



DARPin as Vector for Targeted Alpha Therapy

Initial Clinical Experience with MP0712
and Opportunities for Next Candidates

Discovery on Target, Boston 2026

Christian Reichen, PhD - Director Oncology Research



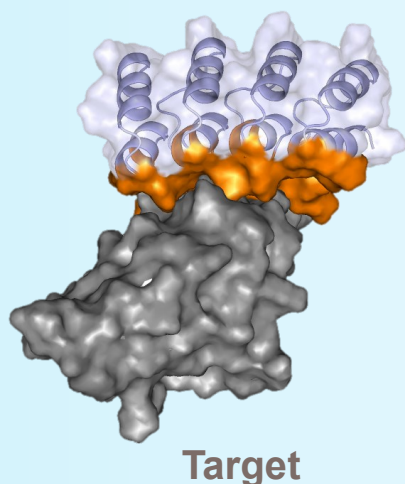
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The DARPin Modality and Our Focus

DARPin
Designed Ankyrin
Repeat Protein



We pioneer DARPins as a new class of therapeutics

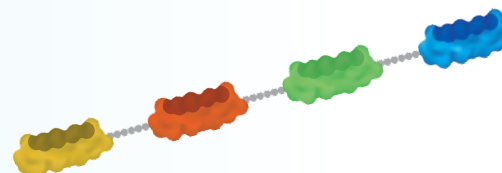
- DARPins close the gap between small molecules and antibodies
- DARPins address complex disease biology (i.e. multi-specifics)
- 8 clinical-stage candidates, > 2500 patients treated

Our company focus

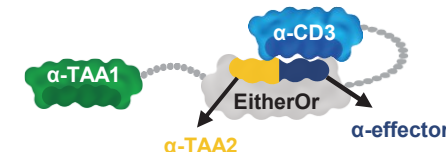
Radio-DARPin
Therapeutics



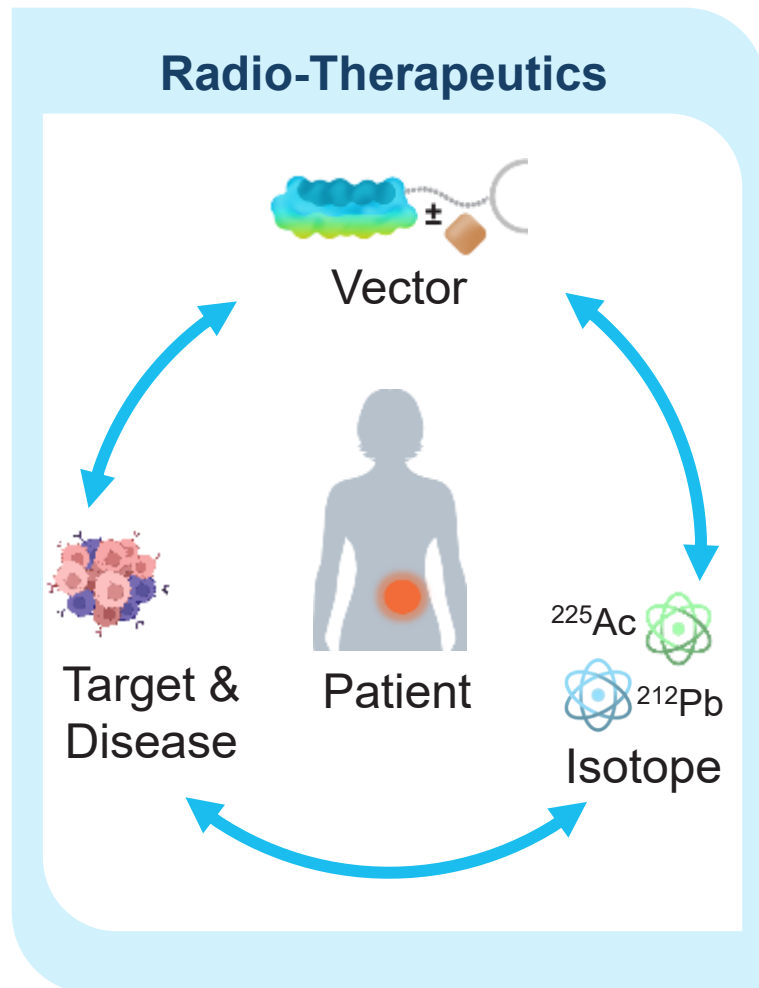
Multi-specific immune
cell engagers



Conditional “Switch”
T cell engagers

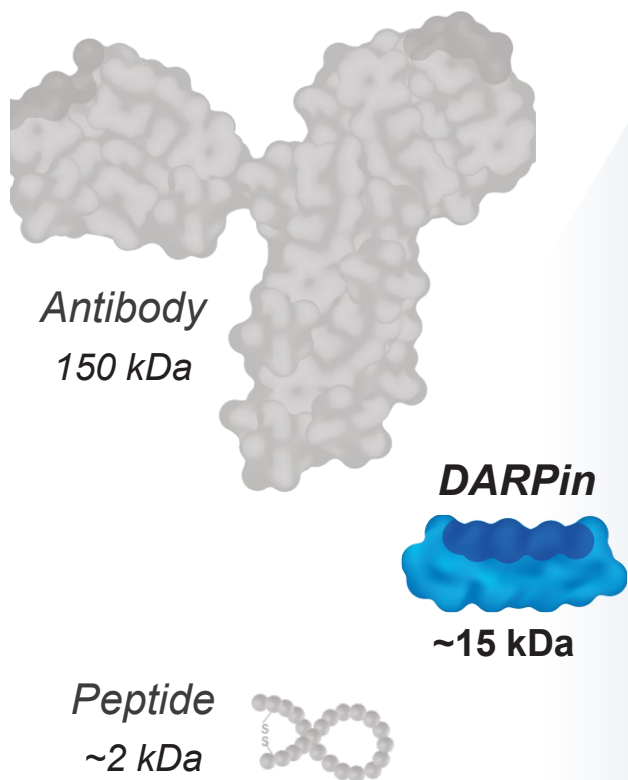


Our Radio-DARPin Pipeline



CANDIDATE	RESEARCH	PRE-CLINICAL	PHASE 1
MP0712	SCLC & NECs $^{212}\text{Pb} \times \text{DLL3}$		oranomed Co-development*
MP0714	$^{225}\text{Ac} \times \text{DLL3}$		
MP0726	Ovarian Cancer <i>MSLN</i>		
Additional Programs (Solid Tumors)	"Mono"-specific (incl. CD70)	^{212}Pb or ^{225}Ac	
	"Multi"-specific		

DARPin Features for Tumor Targeting of Radionuclides



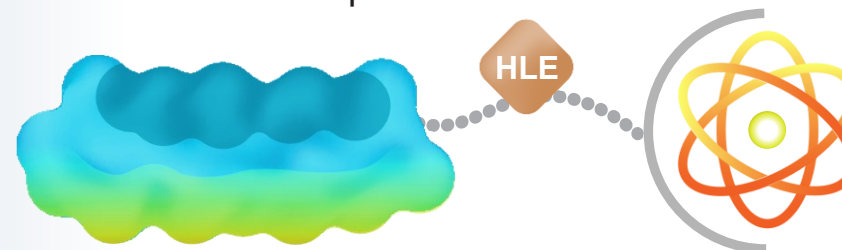
DARPins¹ are small binding proteins derived from natural ankyrin repeat proteins

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

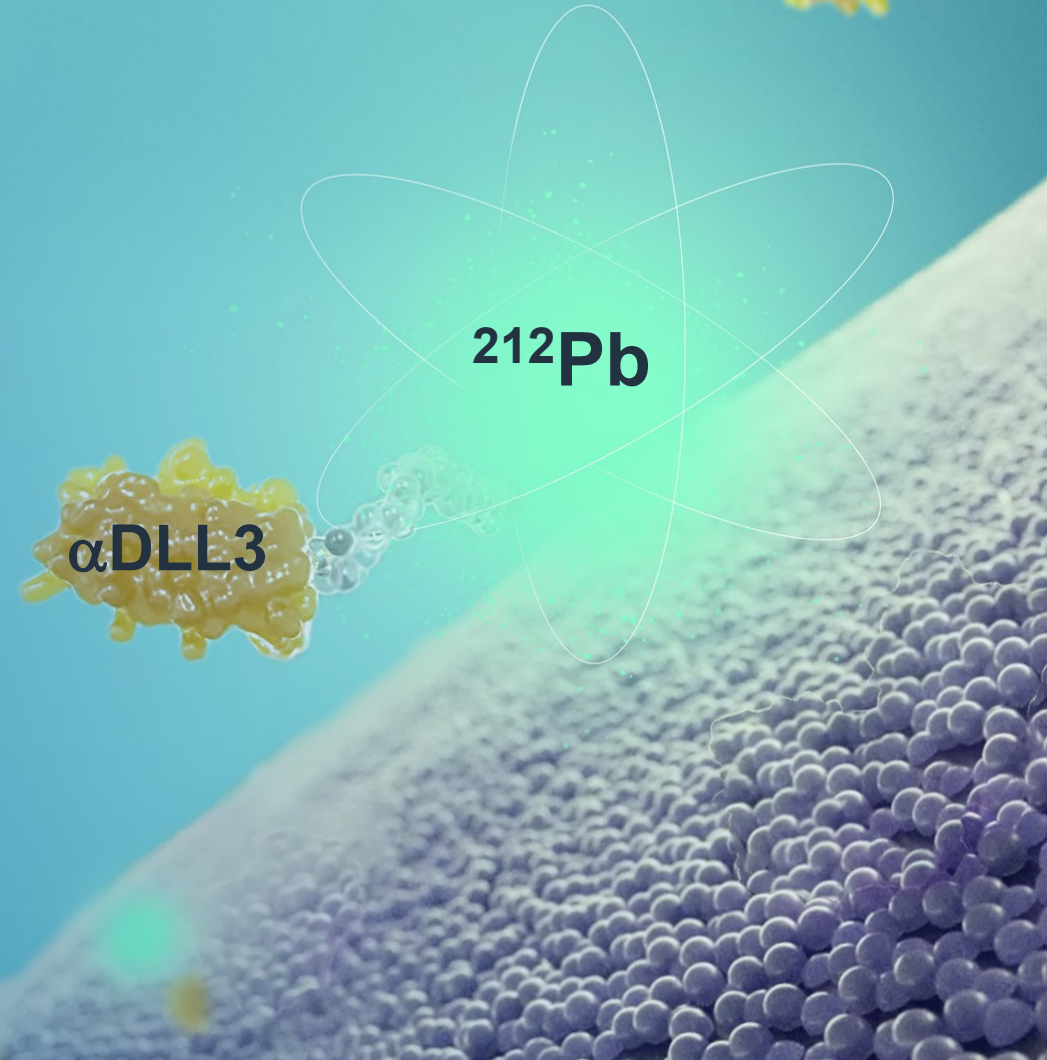
- Proven clinical efficacy
- High energy deposition
- ²¹²Pb and ²²⁵Ac

RADIO-DARPin

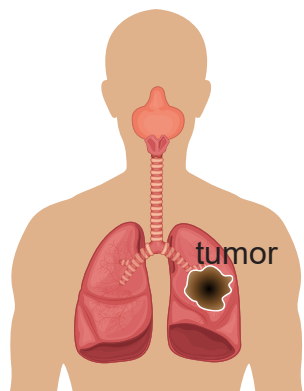
"Isotope-agnostic": Consistent BioD profiles exchanging isotopes and chelators²



Progressing the first Radio-DARPin Therapeutic MP0712 (^{212}Pb x DLL3) for SCLC into the clinic



MP0712: Why DLL3-Targeting Radiotherapy for SCLC?



SCLC: critical unmet medical need (2L)

- mPFS: ~4 months¹
- 5-year OS: ~7–9%^{2,3}

DLL3: validated target

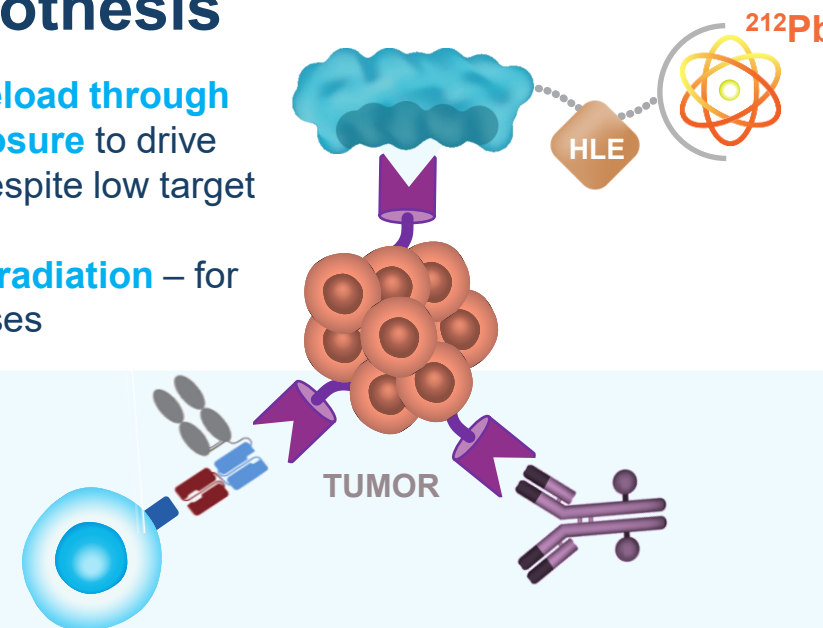


DLL3

- Expressed in >85% of patients with SCLC⁴
- Expression in multiple neuroendocrine cancers (e.g., LC, Bladder, GEP)
- **No expression in healthy tissues**
- Tumor-targeting shown with DLL3 radio-diagnostic mAb (⁸⁹Zr-Sc16.56)⁵
- Clinical validation by T cell engagers (e.g., tarlatamab¹) and ADCs (e.g., ZL-1310⁶)

MP0712 hypothesis

- ✓ **Internalize & reload through sustained exposure** to drive tumor uptake despite low target density
- ✓ **Kill with alpha radiation** – for durable responses



T cell engagers¹

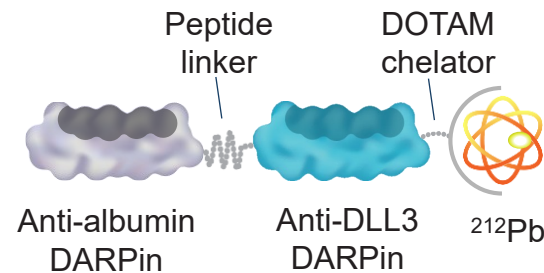
- Tarlatamab approved
- **40% RR**
- 9.7 months DoR
- **Substantial side effects**

Antibody-drug conjugates⁶

- Phase 1/2
- ~70% RR
- **~6 months DoR**
- Manageable side effects

MP0712: Clinical-stage Radio-DARPin–based Targeted Alpha Therapy

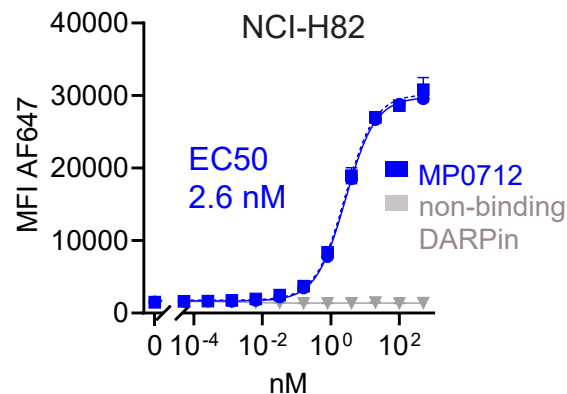
Molecular structure



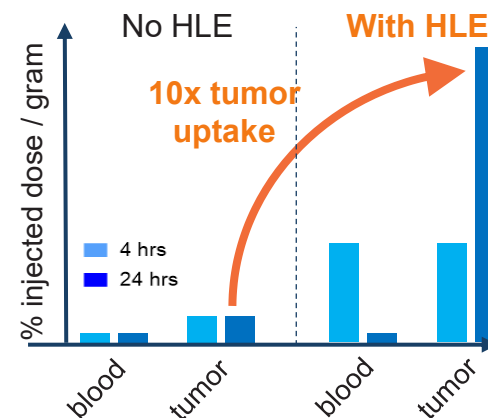
Affinity (SPR)*

Affinity to hDLL3		Affinity to HSA
- HSA	+ HSA	
K_D [nM]	K_D [nM]	K_D [nM]
0.243	0.350	98

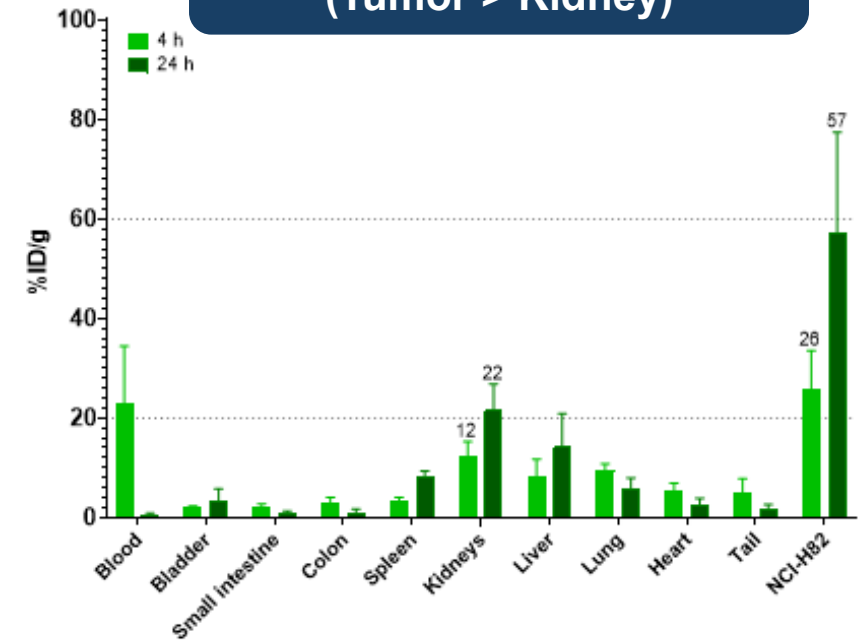
Cell binding**



Optimal half-life for tumor uptake of MP0712



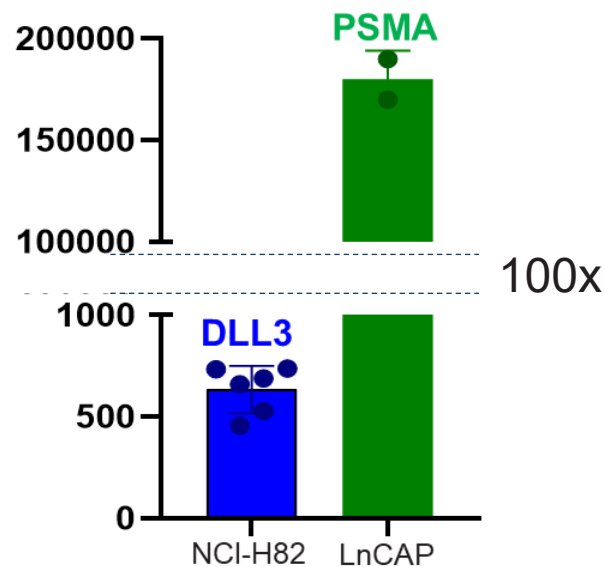
High Tumor Accumulation (Tumor > Kidney)



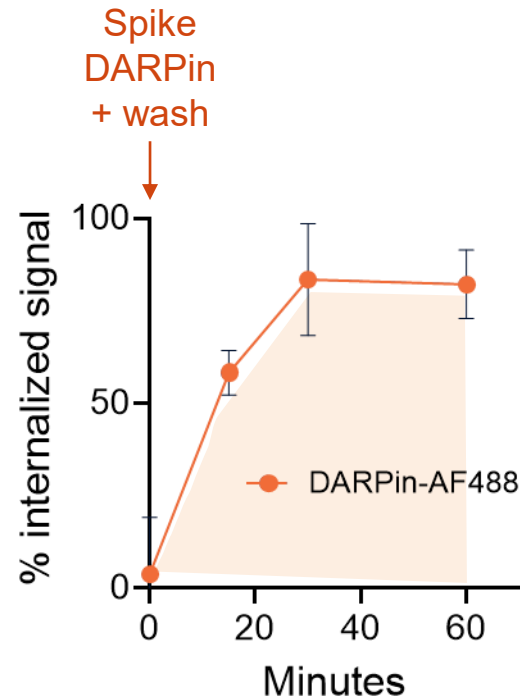
MP0712: Rapid Internalization and Accumulation in Cells

Very low DLL3 copy number

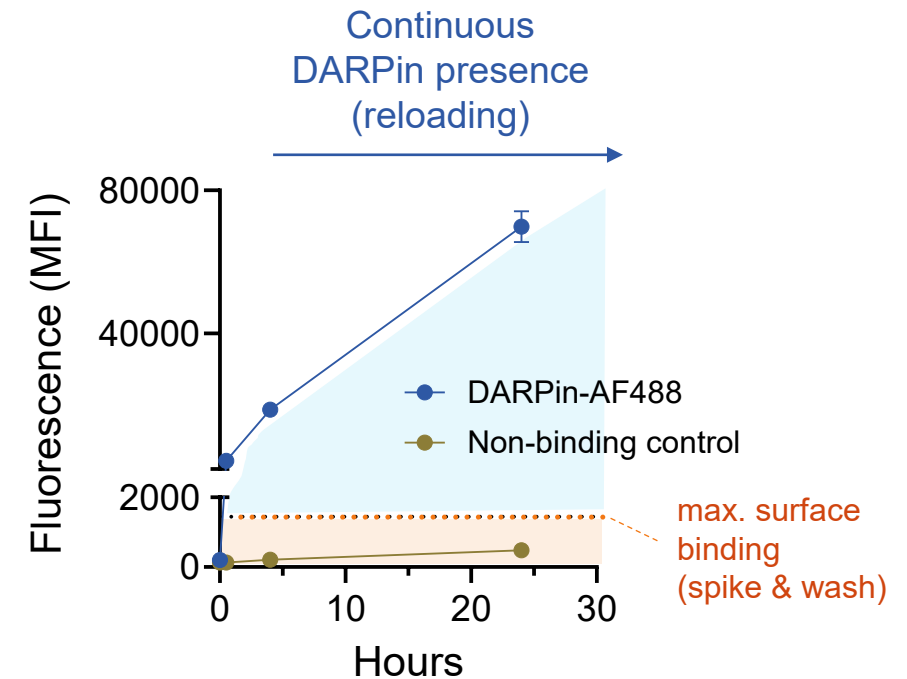
DLL3: <1000 receptors/cell
PSMA: >100'000 receptors/cell



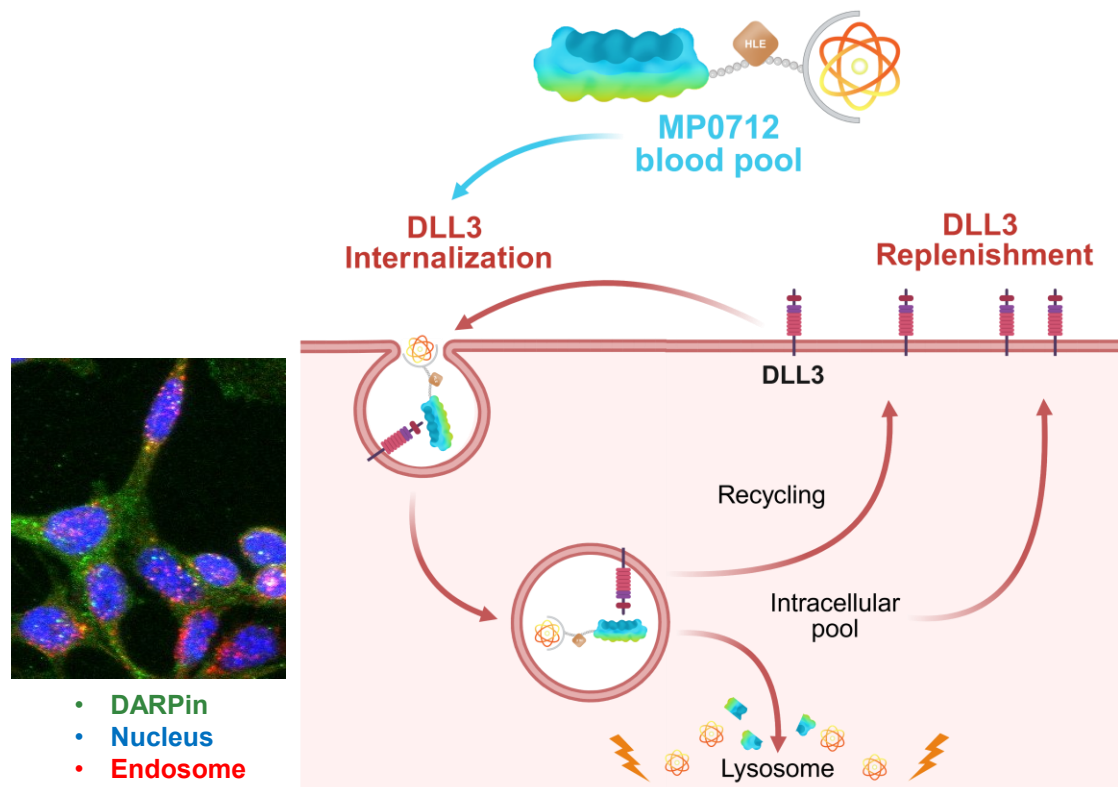
DLL3 DARPin is rapidly internalized*...



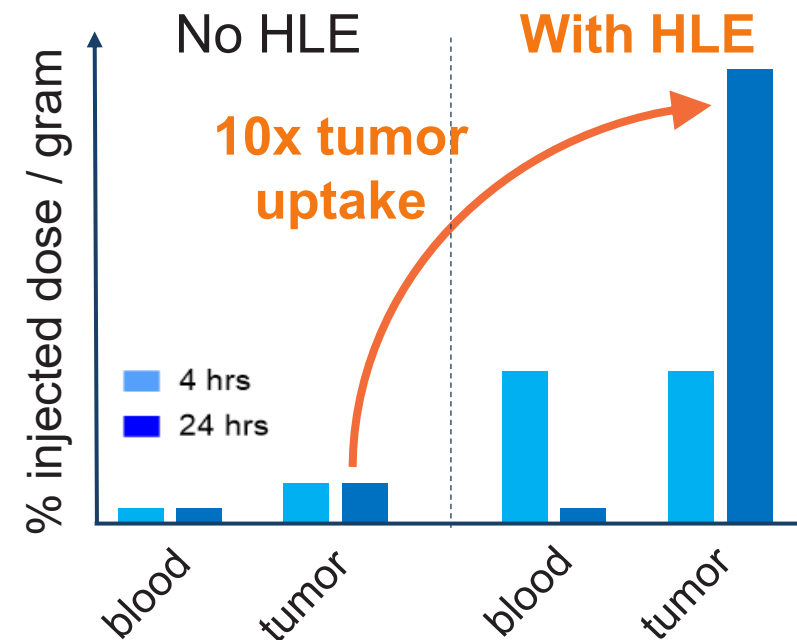
... and accumulates over time in cells**



MP0712: High Tumor Uptake via DLL3 Internalization – Replenishment and Half-Life Engineering



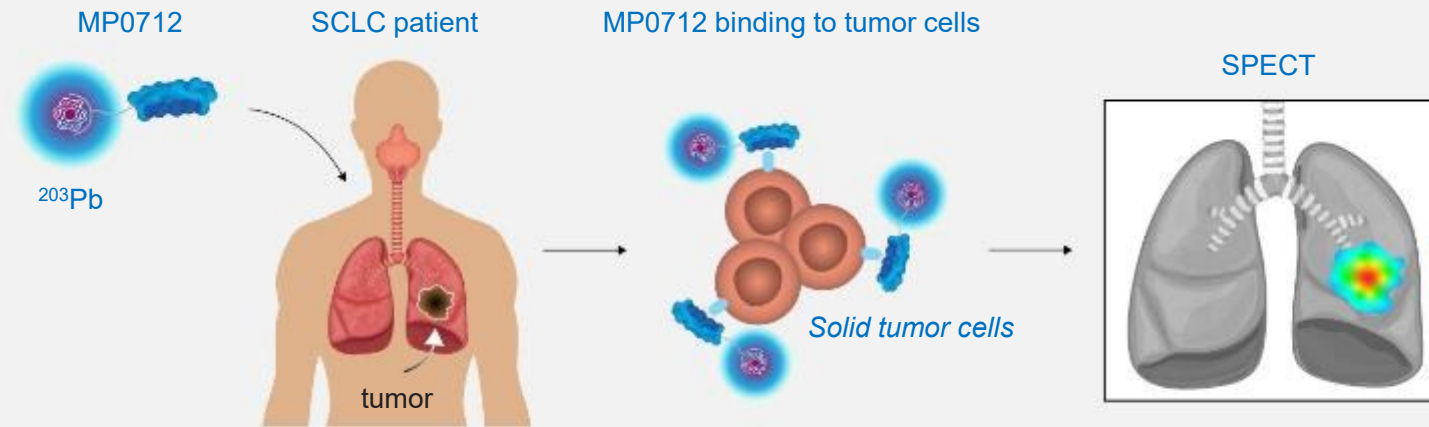
Optimal half-life for tumor uptake of MP0712



DARPin half-life optimization allows to leverage rapid internalization & replenishment of DLL3 for high MP0712 accumulation in tumors

MP0712 Development Pathway

1. Imaging

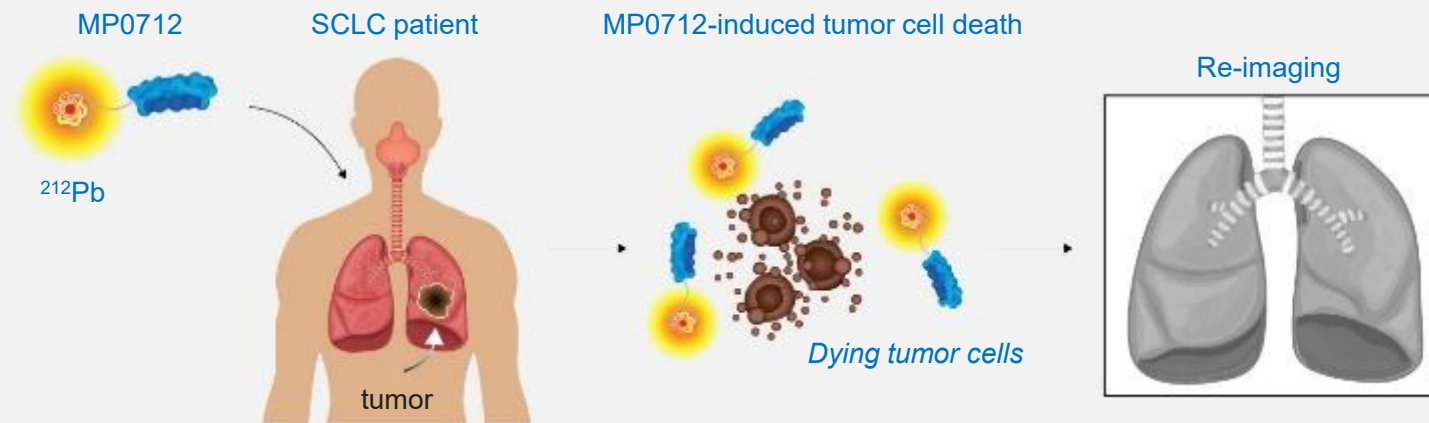


Named Patient Access Program:

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

*Request from NuMeRI,
Pretoria, South Africa**

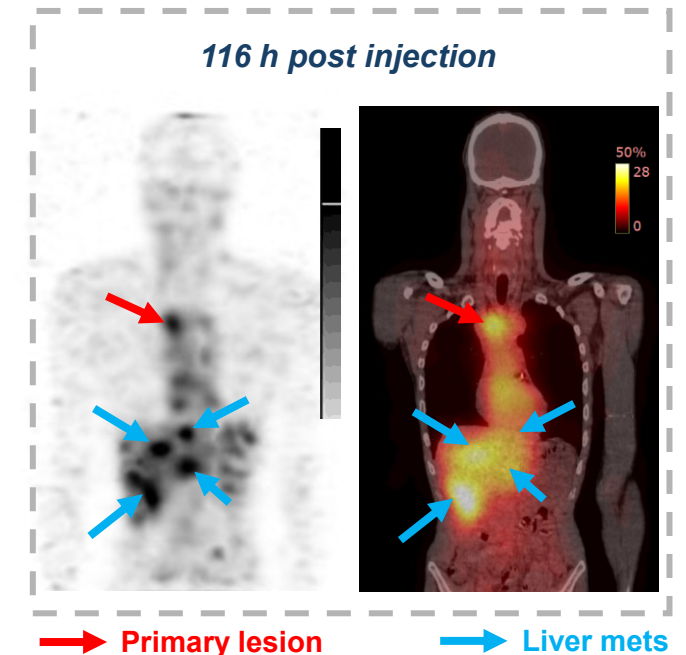
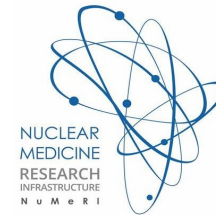
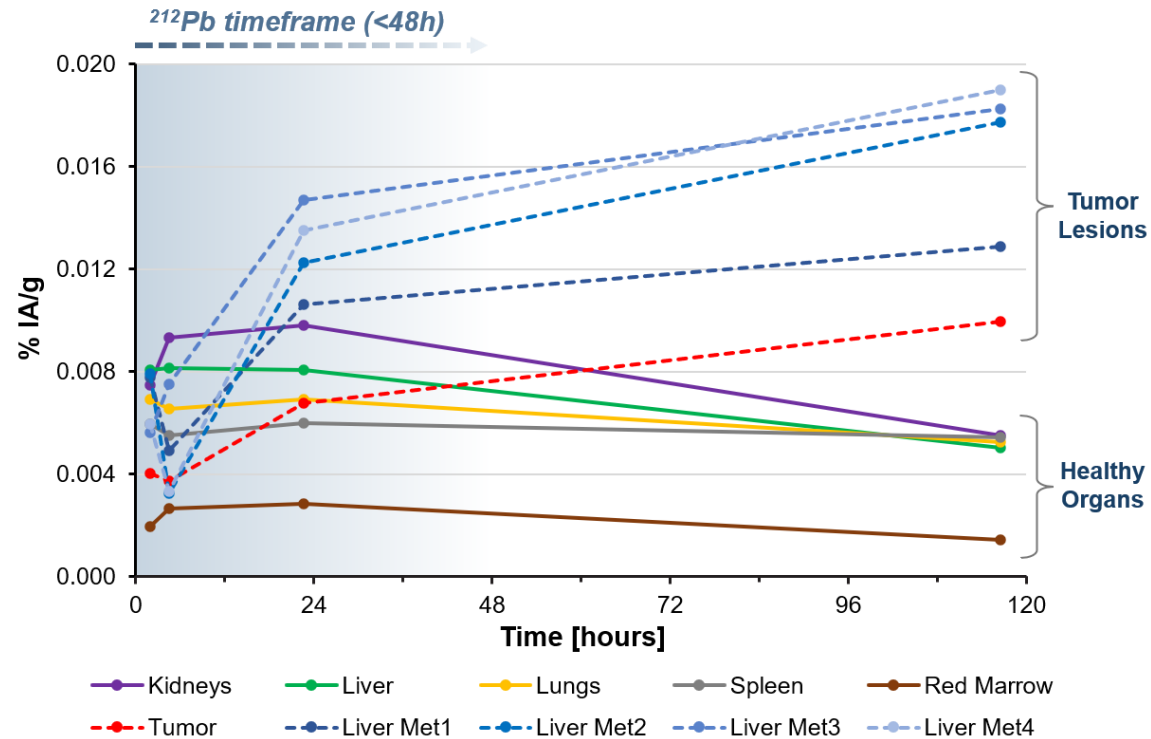
2. Treatment



Phase 1/2a Study:

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

First MP0712 SPECT/CT Imaging with ^{203}Pb Confirms Sustained Tumor Uptake¹



- **Continued tumor uptake** up to 116 h imaging period
- **Healthy organ washout** from 24 h onwards

MP0712 Phase 1/2a Study for SCLC and other NECs

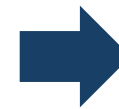
- **First-in-human, US multicenter, Phase 1/2a study of MP0712 monotherapy (NCT07278479)**

- SCLC patients after ≥ 2 prior systemic therapies or not eligible for standard 2L therapy; lung LC NEC patients after ≥ 1 prior systemic therapy
- 6 of 9 centers currently open

Phase 1: Dose Escalation

Main objectives: safety, RP2D

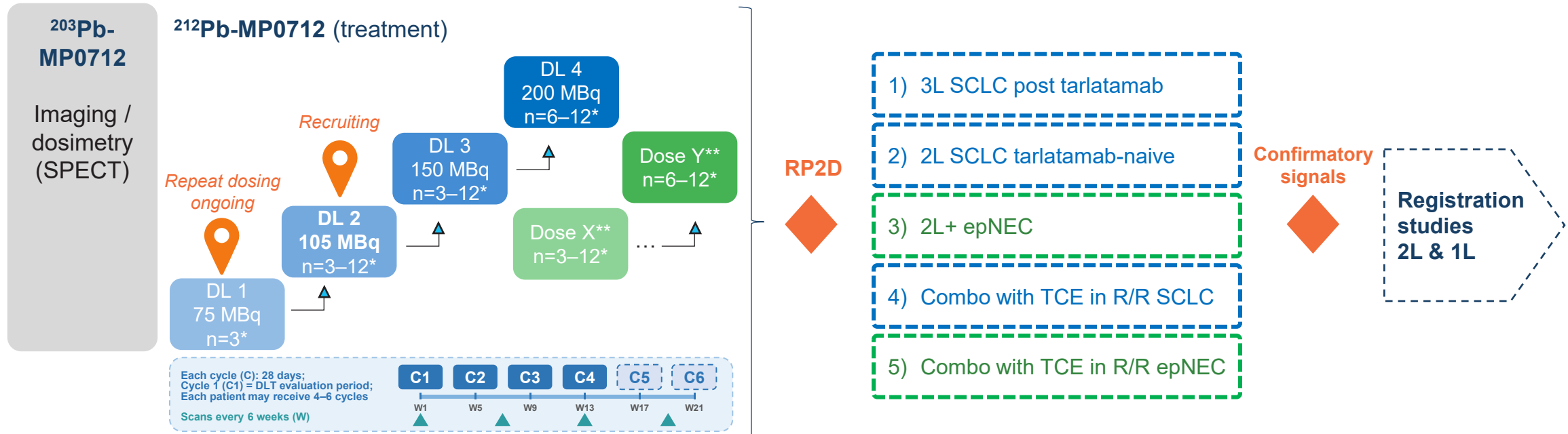
N = 15–39 patients SCLC and lung LC NEC; N = 9–39 patients epNEC



Phase 2a: Dose Expansion and PoC

Main objectives: efficacy signals, confirm safety and RP2D

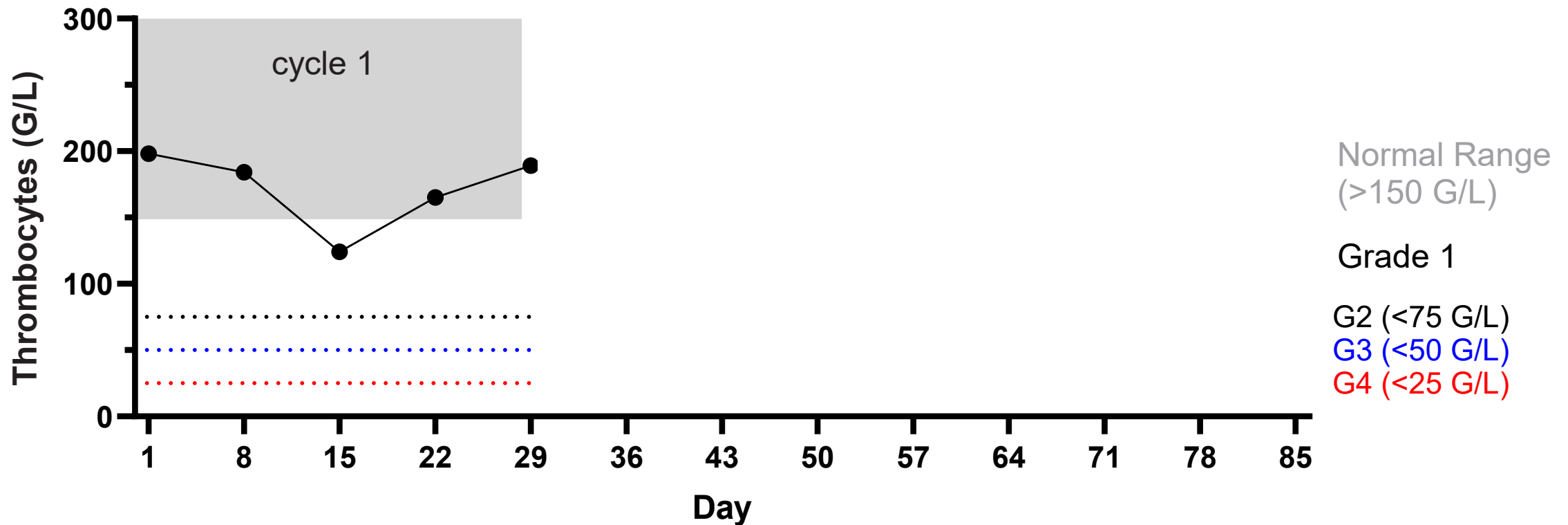
N = up to 5 x 20–30 patients



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

Early Safety Signals Provide Confidence for Therapeutic Window

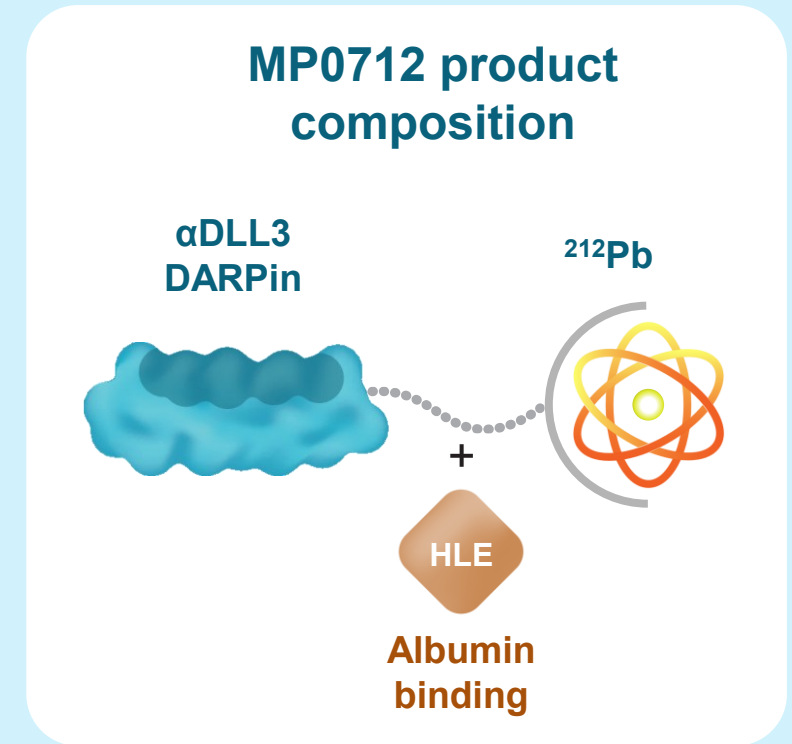
Platelets (n=1 patient)



- Emerging blood counts show mild, transient mid-cycle decreases with full recovery by cycle end to-date
- No dose-limiting toxicity (DLT) reported in fully recruited dose level 1 (75 MBq / dose)

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):
 - Patients continuing treatment per protocol at dose level 1 (75 MBq/dose)
 - No dose-limiting toxicity reported to date
 - All organs of concern well within safety parameters (blood, kidneys, liver)
 - Enrollment for dose level 2 started (105 MBq/dose)
- Additional safety data will be presented by end of 2026; efficacy data in 2027



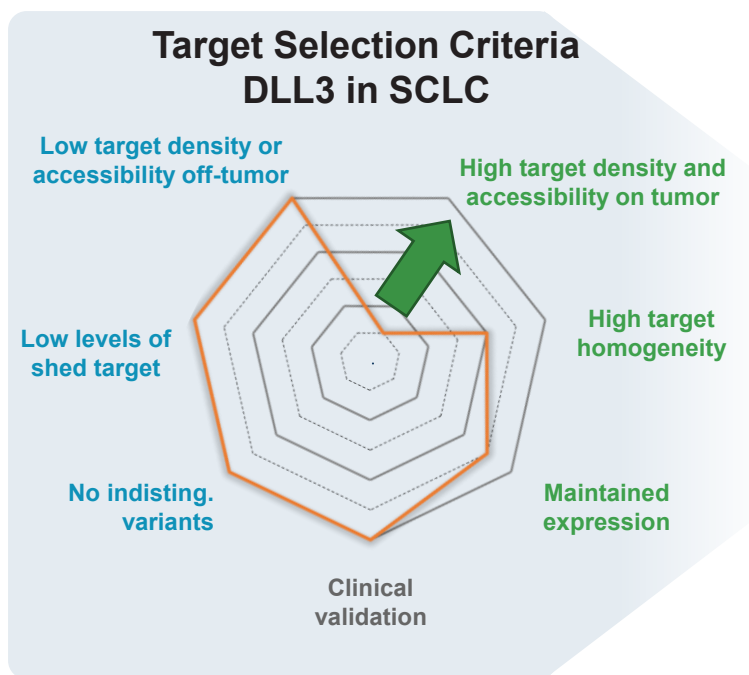


Opportunities for next programs

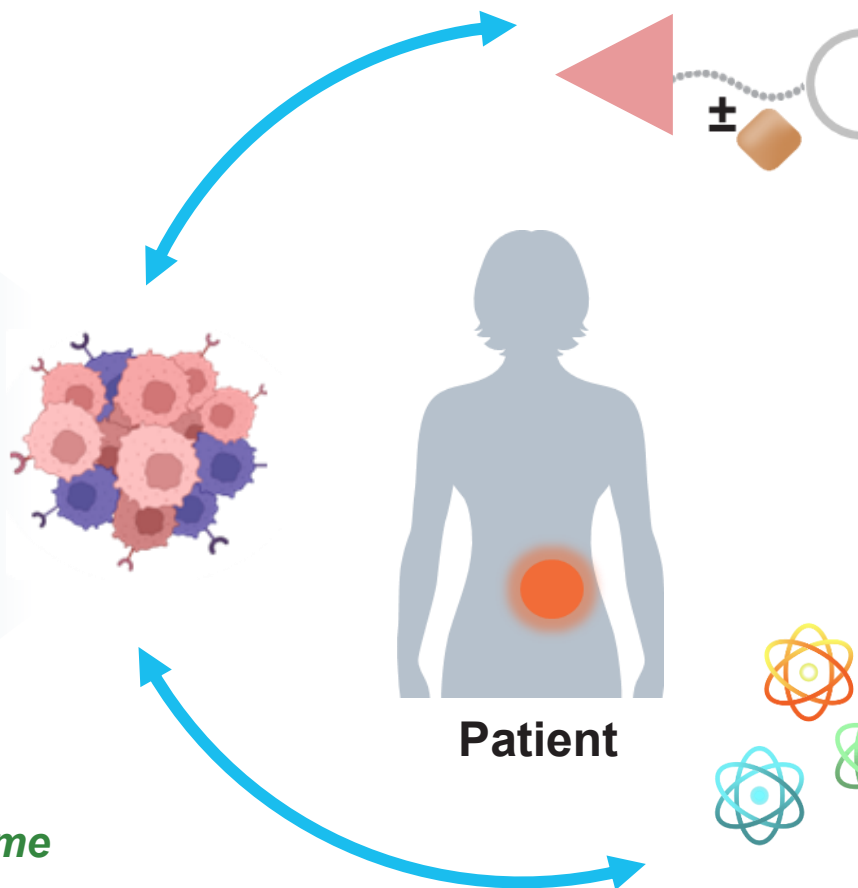


Addressing Target-Specific Challenges Through Molecular Design

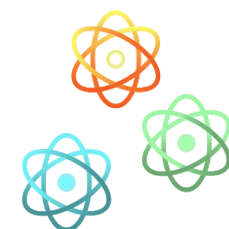
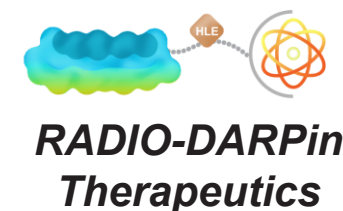
Target & Disease Biology:



MP0712: Low DLL3 density overcome by sustained tumor loading

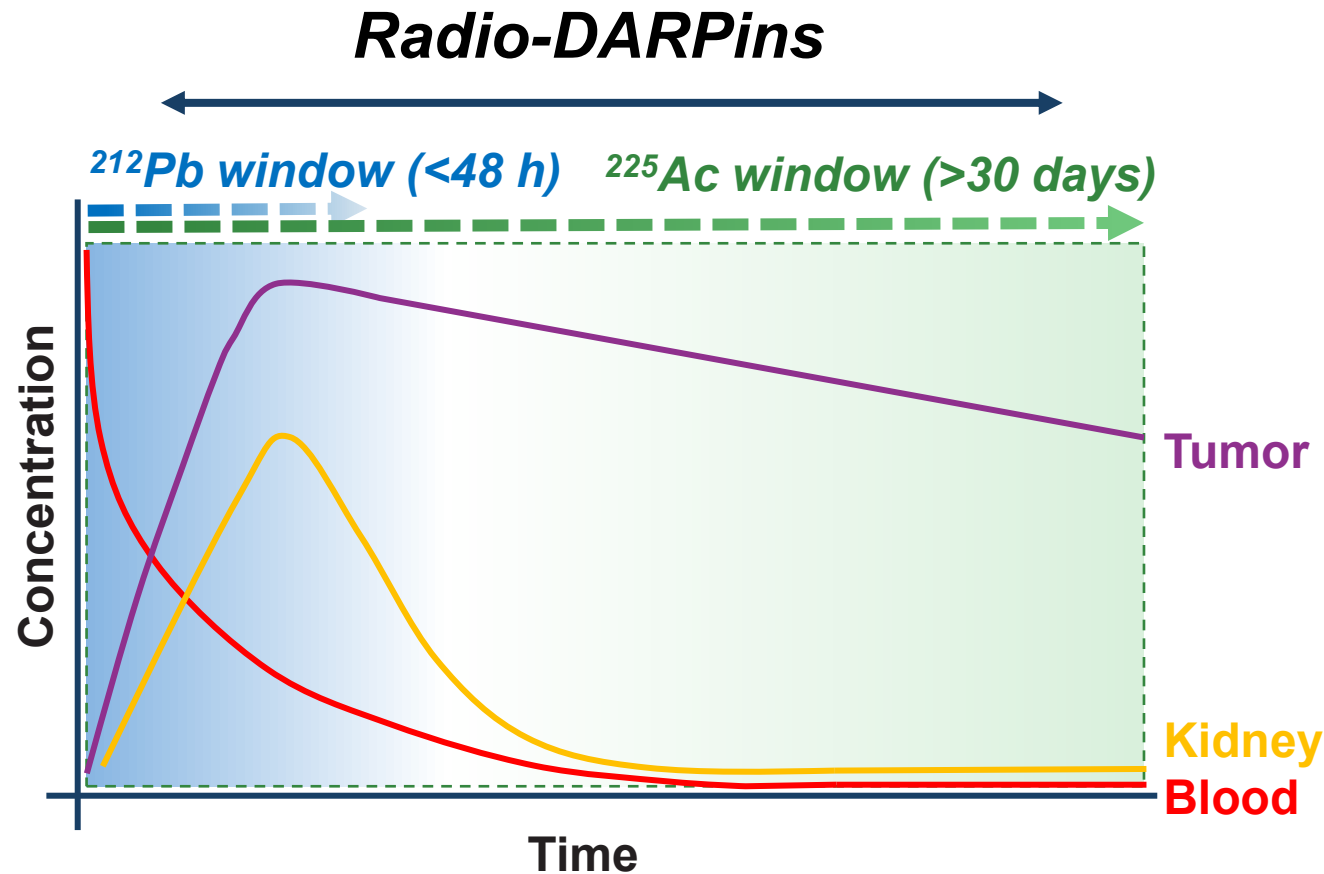


Vector & Modifiers*: LMWs, peptides, mini-proteins and mAbs, designed to address the biology of the target

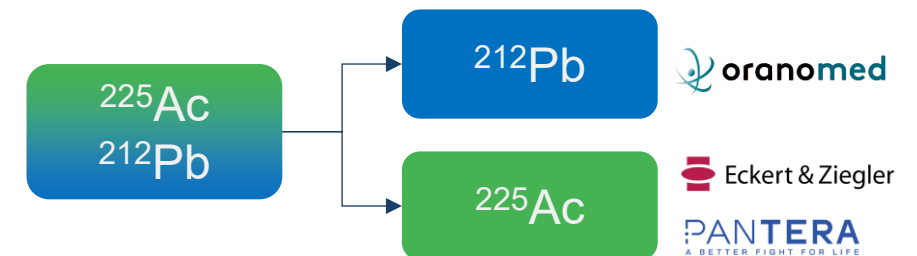


Isotope: matching the vector's characteristics and the biology of the target

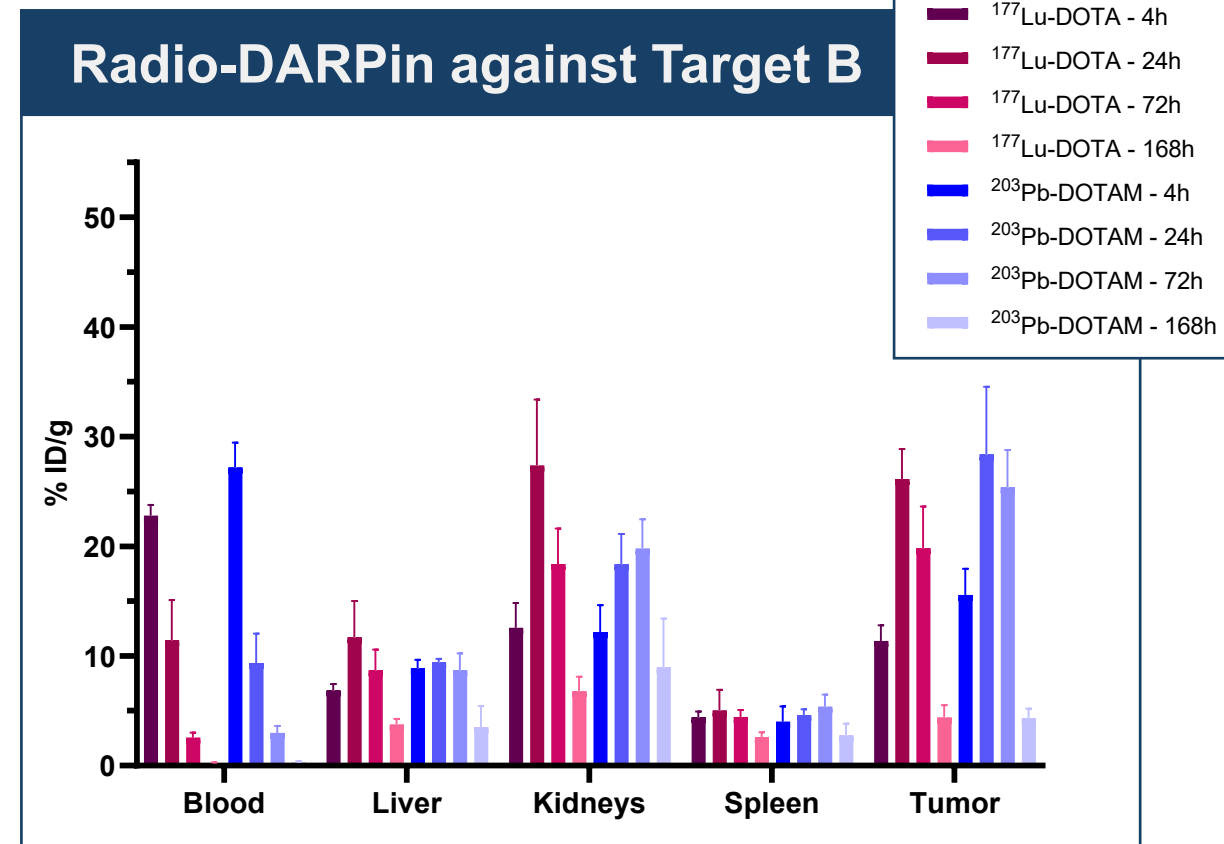
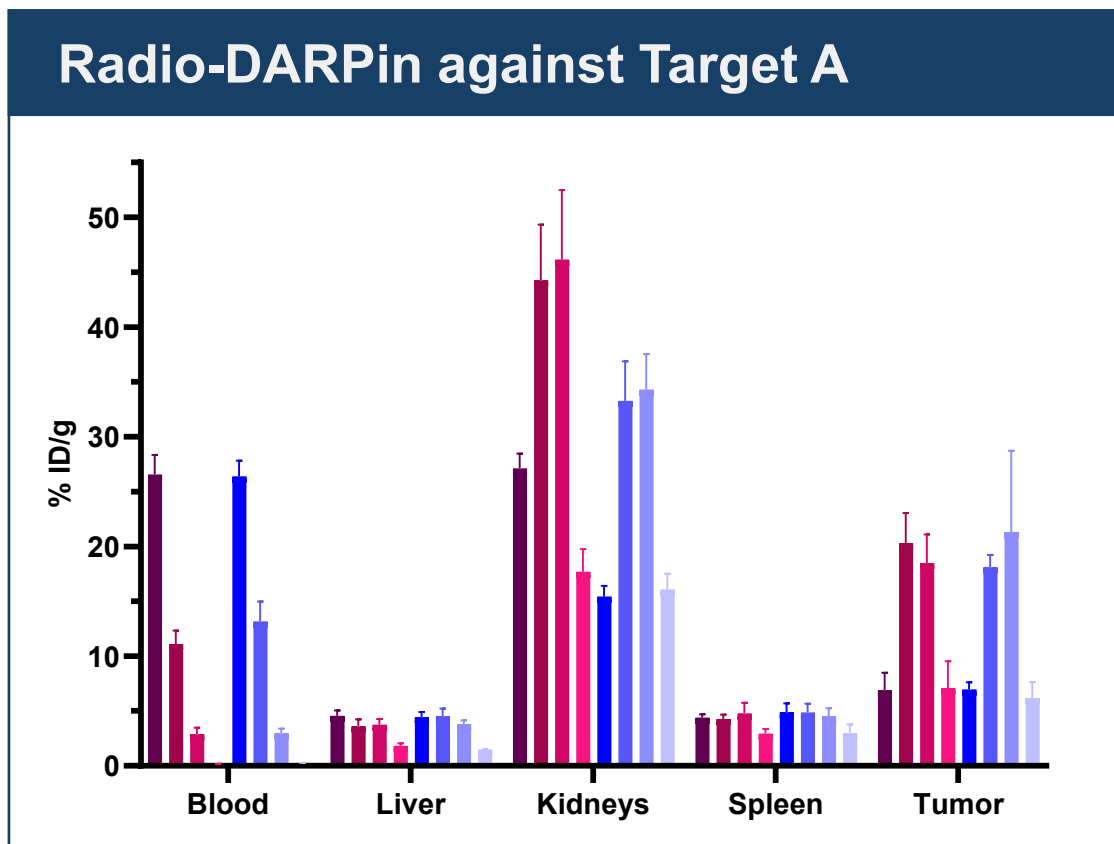
Long Tumor Retention Makes DARPins Alpha-Agnostic



- Based on ^{203}Pb -MP0712 learnings
DARPin profile can work for both ^{212}Pb and/or ^{225}Ac
- DARPins amenable to different isotopes
→ NuMeRI initiated compassionate use of $^{177}\text{Lu}/^{225}\text{Ac}$ x DLL3 (MP0714)



Radio-DARPin Enable Chelator and Isotope Flexibility



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



CD70 x RDT

Targeted Alpha Radiotherapy for Kidney Cancer and Beyond

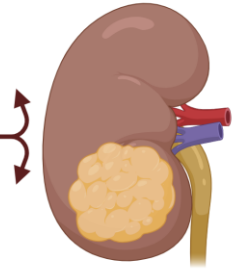


CD70-Targeting Alpha Radiotherapy for RCC & Beyond

ccRCC

Unresponsive to cytotoxic therapies

- Chemo
- EBRT
- ADCs



DNA repair intact

Survival signaling on

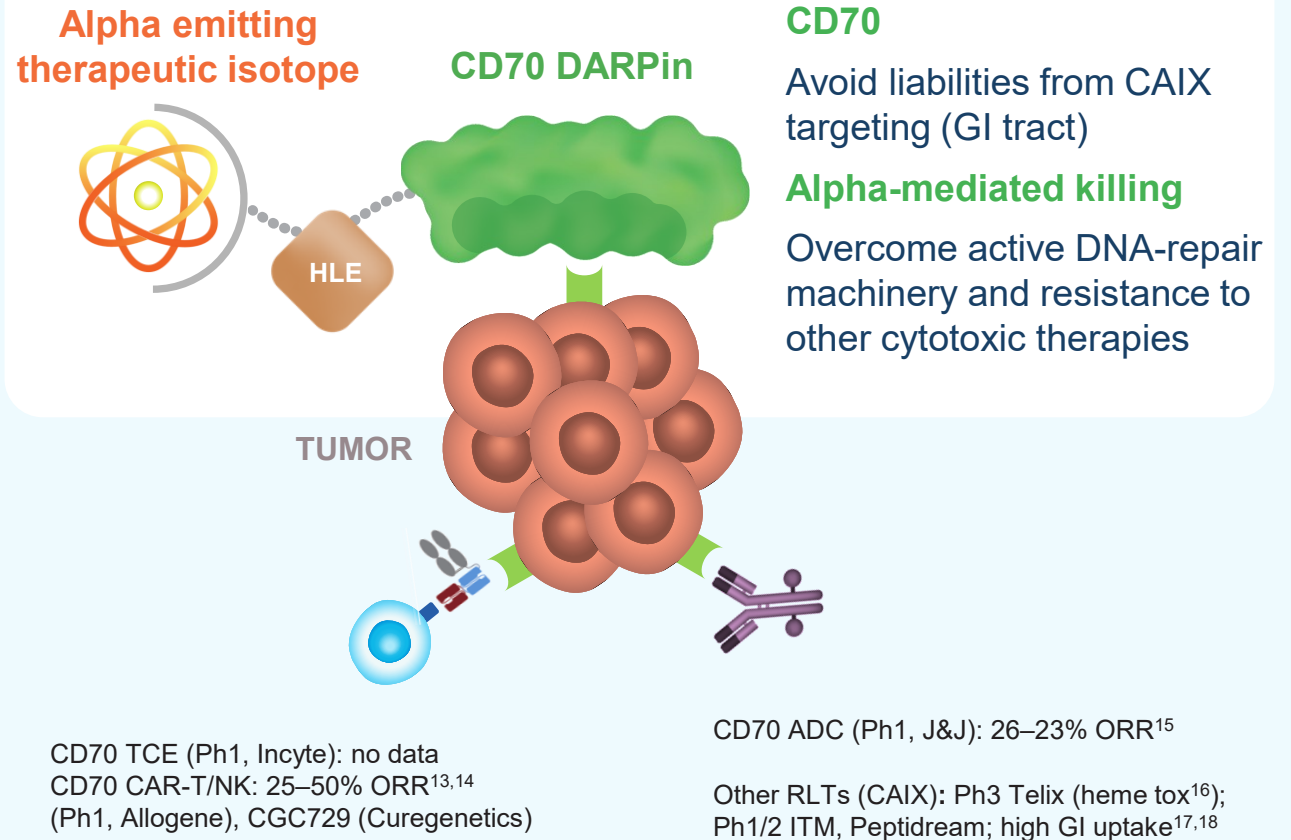
Slow proliferation

Critical Unmet Medical Need (2/3L)

- mPFS: ~5–7 months^{1–3}
- 5-year OS: ~18–25%²
- ccRCC is intrinsically difficult to kill with conventional cytotoxics

CD70 – Validated & Tumor-Selective Target

- >80% of kidney cancer (ccRCC); linked to disease biology; maintained expression in metastases^{4,5}
- Limited expression in healthy tissues^{6,7}
- Clinical validation by diagnostics^{8–12} & CAR-T responses^{13,14}

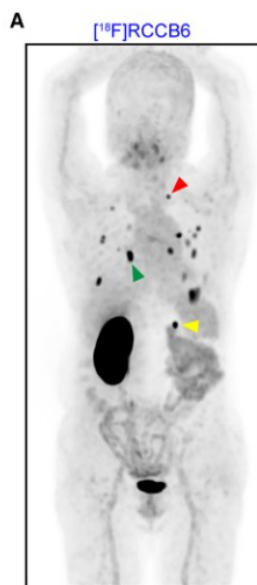


CD70 Confirmed as Target, Therapy Requires Fine-Tuning

CD70 is a promising target...

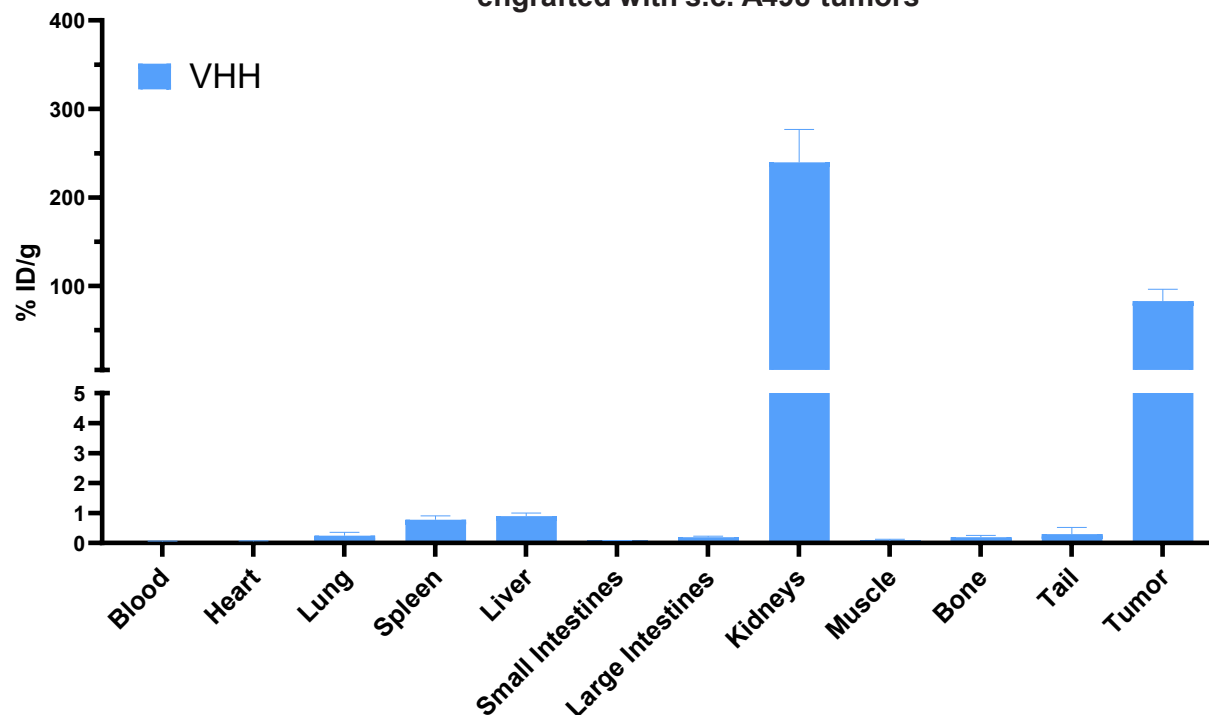
...with high tumor uptake

...but also high kidney



^[18F]RCCB6 (VHH) immunoPET/CT
images in a patient with clear cell
renal cell carcinoma (ccRCC).
Wu *et al.*, EJNMMI, 2024¹

BioD at 4h in mouse
engrafted with s.c. A498 tumors

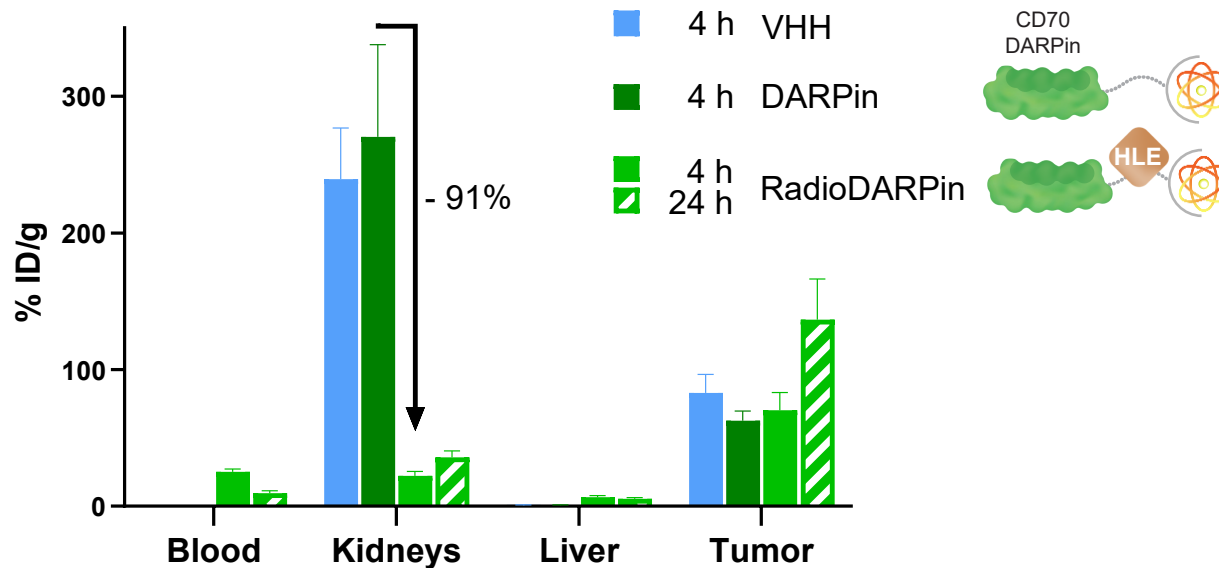


Optimization of CD70-Targeting Radio-DARPin Candidate



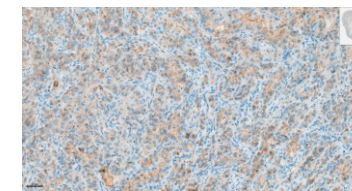
ATH-nude mice xenografted s.c. with A498 human RCC cells

BioD with ^{177}Lu in A498 tumor model

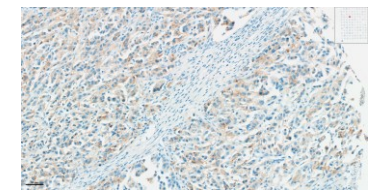


A498 tumors with high CD70 expression

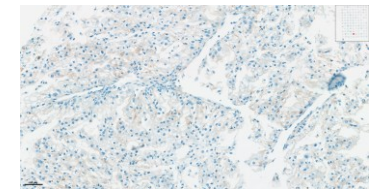
A498 xenograft



Human ccRCC



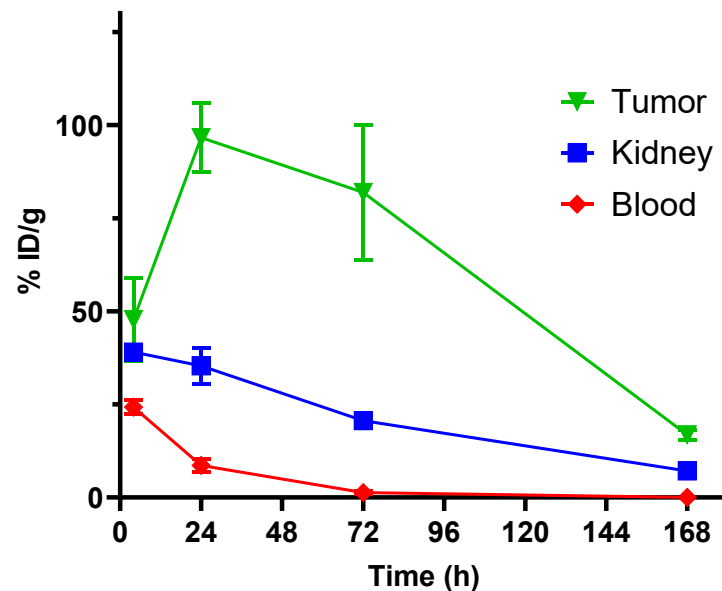
A498 reflects high CD70-expressing human tumors (ABC ~100K)



- Half-life extension (HLE) reduced kidney accumulation by >10-fold
- HLE enabled tumor uptake > 100% ID/g at 24 h

MP0730 Selected Based on Favorable Distribution Profile

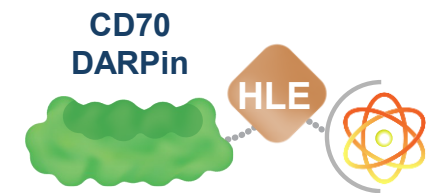
Time-course with ^{177}Lu in A498 tumor model



- Lead candidate MP0730 reached T:K ratio > 3 in mouse model representing high CD70-expressing human tumors

AUC decay corrected for ^{225}Ac

AUC	Blood	Kidney	Tumor	T:K	T:B
MP0730	630	3420	10469	3.1	16.6



MP0730: anti-CD70-Targeted Alpha Radio-DARPin Candidate

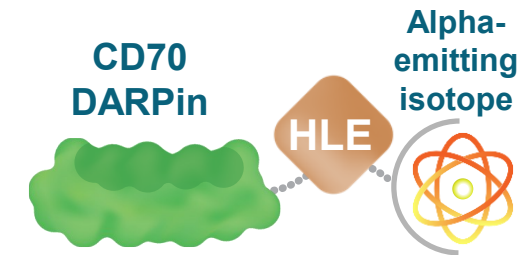
Summary

- CD70 nominated as next RDT target
- MP0730 selected as lead candidate
- CD70-targeting Radio-DARPin optimized based on learnings from MP0712
- MP0730 preclinical data show high tumor uptake and favorable T:K:B supporting further development

Outlook

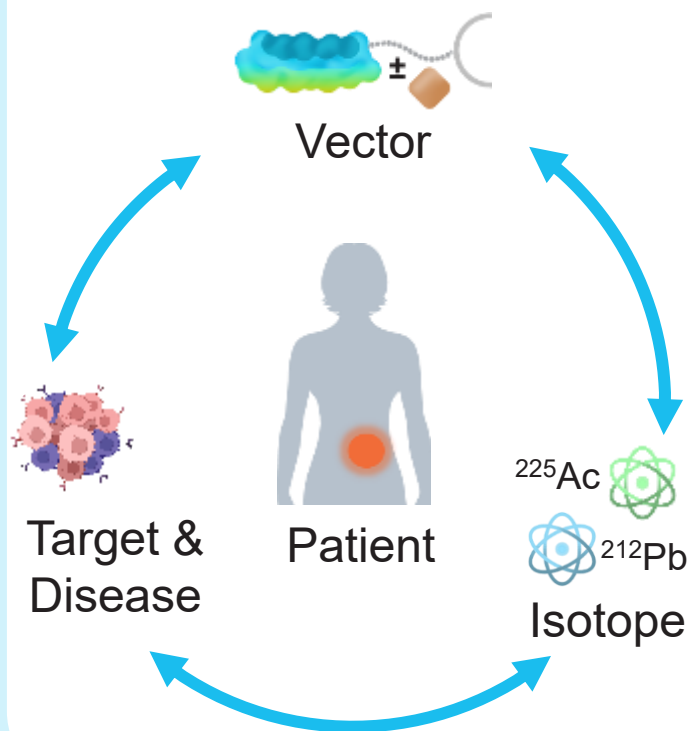
- First-in-human program anticipated to start mid 2027 for the treatment of ccRCC

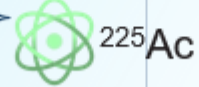
MP0730 product composition



Outlook – What's next in RDT?

Radio-Therapeutics



CANDIDATE	RESEARCH	PRE-CLINICAL	PHASE 1
MP0712	SCLC & NECs ^{212}Pb x DLL3		Initial data 2026 Efficacy 2027
MP0714	^{225}Ac x DLL3		
MP0726	Ovarian Cancer MSLN		Progress to FIH imaging
Additional Programs (Solid Tumors)	"Mono"-specific (incl. CD70) "Multi"-specific	 ^{212}Pb or  ^{225}Ac	Nominate new RDT targets Evaluate candidates in alpha-agnostic manner

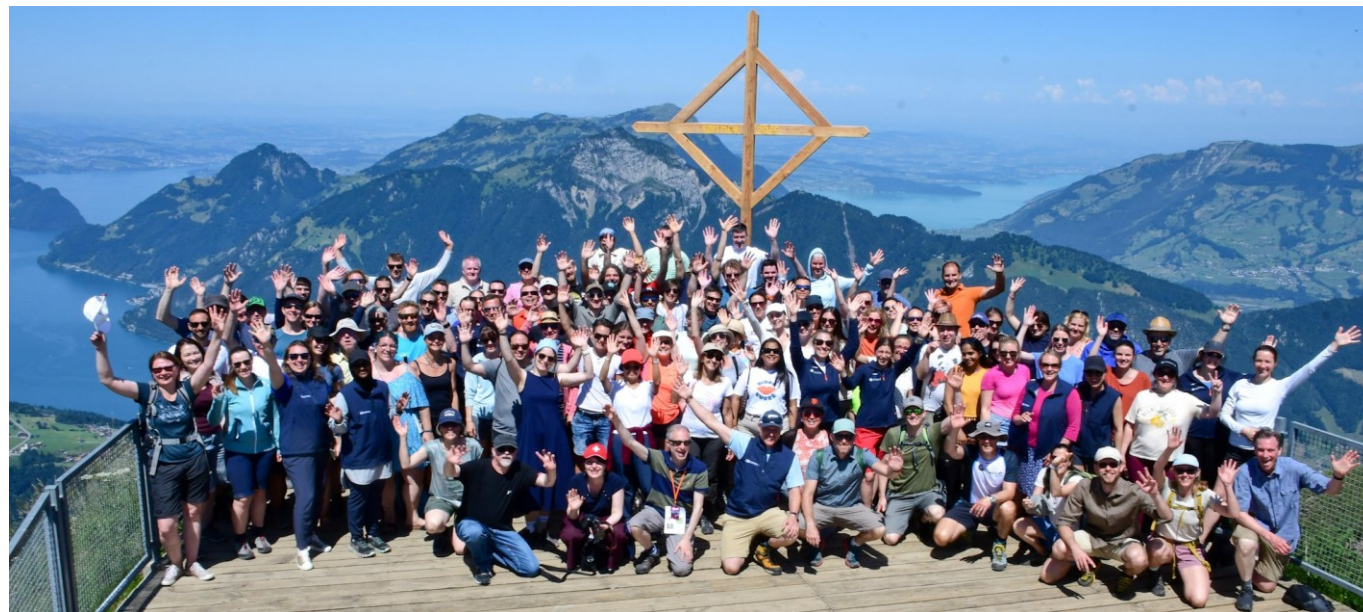
Acknowledgments

The entire teams at
Molecular Partners
and Orano Med



NuMeRI Team

Mike Sathekge
Joseph Kabunda
Honest Ndlovu
Kamo Ramonaheng
Sandile Sibiya
Cindy Davis



Patients and their Families



Thank you for your interest!

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