear Medicine Research Infrastructure; SCLC, small cell lung cancer; SPECT, single-photon emission computed tomography.

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





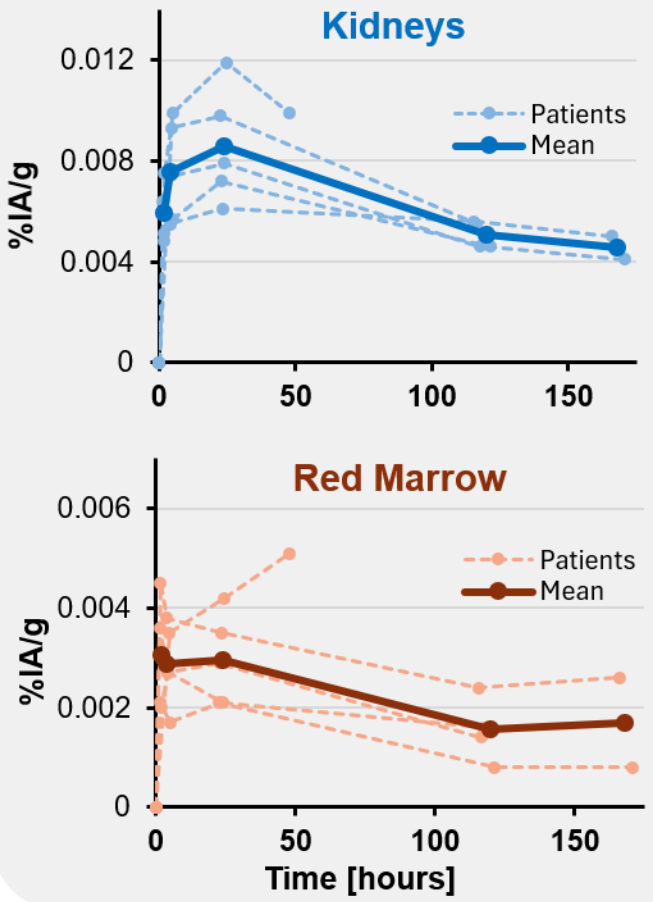
- **Continued tumor uptake** during imaging period (up to 116 h)
- **Higher uptake in liver metastases** as compared to primary lesion
- **Washout from healthy organs** visible from 24 h onwards

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

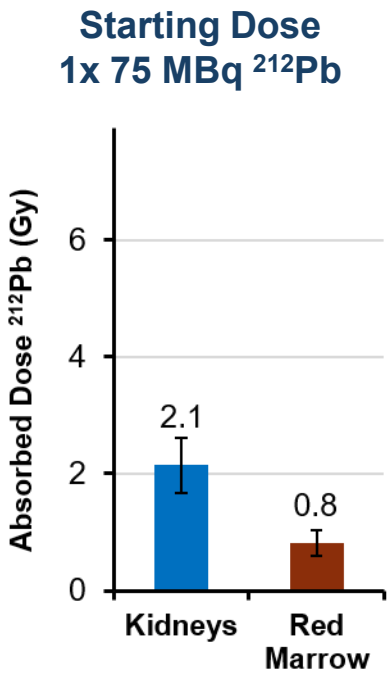
Patient with mSCLC imaged as part of a Named Patient Access Program at NuMeRI, Pretoria, ZA.
Example of patient case series presented with courtesy of Prof. Dr. M. Sathekge.
Complete SPECT/CT imaging data set presented at TWC 2026 (Kabunda et al.).

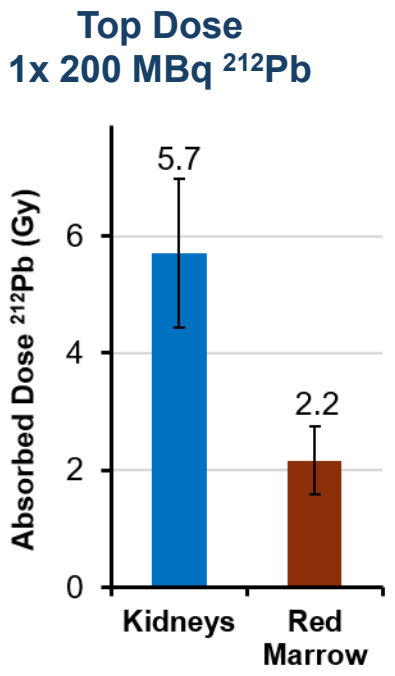
MP0712 Organ Dosimetry and Projection to Phase 1

^{203}Pb Time-Activity Curves



Dosimetry extrapolations





External Beam Radiation (EBRT) limit:

- Kidney 23 Gy – cumulative
- Red Marrow 2 Gy – non-cumulative

- All healthy organs within EBRT limits for Phase 1 starting and top single doses
- Kidneys & red marrow potentially dose-limiting → Monitor hematologic recovery to guide repeated dosing strategies

Dosimetry calculations for ^{212}Pb performed by RAPID, LLC on 5 evaluable patients; RBE = 5. Complete dosimetry dataset presented by Dr. Kamo Ramonaheng (Abstract-ID 260).

EBRT, external beam radiation therapy; RBE, relative biologic effectiveness.

MP0712 Phase 1/2a Study for SCLC and NECs

US multicenter, Phase 1/2a study of MP0712 monotherapy (NCT07278479)

- SCLC patients after ≥2 prior systemic therapies or not eligible for standard 2L therapy
- Lung LC NEC patients after ≥1 prior systemic therapy

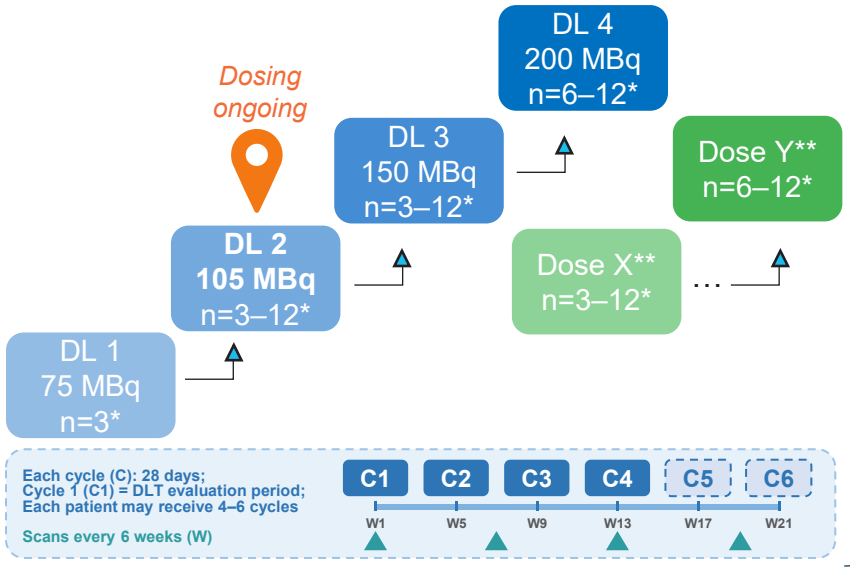
Phase 1: Dose Escalation
Main objectives: safety, RP2D
N =15–39 patients SCLC and lung LC NEC; N = 9–39 patients epNEC

Phase 2a: Dose Expansion and PoC
Main objectives: efficacy signals, confirm safety and RP2D
N = up to 5 x 20-30 patients

^{203}Pb-MP0712

Imaging / dosimetry (SPECT)

^{212}Pb-MP0712 (treatment)



RP2D

1) 3L SCLC post tarlatamab
2) 2L SCLC tarlatamab-naive
3) 2L+ epNEC
4) Combo with TCE in R/R SCLC
5) Combo with TCE in R/R epNEC

Confirmatory signals

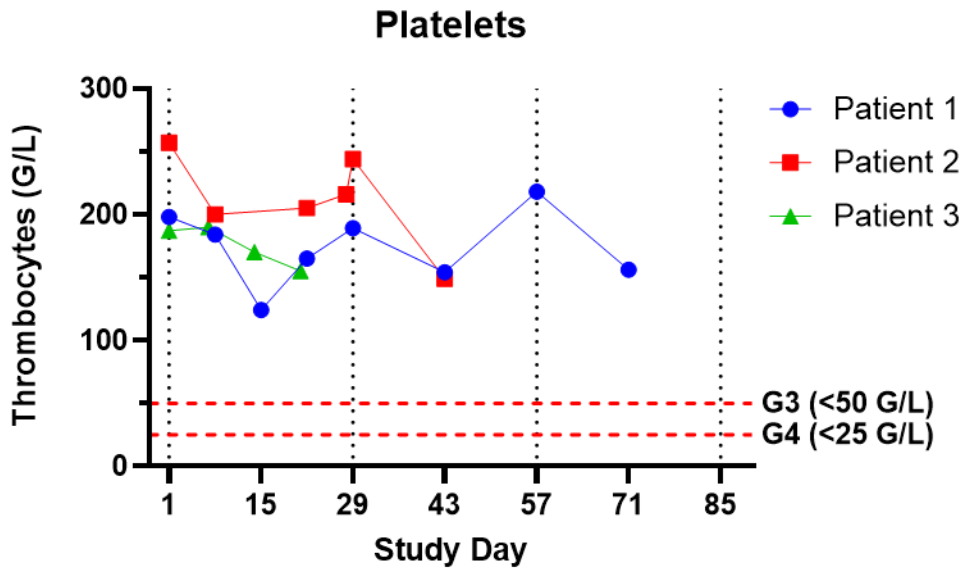
Registration studies 2L & 1L

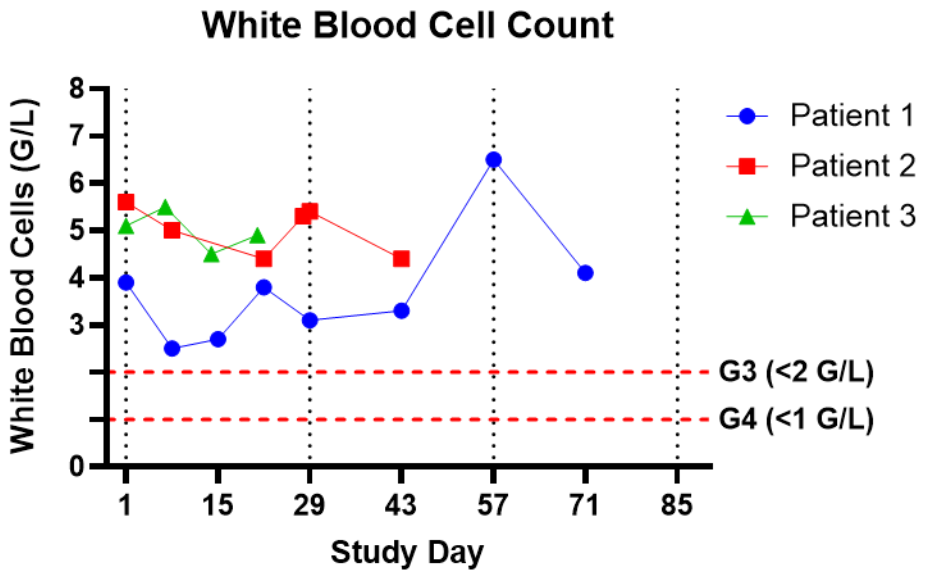
*Evaluable patients (Bayesian Logistic Regression Model guided dose escalation)

**epNEC to start at a dose level previously tested in SCLC or LC NEC of lung at which a first signal of pharmacological activity is detected. RP2D for epNEC is anticipated to be same as RP2D for SCLC/LC NEC of lung. Pre-selection on DLL3 expression foreseen.

1/2/3L, 1st/2nd/3rd line; DL, dose level; epNEC, extrapulmonary NEC; LC NEC, large cell NEC; PoC, proof-of-concept; RP2D, recommended phase 2 dose.

Preliminary MP0712 Phase 1 Safety Data from Cohort 1 are Encouraging





- Mild and transient decreases of blood parameters mid-treatment cycle with full recovery at the end of each cycle; no cumulative toxicity across cycles (examples: platelets, white blood cell count)
- Hemoglobin levels remain stable
- No evidence of hepatic or renal toxicity to date

Additional data will be presented at the North America Conference on Lung Cancer (NACLC) early Dec 2026

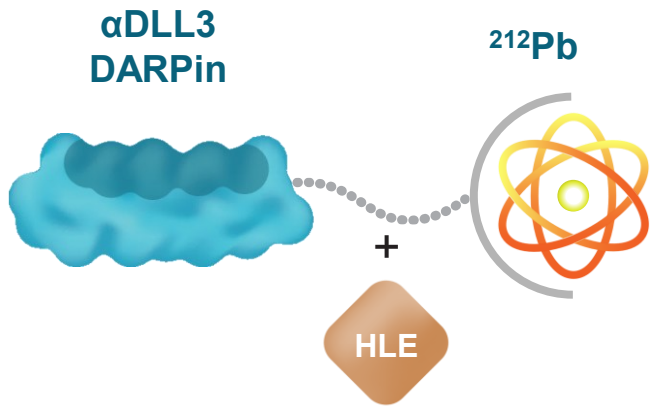
Preliminary MP0712 Phase 1 data (cohort 1 [75 MBq]; data cut-off: 17 Aug 2026)
Study ongoing, results subject to change

G3/4, Grade 3 or 4 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

MP0712 (^{212}Pb x DLL3) – Conclusions & Outlook

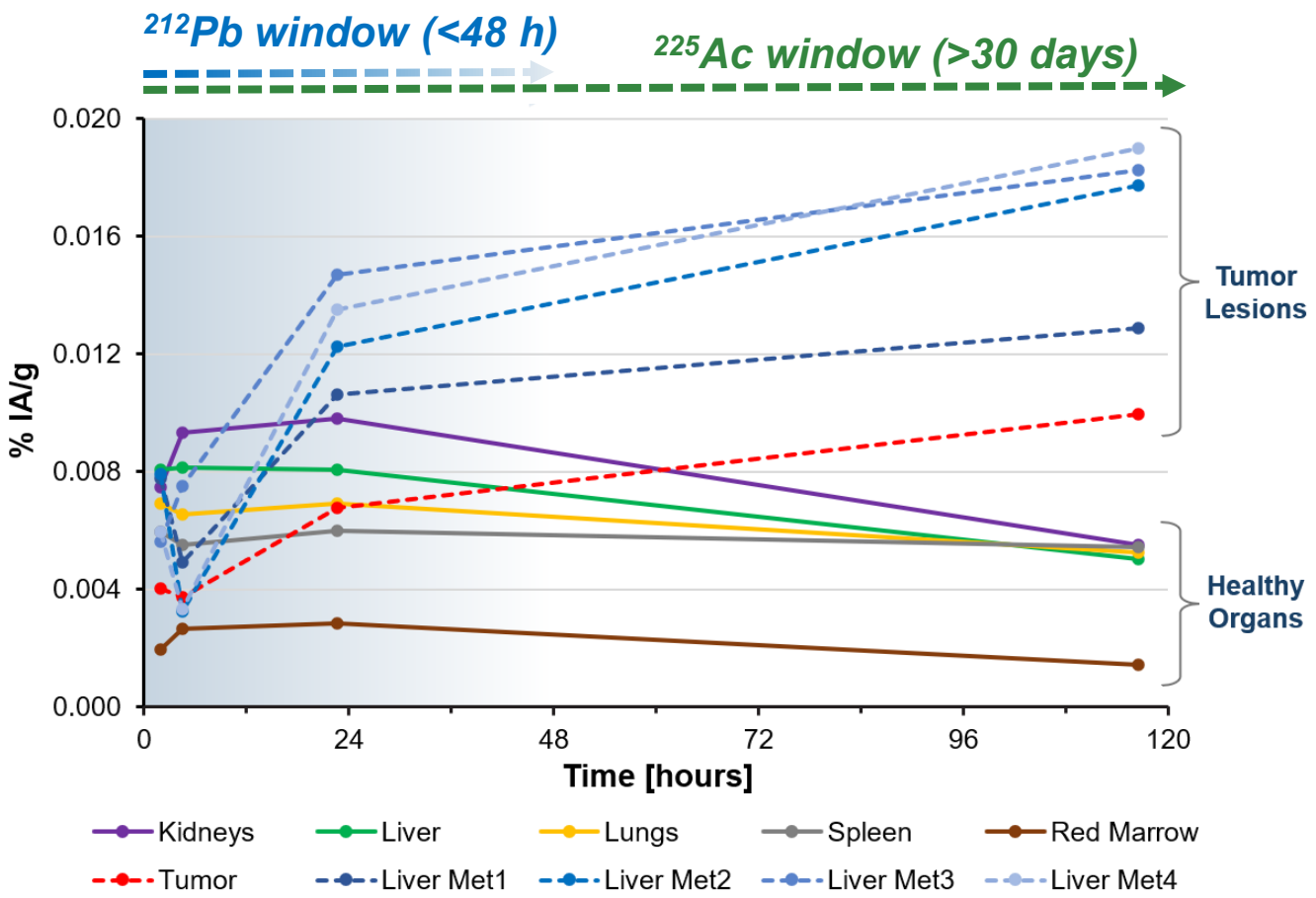
- First-in-human imaging with ^{203}Pb from compassionate care in line with preclinical data, showing robust tumor uptake and retention
- Phase 1/2a study ongoing in the US (NCT07278479):
  - No DLT in cohort 1 (DL1; 75 MBq ^{212}Pb-MP0712)
  - Mild, transient hematologic changes with full recovery
  - MP0712 exposure maintained
  - Dosing in fully recruited cohort 2 (DL2; 105 MBq) ongoing
- ^{203}Pb imaging suggest MP0712 potentially compatible also with longer-lived isotopes

MP0712 product composition

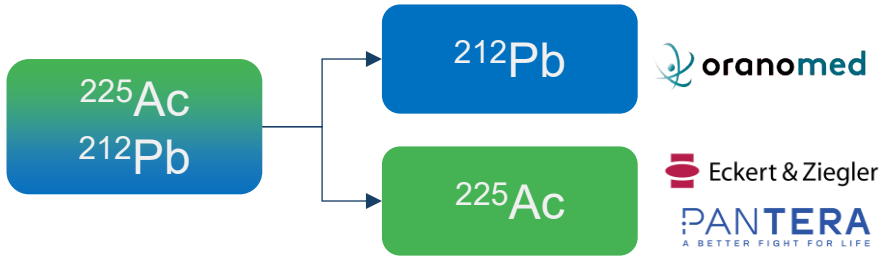


DL, dose level; DLT, dose-limiting toxicity; HLE, half-life extension.

Sustained Tumor Uptake of ^{203}Pb-MP0712 Provides Rationale to also Explore Longer-Lived Isotopes



- Based on ^{203}Pb-MP0712 learnings, DARPin profile can work for both ^{212}Pb and/or ^{225}Ac
- Opportunity to evaluate both isotopes in parallel and decide on the best isotope based on evidence

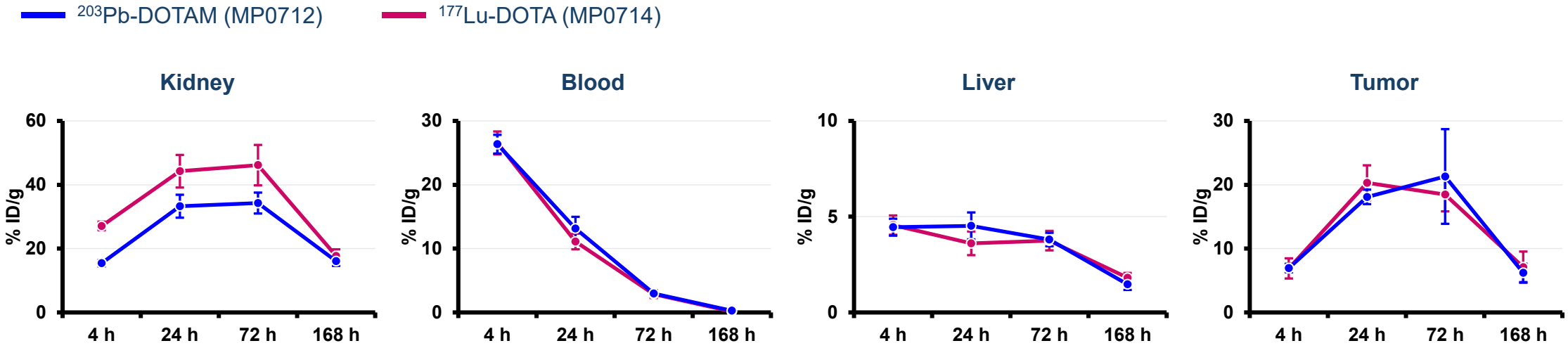


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mSCLC, metastatic small cell lung cancer.

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.).

DLL3 DARPin Demonstrates Chelator & Isotope Flexibility

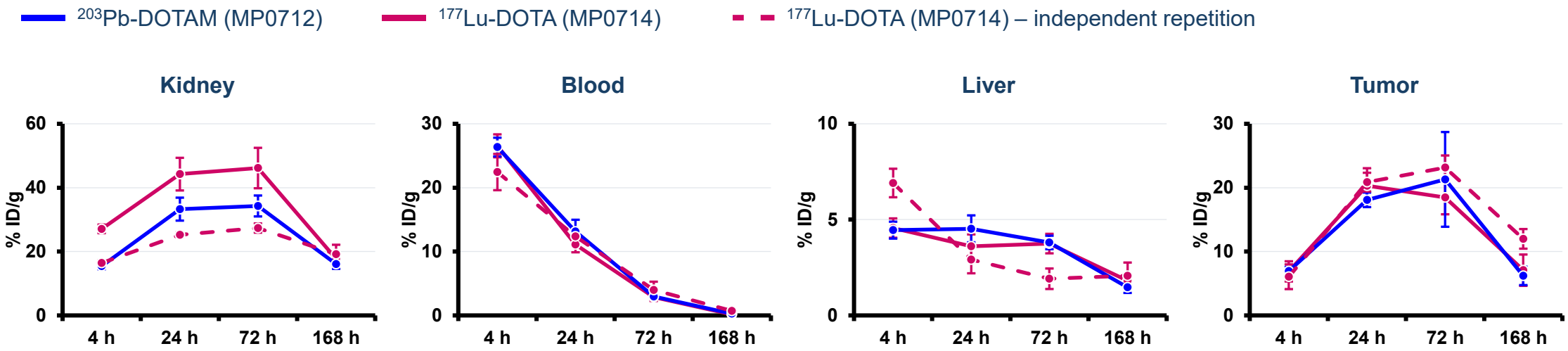
Radio-DARPin against DLL3



BioD, biodistribution; NuMeRI, Nuclear Medicine Research Institute.
^{203}Pb-DOTAM-DARPin injected 1 x 20mCi at 0.01mg/kg and ^{177}Lu-DOTA-DARPin injected 1 x 50µCi at 0.01mg/kg in NCI-H82 s.c. model.

DLL3 DARPin Demonstrates Chelator & Isotope Flexibility

Radio-DARPin against DLL3



- Comparable BioD profile using ^{203}Pb-DOTAM and ^{177}Lu-DOTA, with similar uptake and washout rates
- Assumption: ^{203}Pb-DOTAM and ^{177}Lu-DOTA can be used as surrogates for the therapeutic candidates (^{212}Pb / ^{225}Ac)
- Flexibility for DLL3 & future projects to select therapeutic isotope based on pre-clinical and/or early human imaging data

➢ **Compassionate care work initiated at NuMeRI for MP0714 (^{225}Ac x DLL3), with first patients dosed**

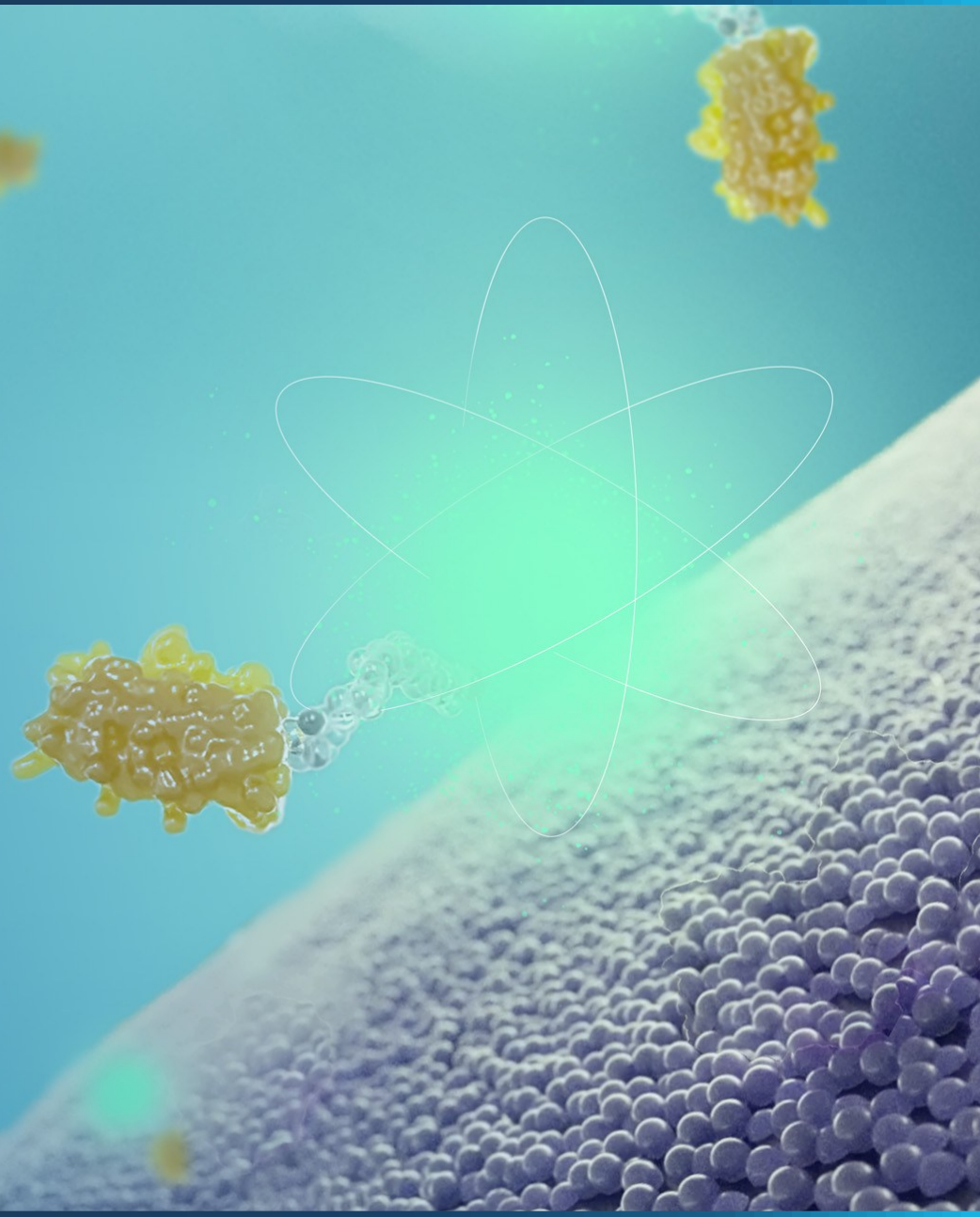
MOLECULAR partners

BioD, biodistribution; NuMeRI, Nuclear Medicine Research Institute.
^{203}Pb-DOTAM-DARPin injected 1 x 20mCi at 0.01mg/kg and ^{177}Lu-DOTA-DARPin injected 1 x 50µCi at 0.01mg/kg in NCI-H82 s.c. model.

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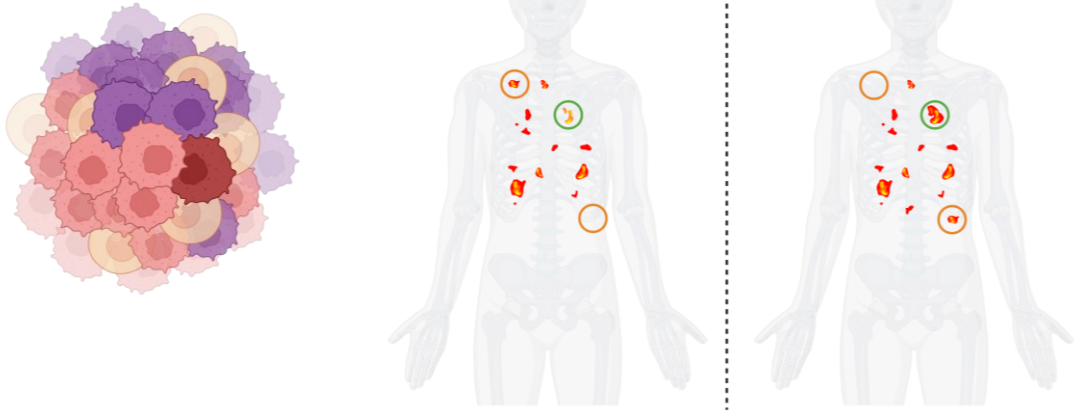
Tackling Target Heterogeneity and Loss of Expression

Multi-specific Radio-DARPin Approaches



Mono-Specific RLTs do not Cover Tumor Complexity

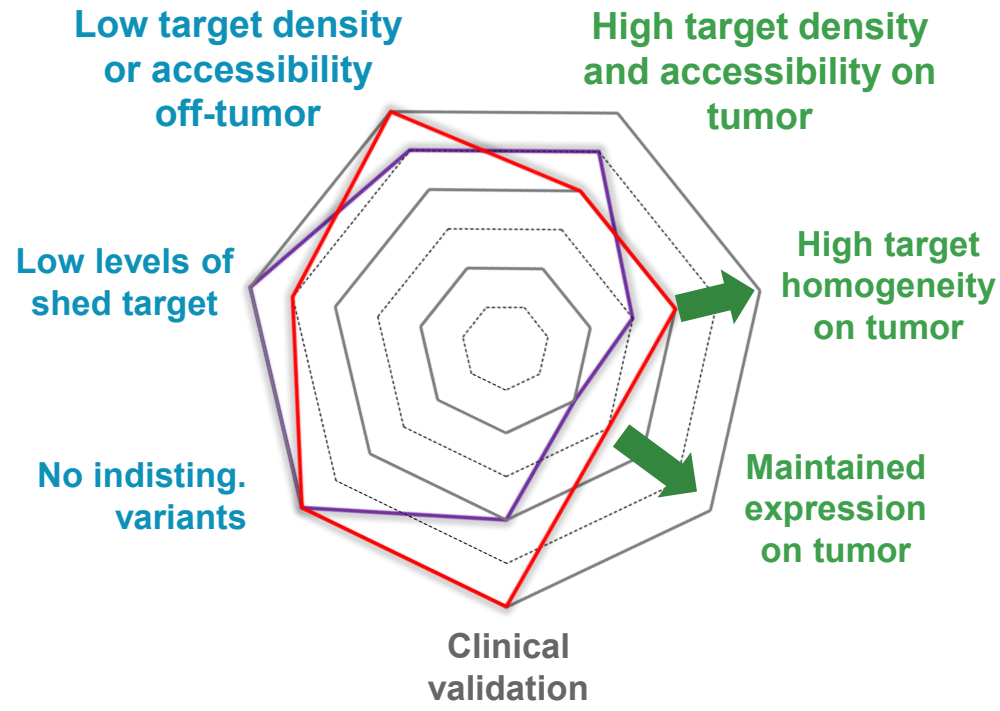
Tumors are highly heterogeneous



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?

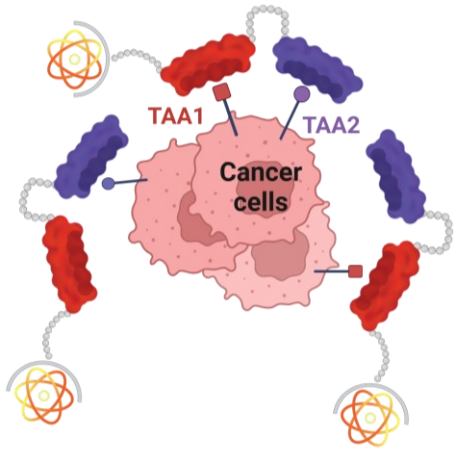


RLT, radioligand therapy; TAA, tumor-associated antigen.

Multi-Specific DARPins as a Solution to Improve Therapeutic Index

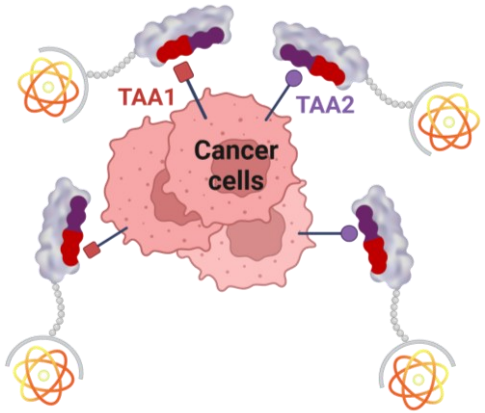
Our molecular designs

Classical bi-specific DARPins



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

Small 2-in-1 dual DARPins



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:

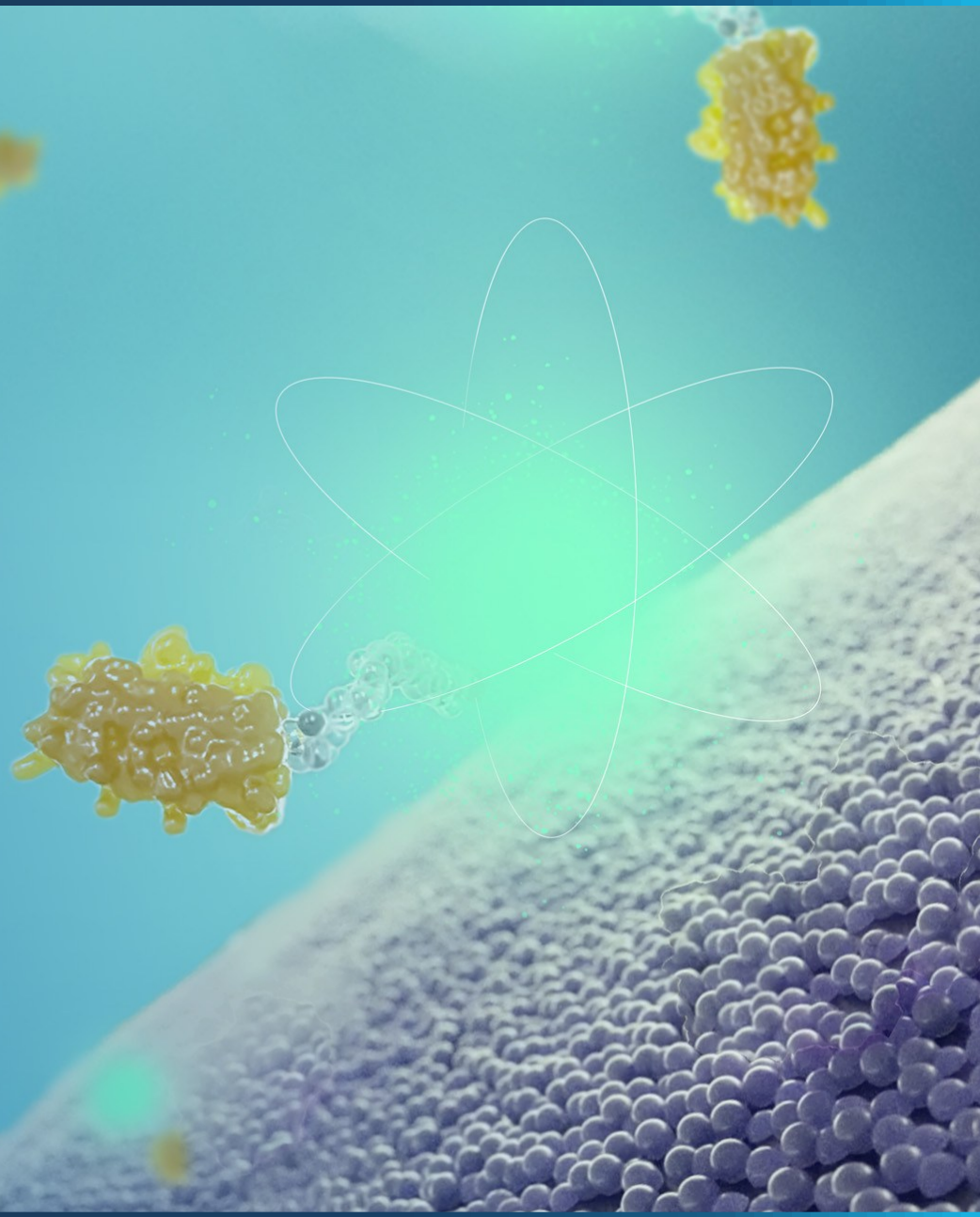
- **No additive tox** from receiving **consecutive** or **mixtures** of RLTs

“Research projects ongoing enabled by our expertise from 6 clinical-stage, multispecific DARPins”

Images created in part with BioRender.com

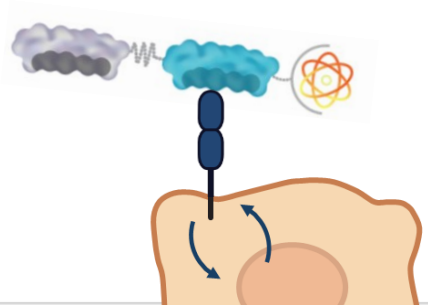
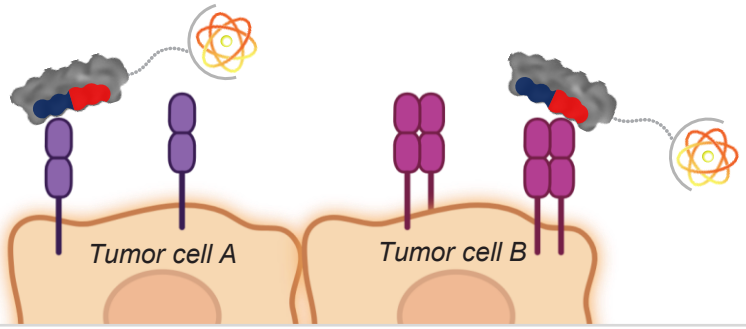
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Conclusions, Outlook and Stimulus for Discussion



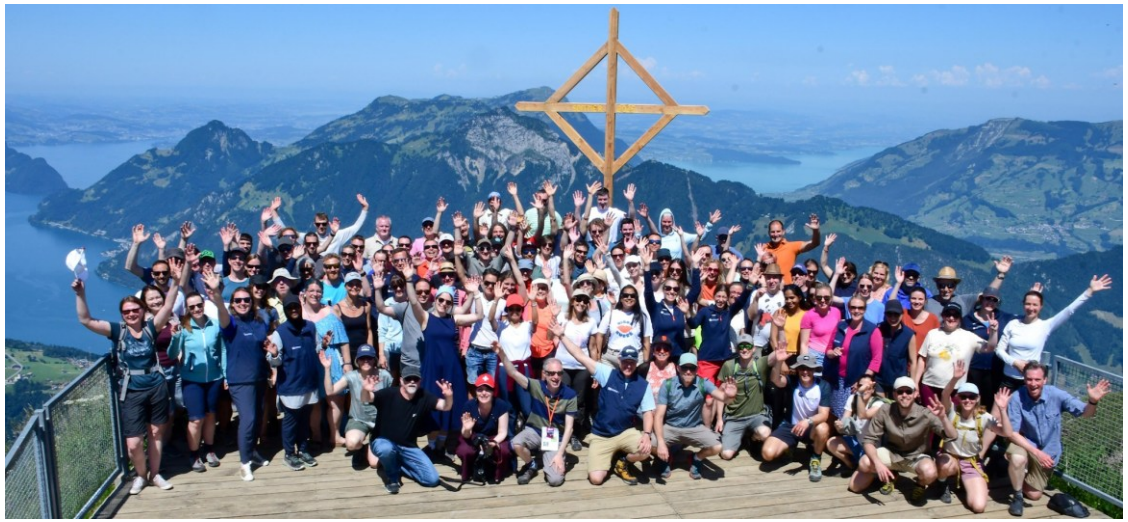
Summary & Outlook

How much Target Expression is Enough?

	DLL3	Multiple Targets
Challenge	**"Low target density"**	**"Target heterogeneity"**
DARPin Design	**Design to leverage rapid internalization & replenishment** of DLL3 	**Bi-specifics** to address tumor heterogeneity & boost tumor uptake 
Status	• **MP0712** (^{212}Pb x DLL3): US Phase 1 dosing patients • **MP0714** (^{225}Ac x DLL3): Compassionate care work initiated at NuMeRI	**Multiple early programs**

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 Targets – but None is Perfect

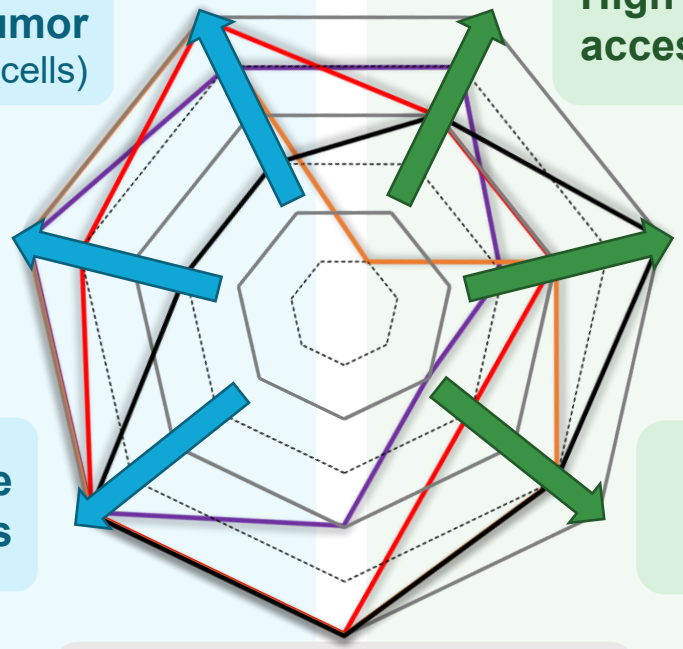
RLT success lies as much in smart molecular design as in target selection

Low off-tumor expression

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

Low levels of shed target

No indistinguishable variants



High 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

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Looking forward to the discussion!



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