MOLECULAR partners

Recent Advances in Developing Radio-DARPin Therapeutics

^{212}Pb - DLL3 for SCLC as a first program

TRP Europe 2024

Daniel Steiner, PhD

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Expanding the Target Space for Radio Therapeutics

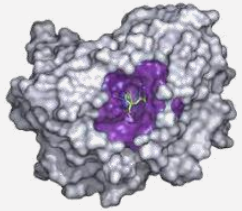
SMALL MOLECULES

Small peptidomimetics & small cyclic peptides

Targets with **cavity** allowing high affinity & specificity binding by “small molecules”

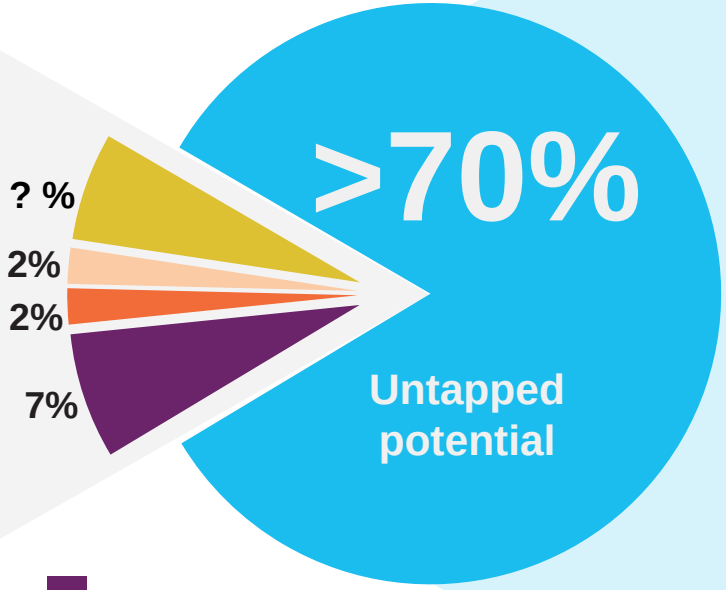
Target Examples:

PSMA
SSTR2



PSMA (1Z8L)

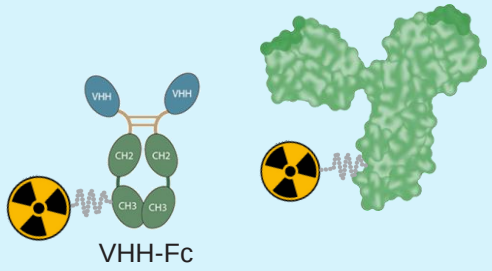
TARGET SPACE*



- PSMA + Prostate
- SSTR2 + NETs
- SSTR2 expansion
- Potential other targets with cavities**
- Other tumor targets & cancers

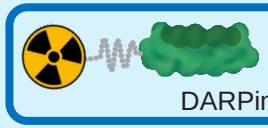
EXPANDING TARGETING MOIETIES

Targets requiring **surface binding** with high affinity & specificity

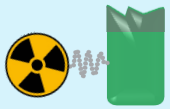


VHH-Fc

ANTIBODIES (150 kDa)

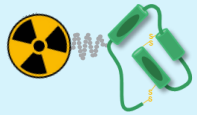


DARPin

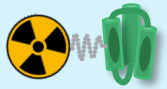


VHH

SMALL PROTEINS (5 - 50 kDa)



Miniproteins



Affibody

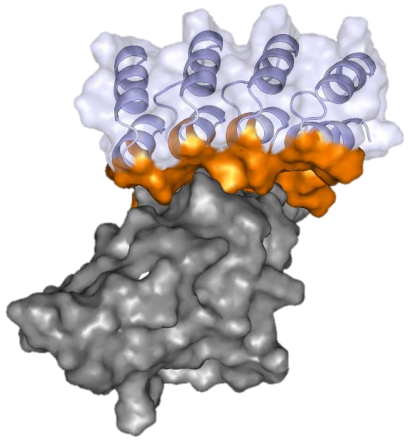
Cyclic, Bi-cyclic…

CYCLIC-PEPTIDES (< 5 kDa)

* Source: Guggenheim Securities Report 2023 ** e.g. FAP, CAIX, FOLR1, NTSR1, Eph2A, GPC3, MC2R, GRPR, ITGB6.
NET, neuroendocrine tumor; PSMA, prostate-specific membrane antigen; SSTR2, somatostatin receptor 2.

DARPin Modality: The Core of our Drug Engine

DARPins are binding proteins derived from natural ankyrin repeat proteins



DARPin **KEY FEATURES**	DARPin **BENEFIT**
Small size (15 kDa)	➢ Deep tissue penetration ➢ High molar concentration
Rigid protein scaffold	➢ Very high affinity & selectivity against broad target range ➢ 2-in-1 DARPin: “Switch”…
Simple & robust architecture	➢ Turn-key multi-specifics ➢ Easy engineering & conjugation

Molecular Partners – Pioneers of DARPins:
7 clinical-stage compounds, reaching **late-stage clinical development,** with > **2500 patients** globally treated

DARPin, designed ankyrin repeat protein; kDa, kilodalton.
Binz HK et al., *J Mol Biol* 2003

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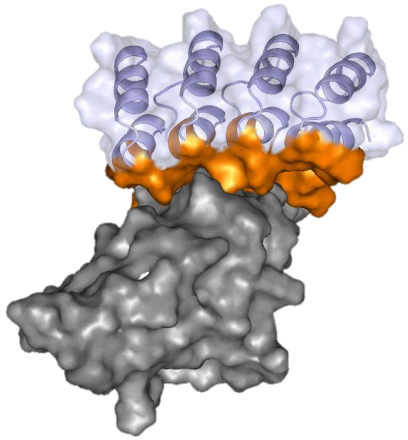

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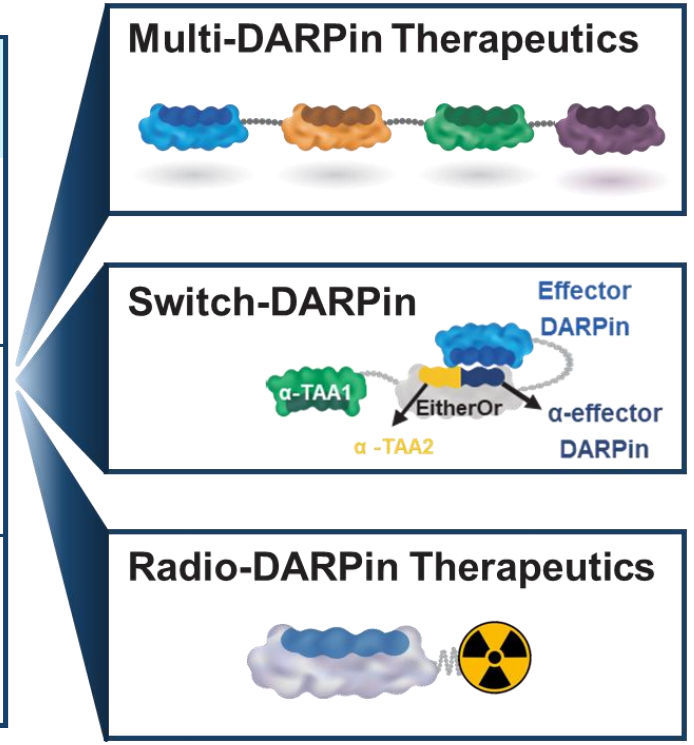

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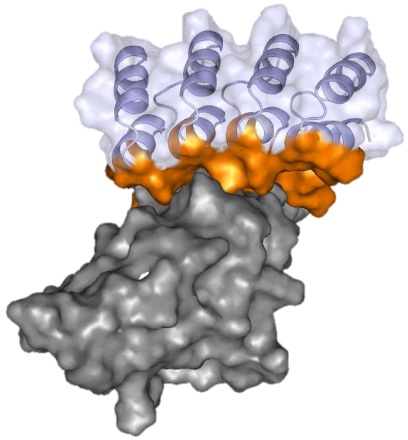

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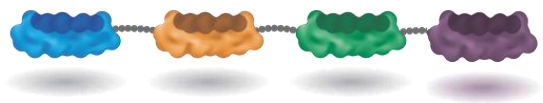
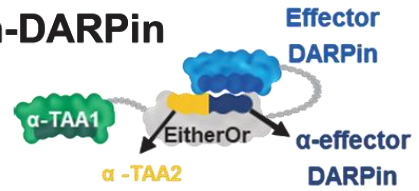
Multi-DARPin Therapeutics



Switch-DARPin



Radio-DARPin Therapeutics

Molecular Partners – Pioneers of DARPins:
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Binz HK et al., *J Mol Biol* 2003

Pipeline

MODALITY	CANDIDATE	RESEARCH	PRE-CLINICAL	PHASE 1	PHASE 2	RIGHTS
Radio–DARPin Therapy (RDT)	**MP0712**	**SCLC & NETs** *^{212}Pb - DLL3*	*Co-development**			MOLECULAR partners
	Undisclosed Programs	**Solid Tumors**	*3 programs**			oranomed
	Undisclosed Programs	**Solid Tumors**	*In-house programs*			MOLECULAR partners
	Undisclosed Programs	**Solid Tumors**	*2 partnered programs*			NOVARTIS
Tetra-specific T-cell Engager	**MP0533**	**r/r AML and AML/MDS** *CD33 x CD123 x CD70 x CD3*				MOLECULAR partners
Switch-DARPin	**MP0621**	**HSCT** *cKit x CD16a x CD47*				MOLECULAR partners
	Next-Gen T-cell Engagers	*CD3 x costim x TAAs*				
Localized Agonist	**MP0317**	**Advanced Solid Tumors** *FAP x CD40*				MOLECULAR partners

*The co-development agreement with Orano Med includes 4 RDT programs, including MP0712.
AML, acute myeloid leukemia; DLL3, Delta-like ligand 3; HSCT, hematopoietic stem cell transplant; MDS, myelodysplastic syndrome; NET, neuroendocrine tumor; r/r, relapsed/refractory; SCLC, small cell lung cancer.

Opportunity to Evolve DARPins as Radiotherapeutics

Breast cancer patient imaged with a Her2 DARPin

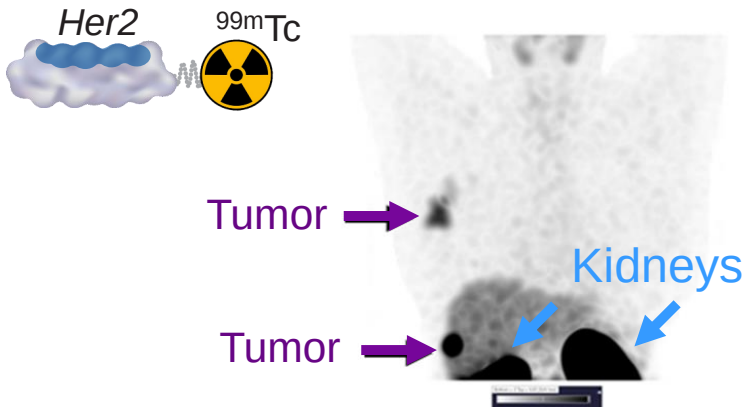
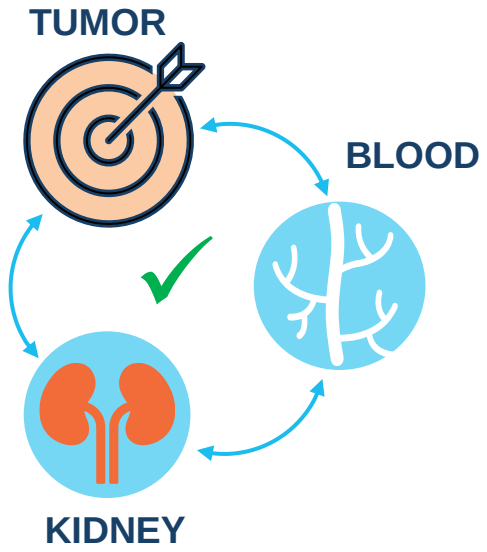


Image kindly provided by Dr. Bragina
Research Centrum for Oncotheranostics, Tomsk [1]

Unlocking DARPins for radiotherapeutic applications

- Increase selective but moderate tumor uptake
- Reduce strong kidney accumulation



Intrinsic DARPin properties

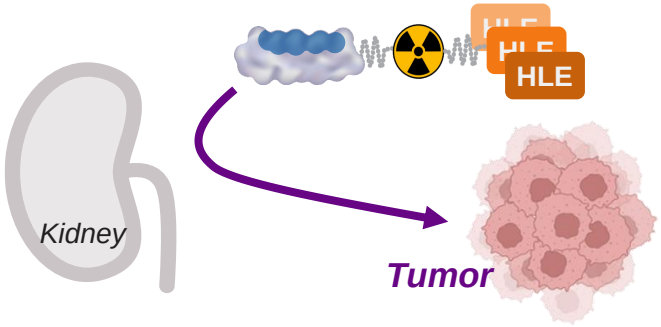
- ✓ **Small size** (~15 kDa)
  - → *Deep tumor penetration*
  - → *Short systemic half-life*
- ✓ **High affinity** (pM range)
  - → *Long tumor retention*
- ✓ **High selectivity**
  - → *Low accumulation in other tissues*
- ✓ **High stability**
  - → *Surface engineering*

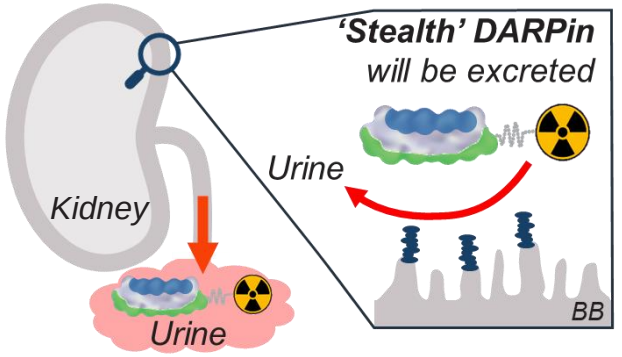
[1] Bragina et al., *J Nuc Med* 2021.
Her2, human epidermal growth factor receptor 2; Tc, technetium.

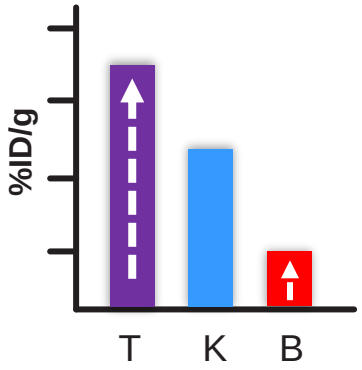
Radio-DARPin Platform Ready to Deliver Product Candidates

Increased tumor uptake
by half-life extension (*HLE*)*

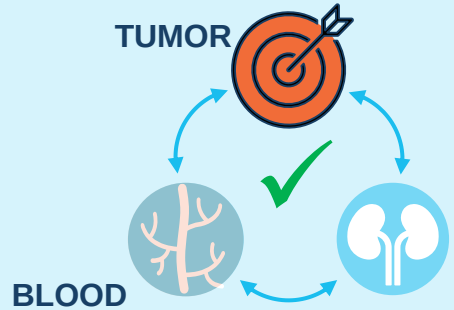
Reduced kidney accumulation
by surface engineering (*Stealth-DARPin*)*

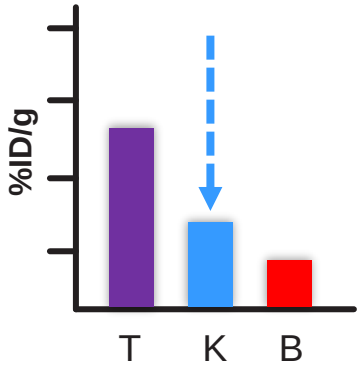






Optimized biodistribution properties





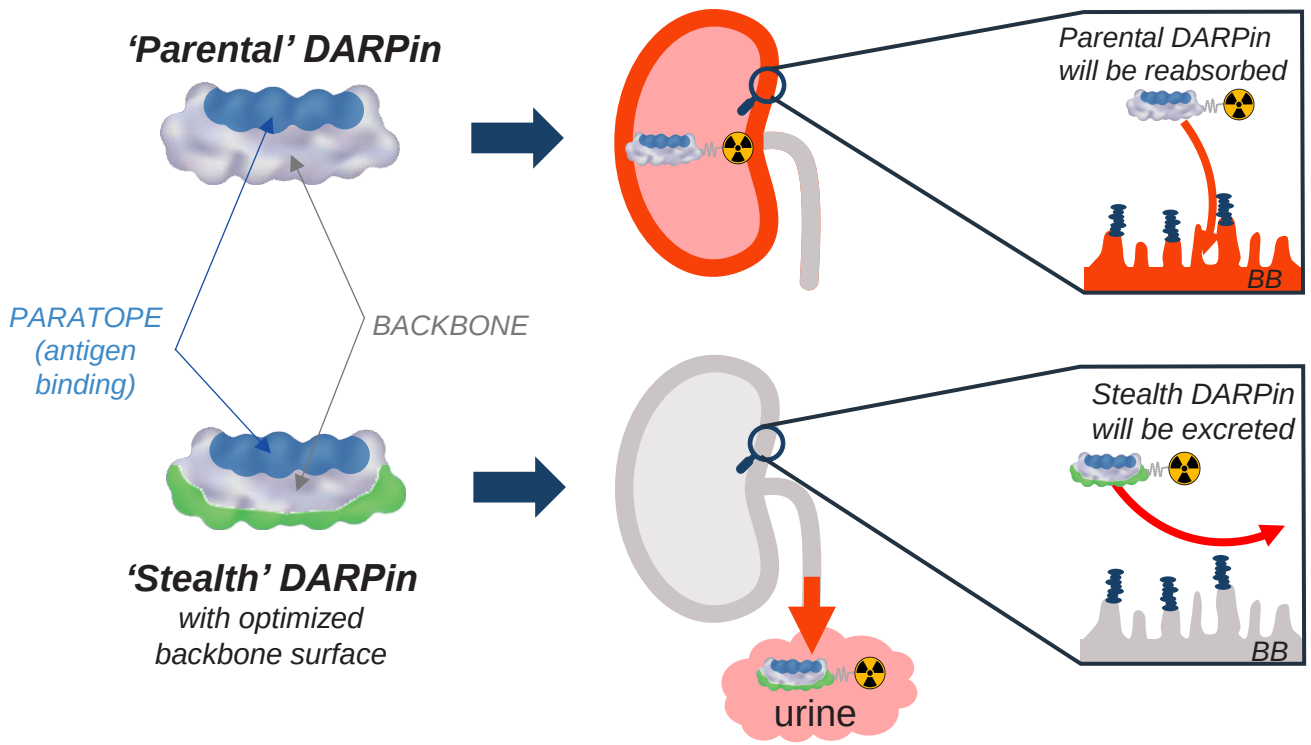
BB: Brush border of proximal tubular cells in the kidney with megalin/cubilin receptor complex

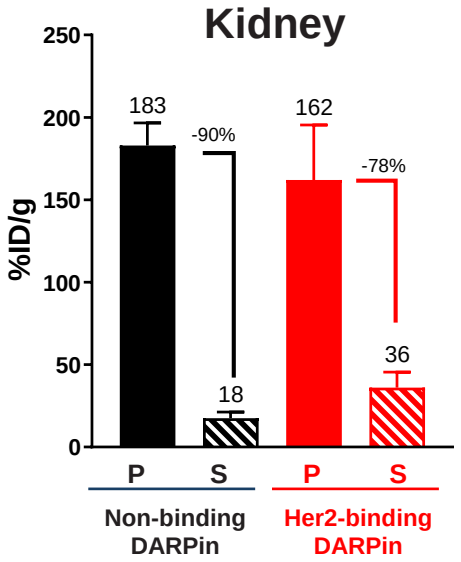
*Data presented at various scientific conferences, including: AACR 2023 (Bosshart et al.), SNMMI 2023 (Lizak et al.), EANM 2023 (Lizak et al.), and others.
B, blood; D, dose; HLE, half-life extension; K, kidney; kDA, kilodalton; pM, picomolar; T, tumor.

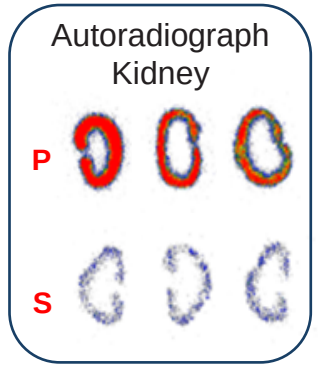
Surface Engineering to Reduce Kidney Accumulation

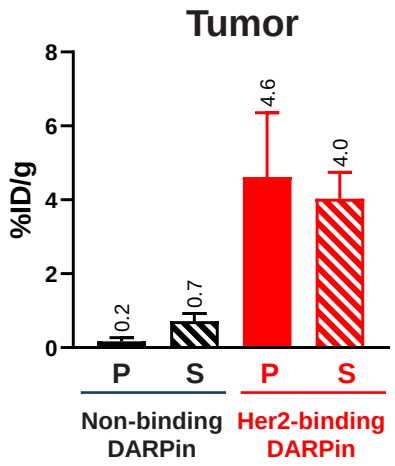
Enabled by the high stability of DARPin scaffold

Surface engineering of DARPins as a strategy to increase renal excretion









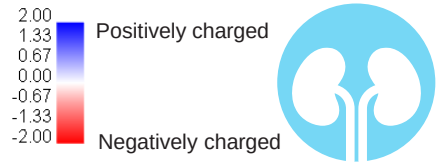
P: Parental

S: Stealth (surface engineered)

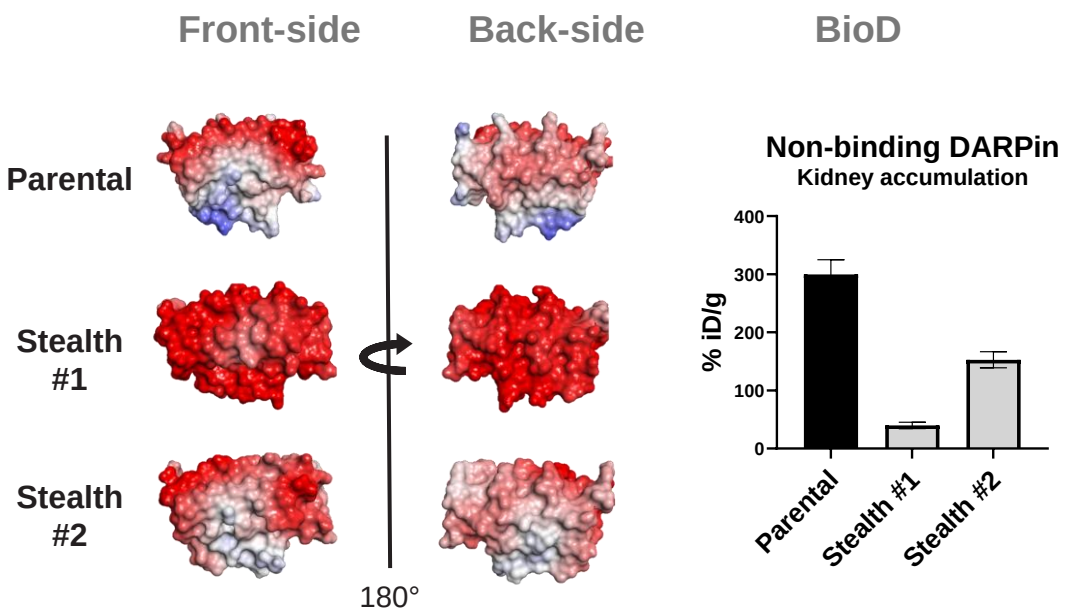
BB: Brush border of proximal tubular cells in the kidney with megalin/cubilin receptor complex

SKOV3 tumor mouse model, 111-In/DTPA labelled DARPin, 4 h post injection

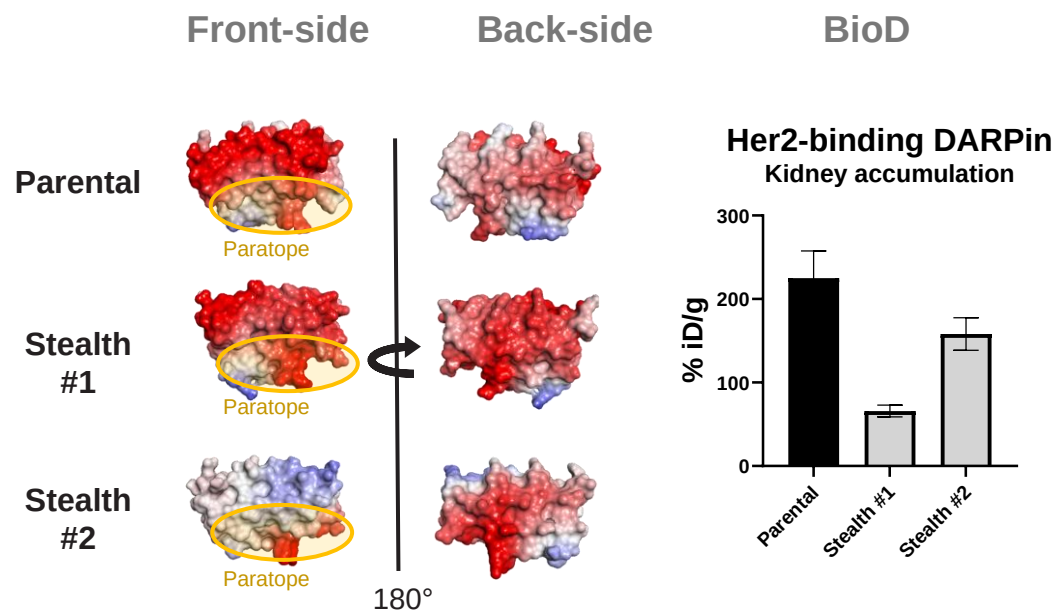
The Science Behind the Stealth DARPin Designs



Non-binding DARPin



Her2-binding DARPin

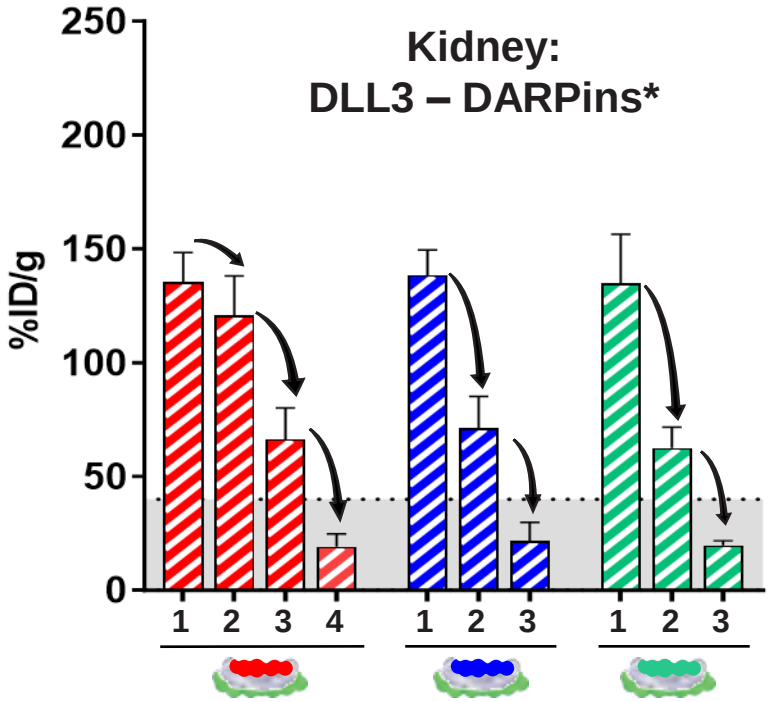


Surface charge engineering enabled by the robust DARPin scaffold strongly reduces kidney accumulation

- General concept: removal of positively charged and/or introduction of negatively charged amino acids
- Total net charge, charge distribution and specific position of charged amino acids matter

Homology model of each DARPin was generated, QMap (charge distribution) at pH 7.4 was calculated with Discovery Studio.

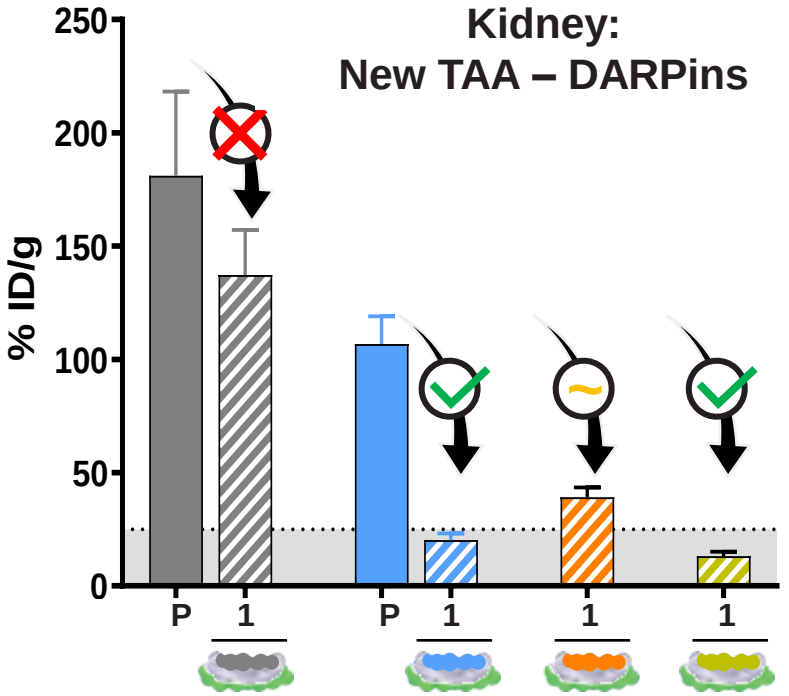
Evolution and Scale of Surface Engineering for RDT Engine



Integration of learnings across different TAAs and **>140 engineered DARPins**

P: Parental

1-4: Surface Eng. Rounds



AT PROGRAM START: Iterative rounds of DARPin surface engineering and *in vivo* testing needed to reach low kidney accumulation

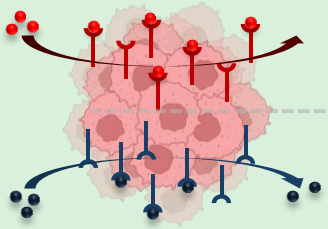
TODAY: A <u>single</u> round of DARPin surface engineering to reach low kidney values for most DARPin binders

* Kidney value of best surface variant per engineering round displayed in graph: 4h timepoint in wt or tumor-bearing mice; DARPins conjugated to different chelators and labelled with different radioisotopes.

Multi Parameter Optimization to Improve Tumor Uptake

1. Small targeting moieties extravasate and diffuse faster

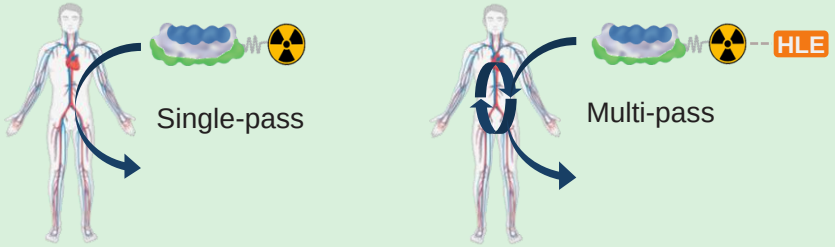
2. High affinity increases tumor uptake of small targeting moieties [1,2]

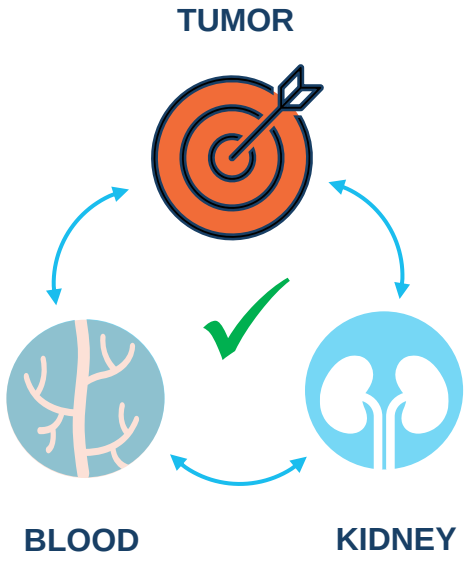


High affinity → slow wash-out & long residence time on tumor

Low affinity → faster wash-out & shorter residence time on tumor

3. Extended half-life to maintain concentration gradient blood to tumor





Optimizing Tumor : Kidney : Blood ratio

1. Schmidt & Wittrup, *Mol Cancer Ther* 2009.
2. Zahnd et al., *Cancer Res* 2010.

Systemic Half-life Extension (HLE) Increases Tumor Uptake

Surface engineered

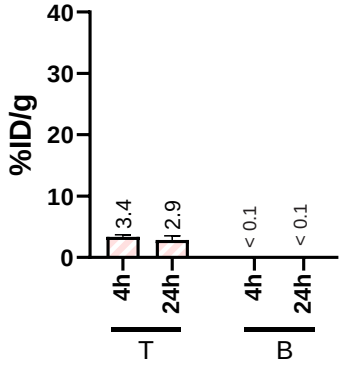
Surface engineered + HLE

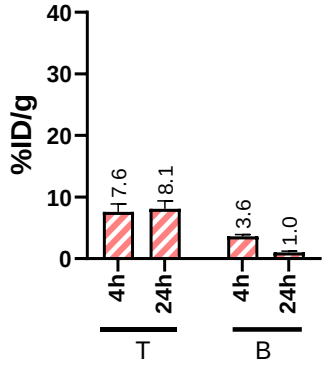
increase in blood exposure

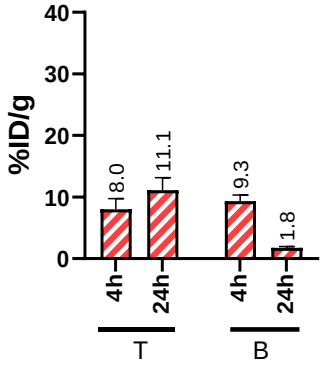
T: Tumor; **B**: Blood

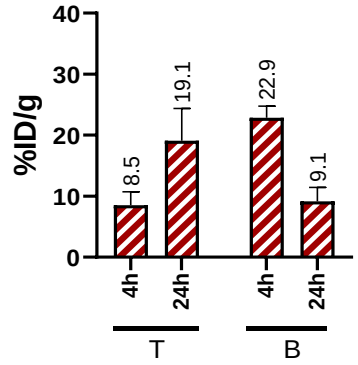
HER2 DARPin

PAUL SCHERRER INSTITUT PSI



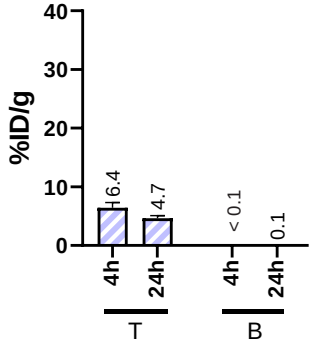


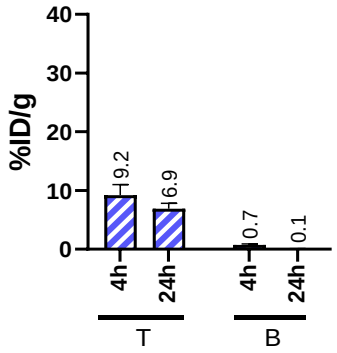


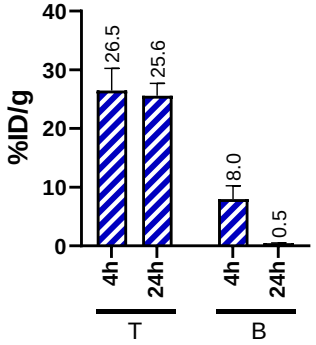


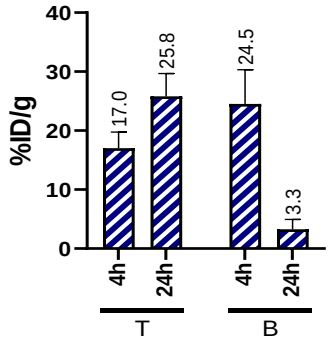
DLL3 DARPin

oranomed
²¹²Pb for Targeted Alpha Therapy









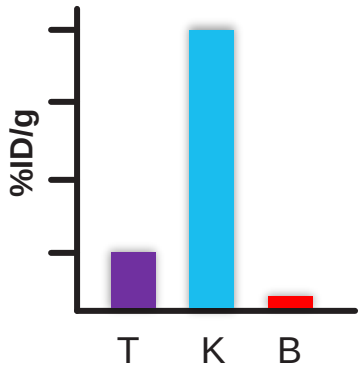
HLE toolbox with different "strengths & properties" for optimized BioD profiles

Her2 and DLL3 DARPins conjugated to different chelators, labelled with different radioisotopes; and tested in different mouse tumor models; αSA: HLE moieties binding to serum albumin.

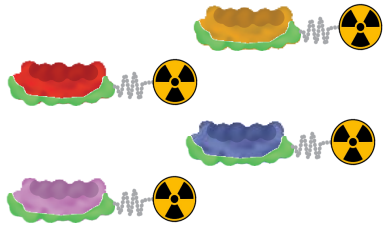
The Engineering Principles for RDT Candidates

T: Tumor
K: Kidney
B: Blood

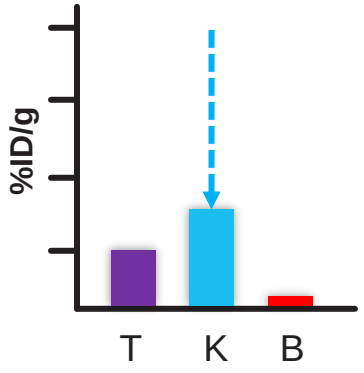
1 STARTING POINT
Diverse high affinity DARPins



2 STEALTH DESIGN
Reduced accumulation in kidney

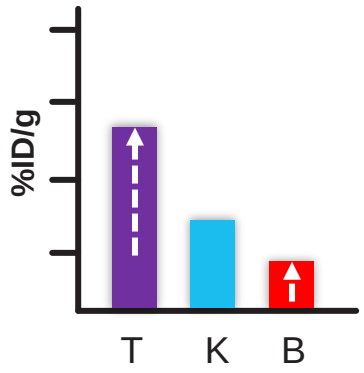


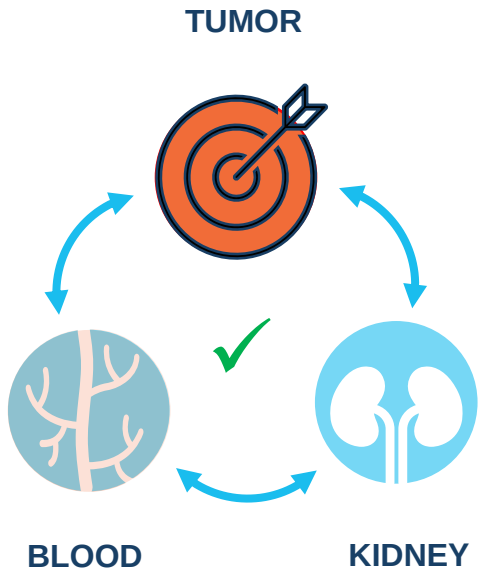
Identify candidates with <25% ID/g in kidney



3 HALF-LIFE TUNING
Increased tumor uptake

Increase tumor uptake while keeping systemic $t_{1/2}$ low





Integration of stealth design into DARPin libraries

In-vivo screening directly in HLE-format

Rationale for Developing ^{212}Pb-based RDTs

^{212}Pb has beneficial properties as radioisotope [1]

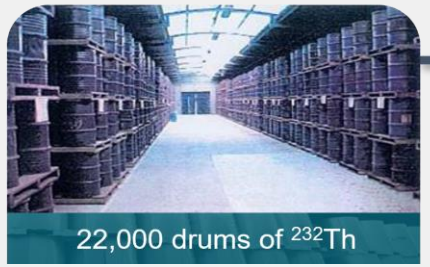
1) **Efficacy** – short decay half-life is leading to high energy deposition on tumor in short time frame, may spare infiltrating immune cells and might be beneficial for early combination with immunotherapy
2) **Safety** – clean decay chain – ^{212}Pb is an alpha precursor with limited release of free daughter radionuclides
3) **Waste management** – less problematic thanks to short half-life

Orano Med as leader in ^{212}Pb targeted α-therapies

- Independent, unlimited supply of ^{212}Pb
- Regional manufacturing capabilities to commercial
- Clinical capabilities demonstrated with ^{212}Pb and AlphaMedix™ in Phase 2 study in collaboration with RadioMedix

Strong collaboration between MP / OM since early 2023

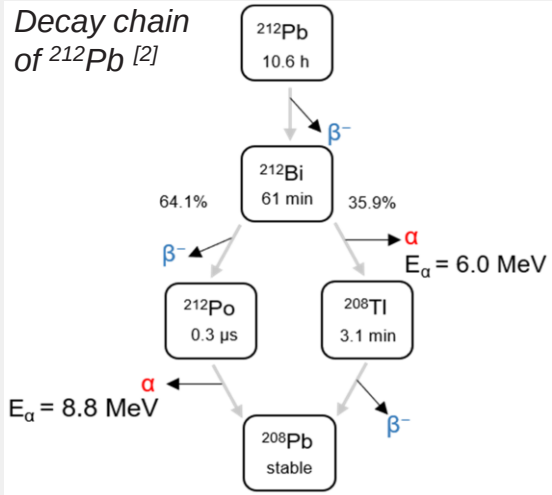
- Deep complementary capabilities and expertise
- Committed and trustful collaboration
- Strong platform & product progress



^{232}Th 14 Bn years → ^{228}Ra 5,7 years → ^{228}Th 1,9 years → ^{224}Ra 3,6 days → ^{212}Pb 10,6 hours

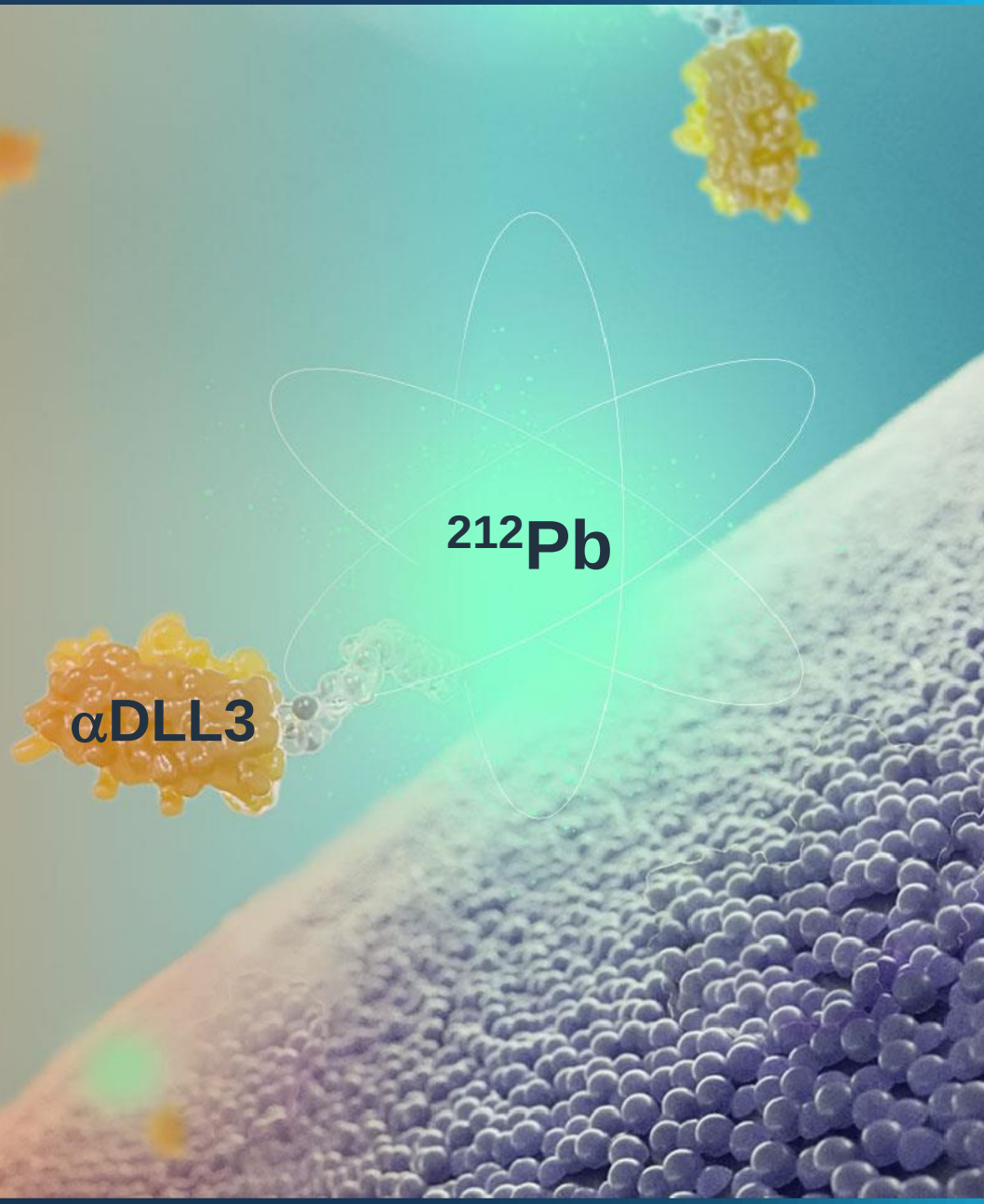
Lead-212 is obtained **chemically** by **successive extractions and purifications** of the descendants of thorium-232

Decay chain of ^{212}Pb [2]



1. Zimmermann, *J Nucl Med*, 2023
2. Li et al., *Materials* 2021

Preclinical Assessment of MP0712: ^{212}Pb Radio-DARPin Therapeutic Targeting DLL3 for SCLC



DLL3, Delta-like ligand 3; SCLC, Small Cell Lung Cancer

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

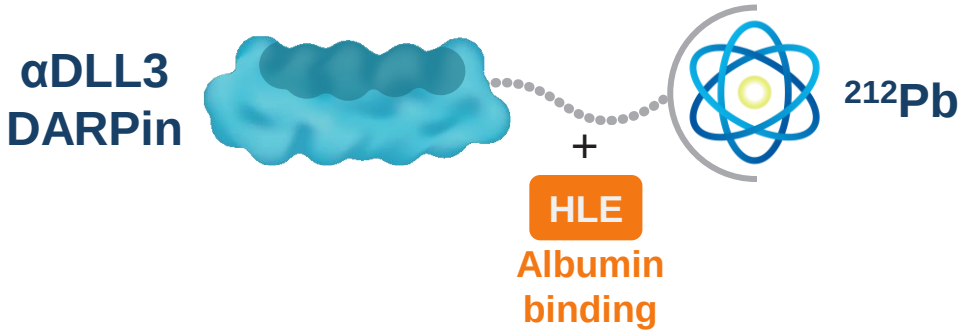
SCLC – High unmet need and limited treatment options

- SCLC is an aggressive cancer with high unmet medical need**:** mPFS ~3m in 2L; 5y OS ~3%[1,2]

DLL3 – promising target for SCLC

- DLL3 is expressed in >85% of SCLC patients and in other NETs
- Homogeneous tumor expression and no expression in healthy tissues
- Tarlatamab approval (Amgen, DLL3-TCE) validates DLL3 as a target and leaves clear room for improvement: 2L+; ORR ~40%

Combining Radio-DARPin features with the power of ^{212}Pb for next-gen targeted alpha therapy



DLL3 DARPin optimized for efficacious and safe delivery of radio-isotopes

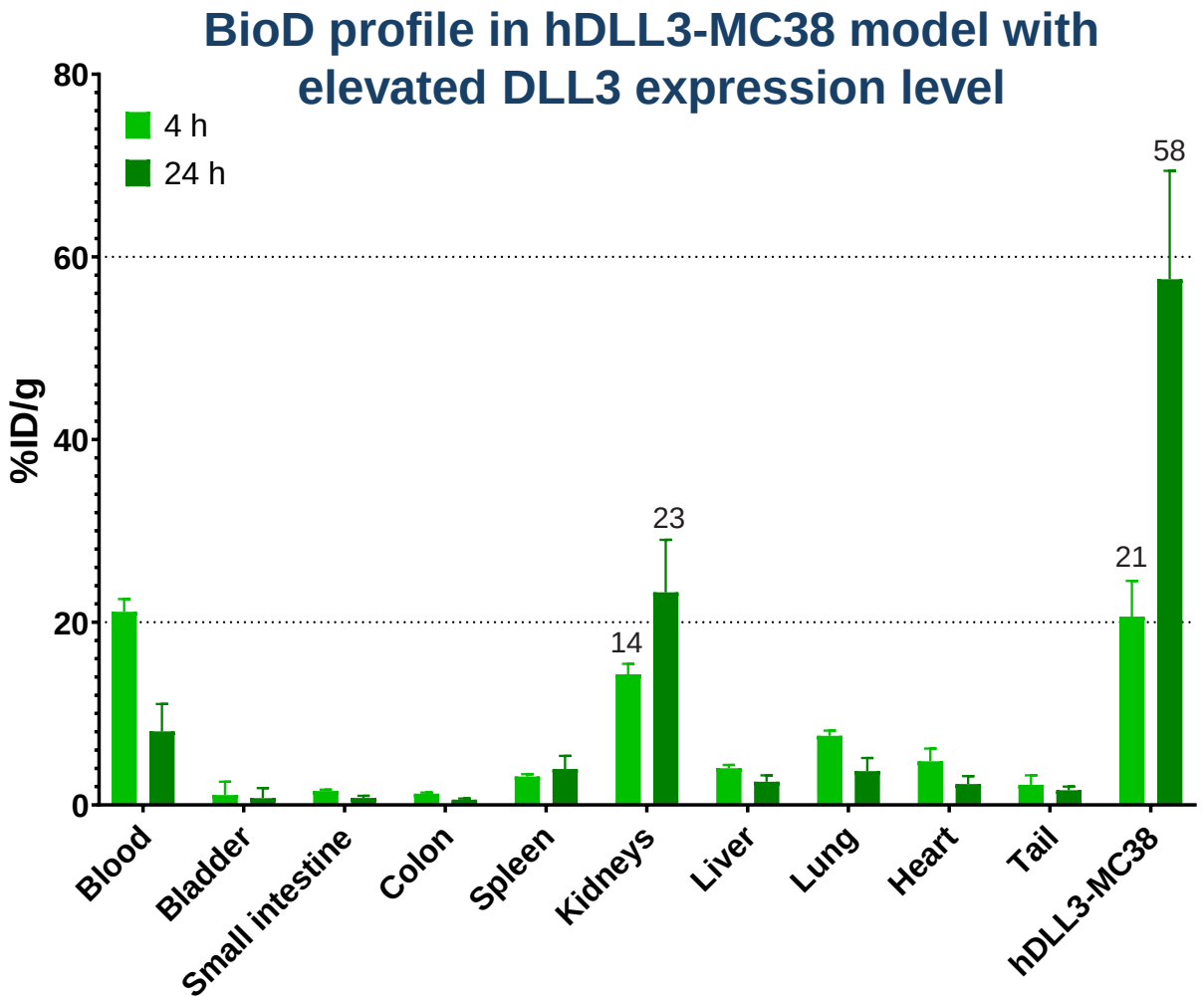
^{212}Pb as potent therapeutic isotope for rapid and clean α-radiation

MOLECULAR partners

oranomed
^{212}Pb for Targeted Alpha Therapy

TCE, T cell engager; HLE, half-life extension moiety.
1. Treatment of refractory and relapsed small cell lung cancer, UpToDate;
2. SEER; 3. Rojo et al., Lung Cancer 2020; 4. Strosberg et al., ASCO 2024

Identification of ^{212}Pb-DLL3 Candidates with Attractive BioD Profile



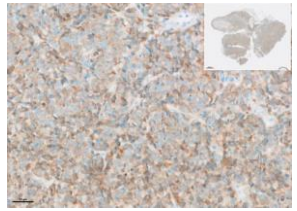
- Candidate screening and optimization in hDLL3-MC38 model
- Strong tumor uptake & encouraging biodistribution profile with **T:K Ratio >2**
- **MP0712 selected as Lead Candidate** for ^{212}Pb-DLL3 Radio-DARPin Therapy

Mice xenografted s.c. with hDLL3-MC38 (Biocytogen)
Dose: 10 µCi of ^{212}Pb at 0.01 mg/kg of DLL3 DARPin
BioD, biodistribution; T:K, tumor to kidney ratio.

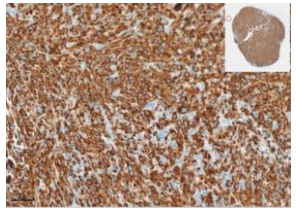
MP0712 Shows Favorable Biodistribution and Tumor Specificity

DLL3 expression & distribution by IHC

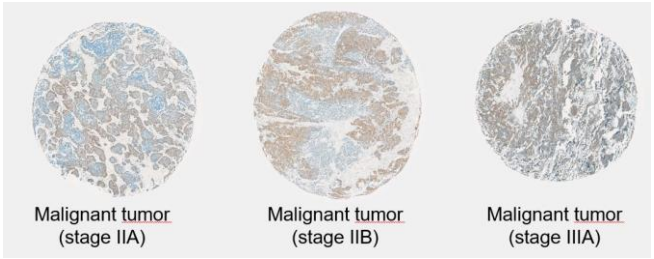
NCI-H82 tumors



hDLL3-MC38 tumors



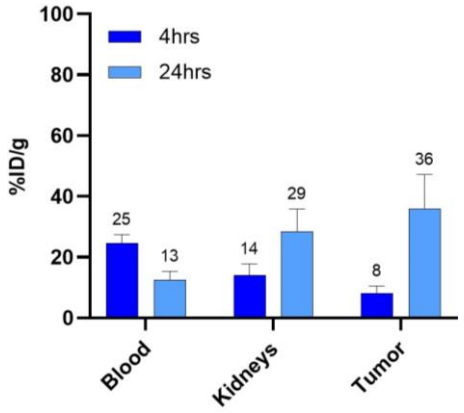
Malignant human SCLC tumors



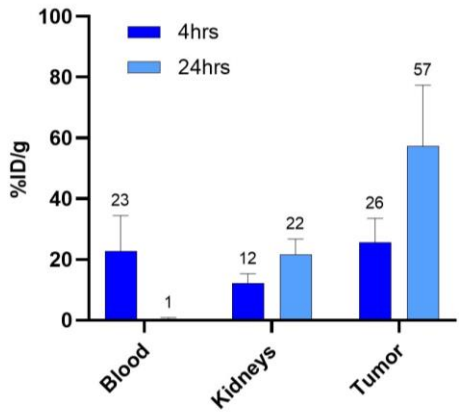
*R2G2 mice xenografted **s.c.** with **NCI-H82***

*R2G2 mice xenografted **i.v.** with **NCI-H82***

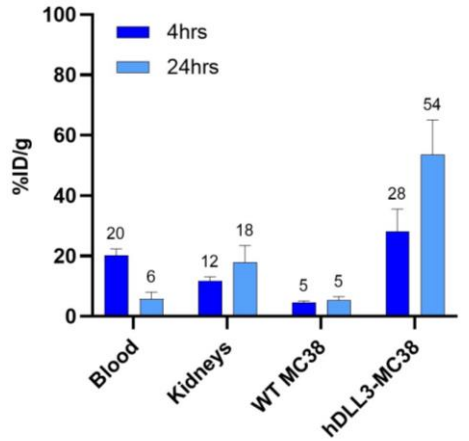
*ATH nude mice double xenografted **s.c.** with **hDLL3-MC38** + **WT-MC38***



T:K at 4h = 0.6 / at 24h = 1.2



T:K at 4h = 2.1 / at 24h = 2.6



T:K at 4h = 2.3 / at 24h = 3.0

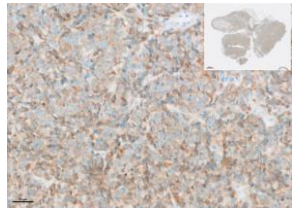
- **Selective uptake in DLL3-expressing tumors confirms high target specificity of MP0712**
- **MP0712 reaches T:K ratios > 2 in mouse model matching clinically relevant DLL3 expression levels**

MP0712 biodistribution studies done in different mouse models expressing DLL3 / ^{212}Pb-DOTAM-DARPin injected 1 x 10µCi at 0.01mg/kg.

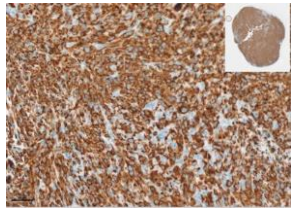
MP0712 Shows Homogeneous Tumor Distribution

DLL3 expression & distribution by IHC

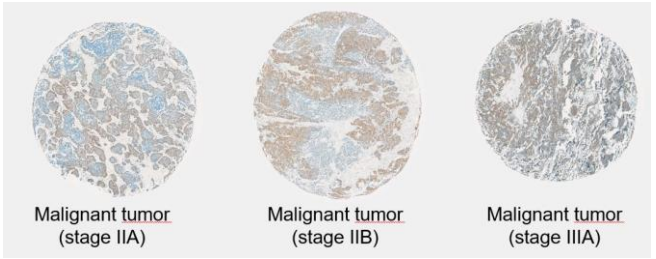
NCI-H82 tumors



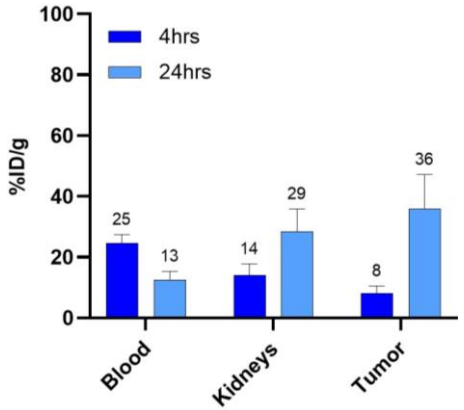
hDLL3-MC38 tumors



Malignant human SCLC tumors



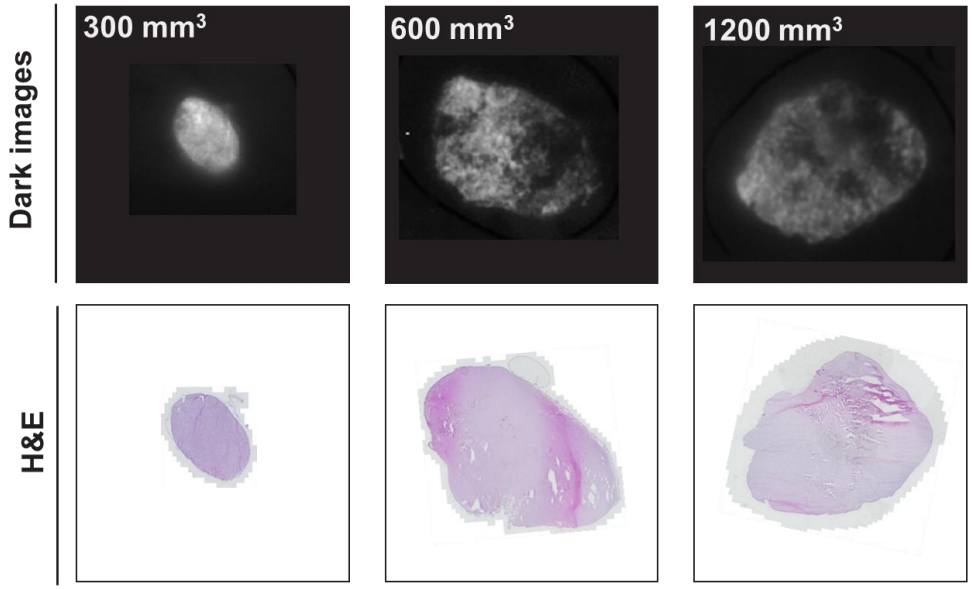
*R2G2 mice xenografted **s.c.** with **NCI-H82***



T:K at 4h = 0.6 / at 24h = 1.2

Sections of tumors with different size

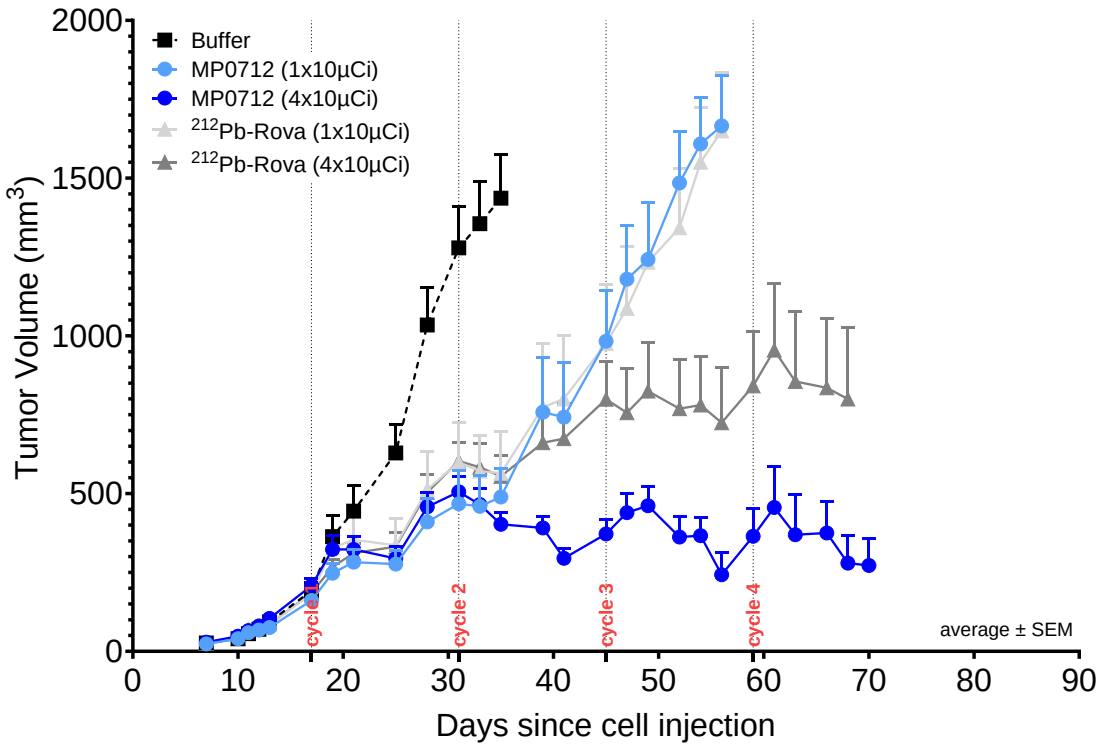
(NCI-H82 s.c. model, alpha camera at 1h)



- **Imaging by alpha camera shows a homogeneous tumor distribution in DLL3-low model (NCI-H82) even at tumor sizes beyond 600 mm³**

MP0712 biodistribution studies done in different mouse models expressing DLL3 / ^{212}Pb-DOTAM-DARPin injected 1 x 10μCi at 0.01mg/kg.
Imaging: DLL3 / ^{212}Pb-DOTAM-DARPin injected 1 x 100μCi at 3.2ug/animal

MP0712 Shows Good Efficacy & Tumor Stabilization

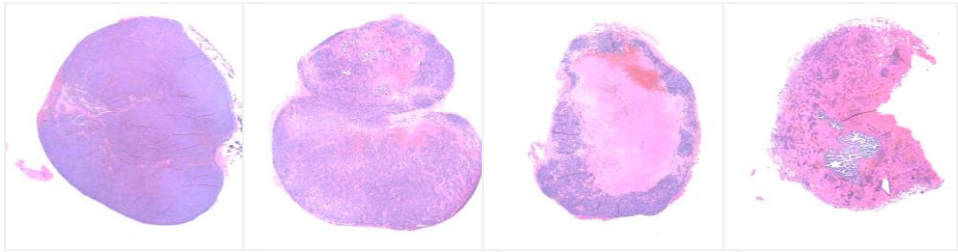


Median survival

Buffer	MP0712 1x10 µCi	MP0712 4x10 µCi	Rova 1x10 µCi	Rova 4x10 µCi
4.7 wks	7.9 wks	**15.7 wks**	7.9 wks	8.9 wks

*R2G2 mice xenografted **s.c.** with* ***NCI-H82***

Effect of MP0712 on tumor necrosis



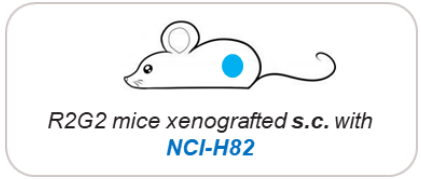
Cycle 1 *Cycle 2* *Cycle 3* *Cycle 4*

→ Significant necrosis after cycles 3 and 4

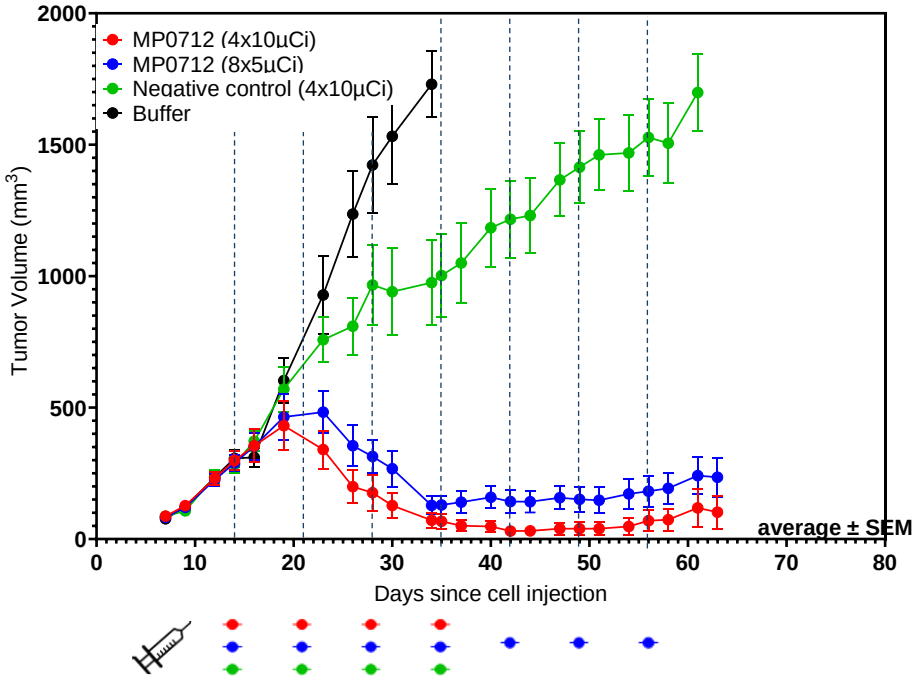
- **MP0712 induced tumor stabilization in NCI-H82 tumor model at 10µCi / 0.37 MBq injected every two weeks**
- **A significant induction of necrotic vs tumor tissue is observed post MP0712 treatment**

Efficacy study in NCI-H82 tumor model / MP0712 and ^{212}Pb-Rova injected 1 x 10mCi at 0.01mg/kg or 4 x 10µCi at 0.01mg/kg every 2 weeks.

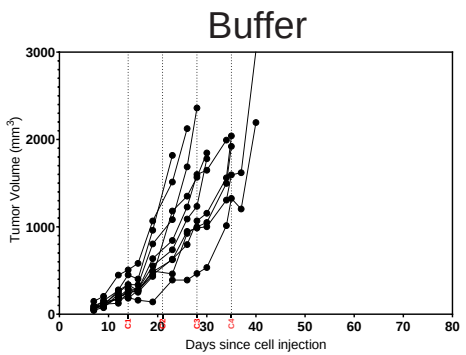
Increased Dosing Frequency Results in Complete Tumor Regression

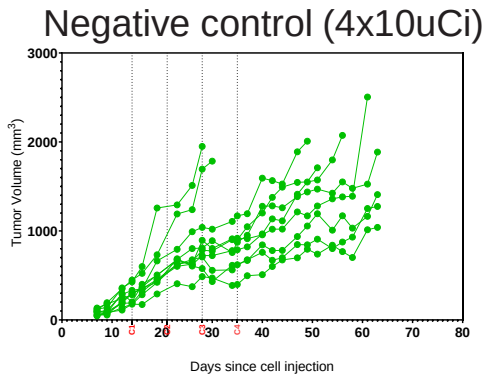


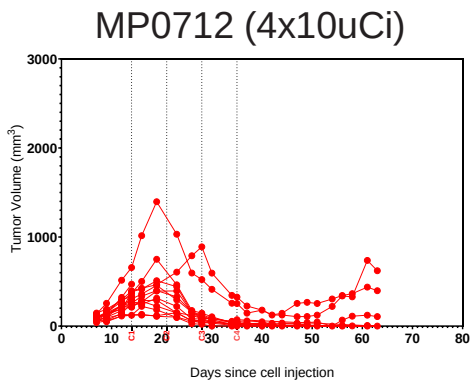
*R2G2 mice xenografted **s.c.** with*
NCI-H82

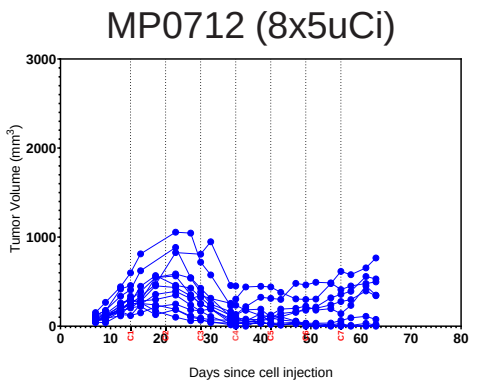


Tumor growth curve for each animal



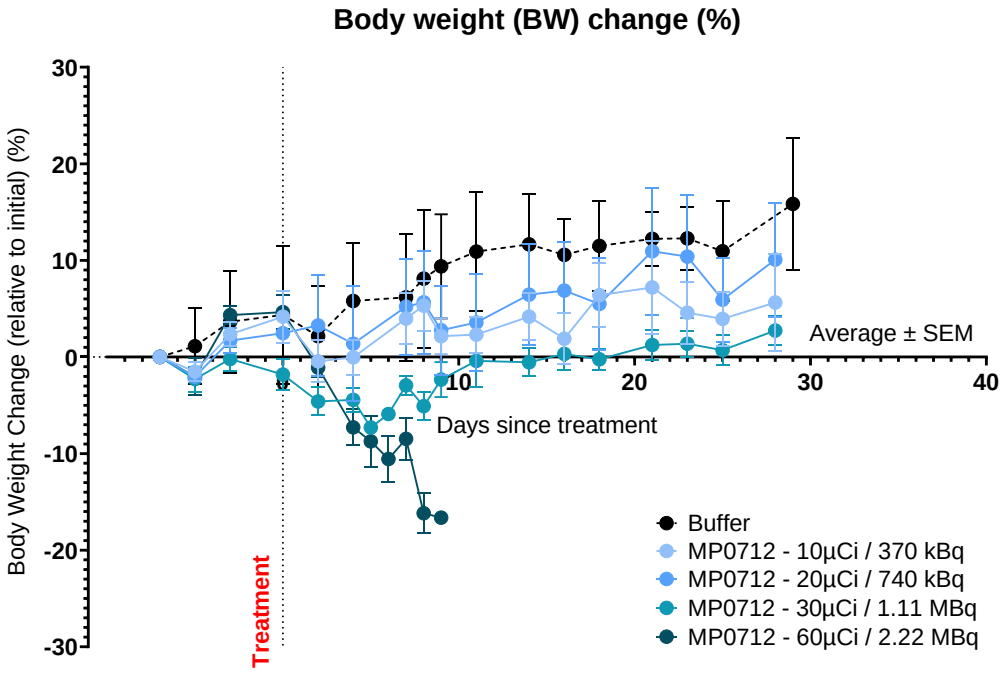


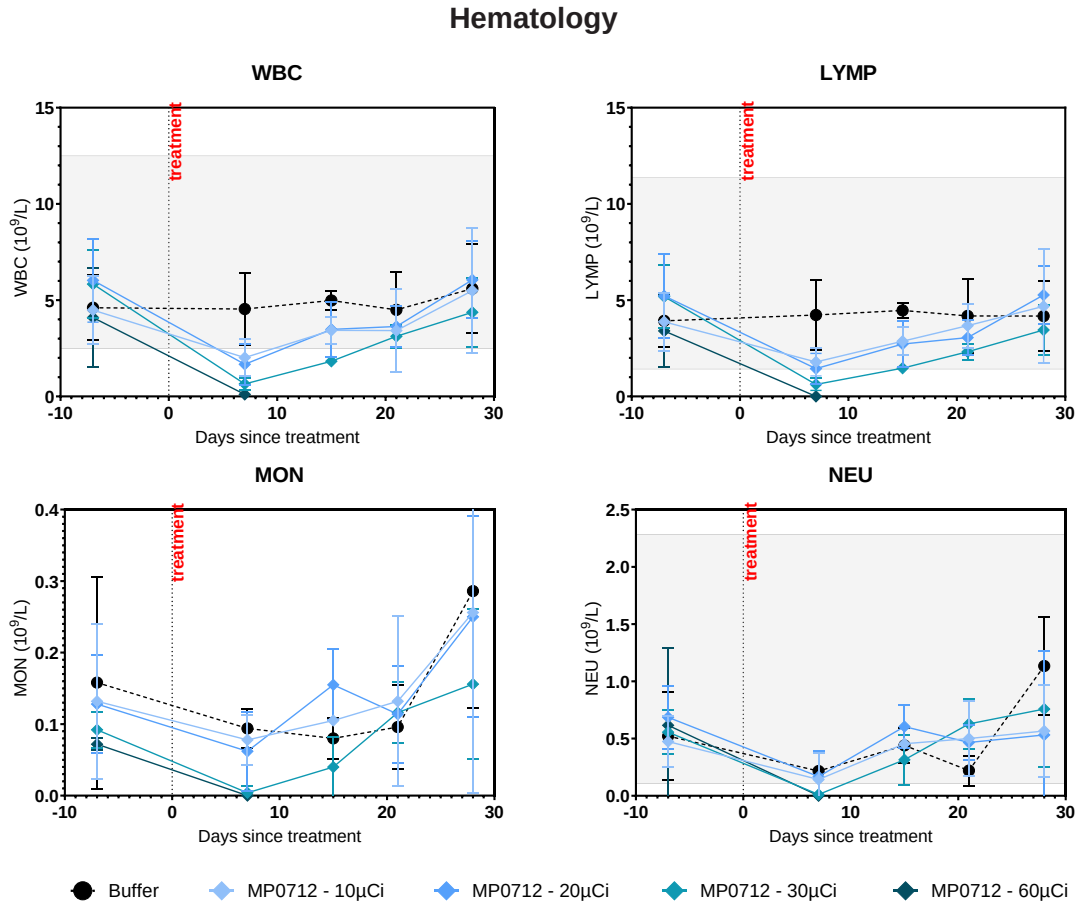




- **MP0712 induces complete a durable tumor regression in NCI-H82 tumor model at 10µCi injected every week**
- **At day 63, complete tumor regression is seen for ~70% of mice at 4 x 10uCi ~20% of mice at 8 x 5uCi**

MP0712 Shows a Favorable Safety Profile

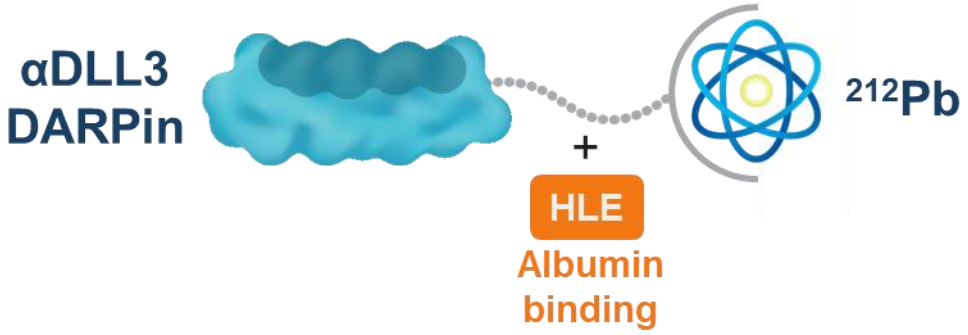




- **Complete recovery of body weight loss after 10 days**
- **Complete recovery of hematologic profile after 28 days**
- **MP0712 treatment up to 30µCi / 1.11 MBq well tolerated**

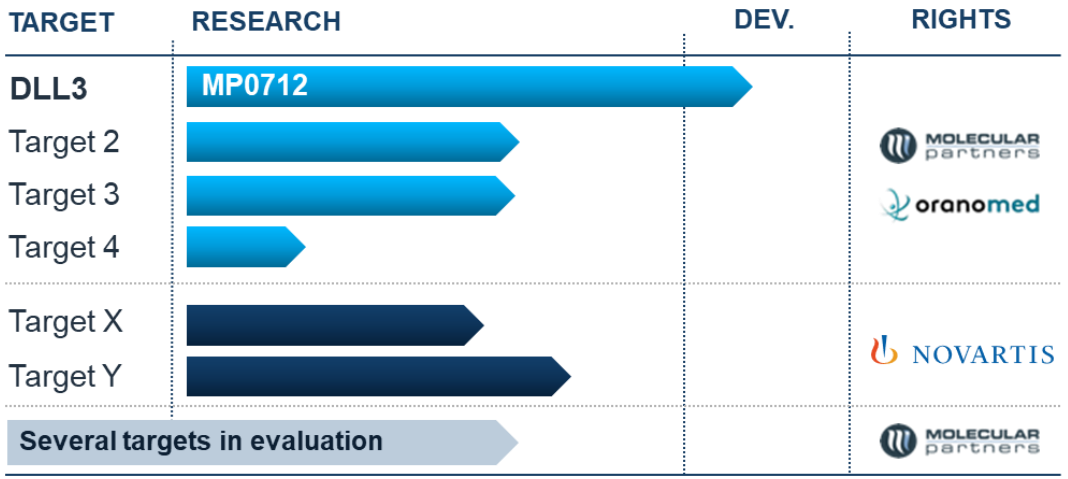
Summary – Radio-DARPin Therapy (RDT) & MP0712

- ✓ **Successful RDT platform optimization**
  - Attractive biodistribution profile (tumor, kidney, blood)
- ✓ **MP0712: ^{212}Pb-DLL3 RDT Lead candidate**
  - High and homogeneous tumor uptake
  - T:K > 2 in mouse models expressing DLL3
  - Good efficacy & tumor regression
  - Favorable safety profile *in vivo* up to 30µCi
- ✓ **IND-enabling package** about to be completed
- ✓ Initial **FIH clinical data expected in 2025**

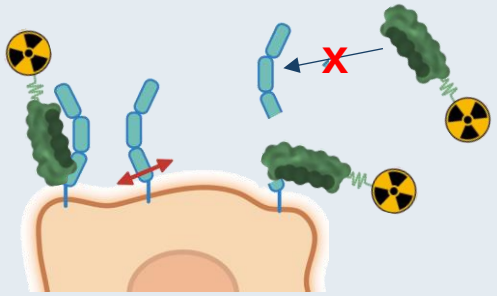


RDT Outlook

- ➢ **Advance MP0712** and additional **pipeline candidates**
- ➢ Continue to evolve RDT platform for **next differentiated RDT programs**
- ➢ **Progress collaboration projects** with Orano Med and Novartis

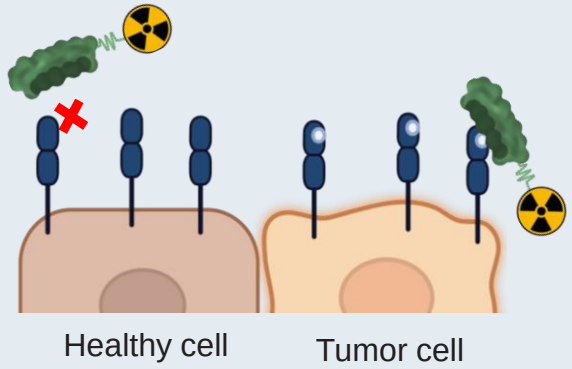


Leveraging DARPin Features to Generate Differentiated RDTs

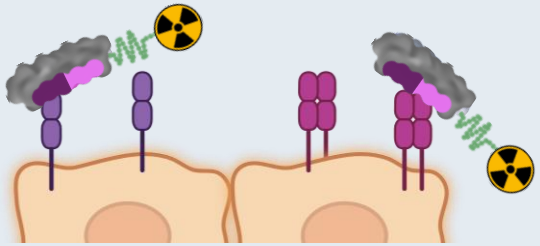


Selectivity for **membrane-bound antigens** over **shed antigens** to prevent antigen sink and ensure high tumor uptake

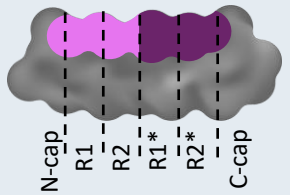
Selectivity for tumor antigens that exhibit **high surface homology** with receptors expressed on healthy cells for safety



2-in-1 DARPin



Small bi-specific DARPins to **enhance tumor distribution** & **address tumor heterogeneity,** especially for targeted α-therapy



Fusion of paratopes into one DARPin

Acknowledgments

Entire Team at Molecular Partners AG

Orano Med Team

oranomed
^{212}Pb for Targeted Alpha Therapy

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Roger Schibli
Martin Behe
Alain Blanc
Tanja Chiorazzo
Stefan Imobersteg

PAUL SCHERRER INSTITUT
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Thank you for your interest!

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