



^{212}Pb -DLL3 Radio-DARPin shows promising Preclinical Antitumor Efficacy in Small Cell Lung Cancer

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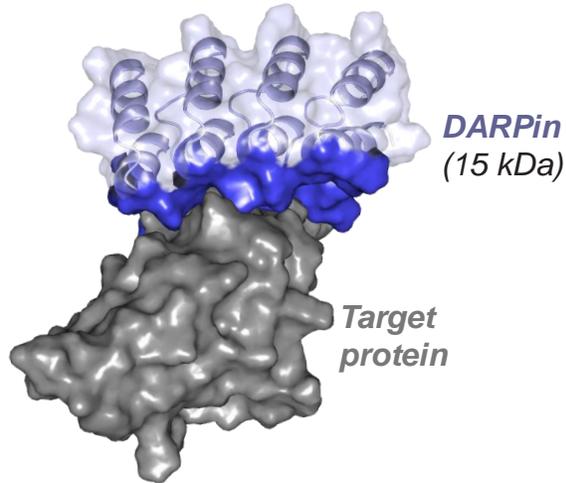
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Disclosures

- The presented research was funded by Molecular Partners and Orano Med
- All authors are employees of Molecular Partners and Orano Med
- Christian Lizak has ownership of stocks in Molecular Partners

DARPin Therapeutics: Opportunity in Nuclear Oncology?

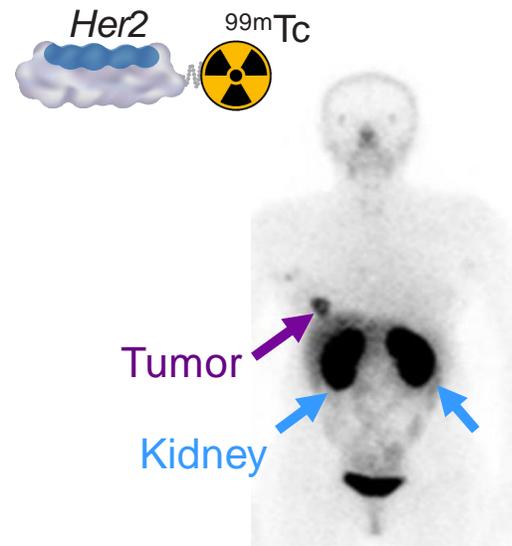
DARPin in Oncology & Beyond



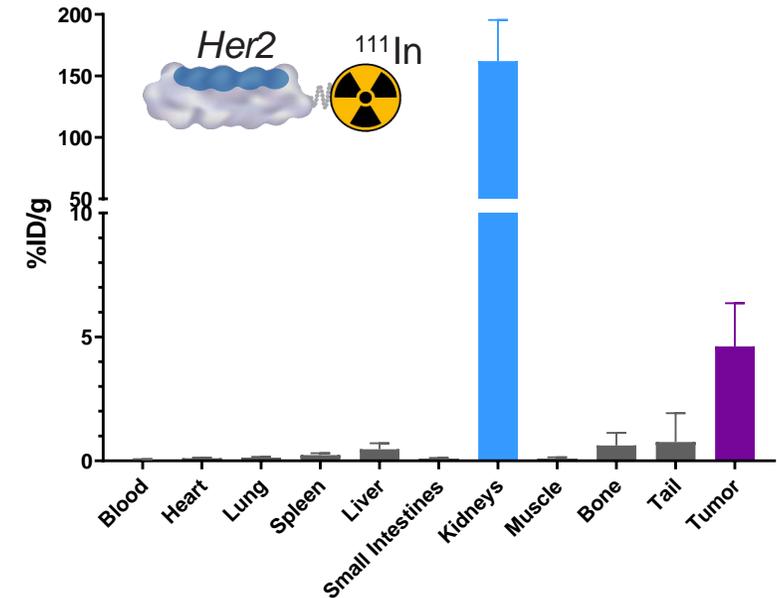
- Close the gap between small molecules & antibodies
- Broad target range, binders against >60 targets
- 7 clinical-stage compounds, >2500 patients treated

The Challenge for Radiotherapeutic Applications

Imaging of Breast Cancer



1st BioD in Tumor Mouse Model

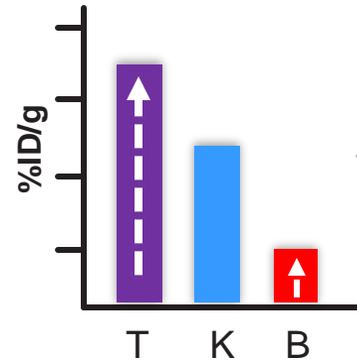
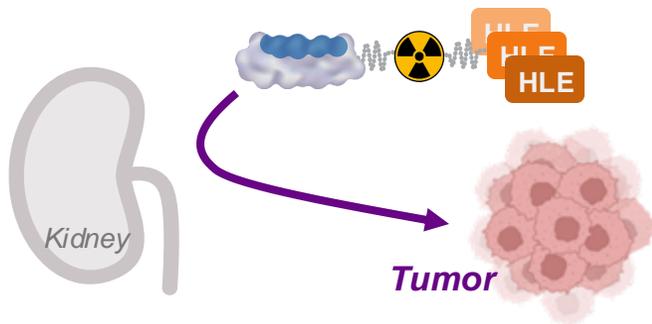


Unlocking DARPins for Radiotherapeutic Applications

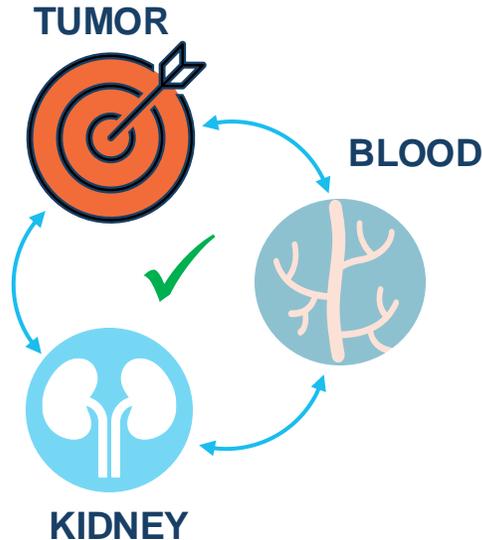
- 1) Increase Tumor Uptake
- 2) Reduce Kidney Accumulation

Radio-DARPin Platform Ready to Deliver Product Candidates

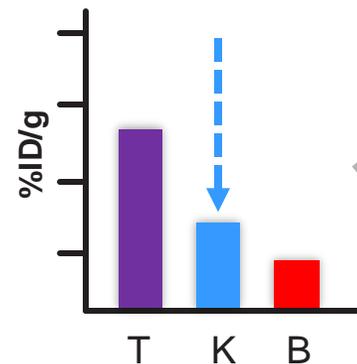
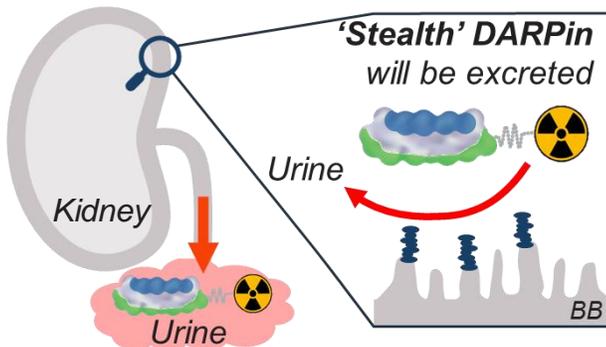
Increased Tumor Uptake
by half-life extension (HLE)*



Optimized Biodistribution Properties



Reduced Kidney Accumulation
by surface engineering (Stealth DARPin)*



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

The first ^{212}Pb -DLL3 Targeted Radiotherapy

Combining distinctive DARPin features with the power of ^{212}Pb for efficacious cancer therapy

SCLC as Indication

- Aggressive cancer with high unmet medical need
 - 2L: mPFS ~3m; 5y OS ~3%^{1,2}
- DLL3 is expressed in >85% of pts³

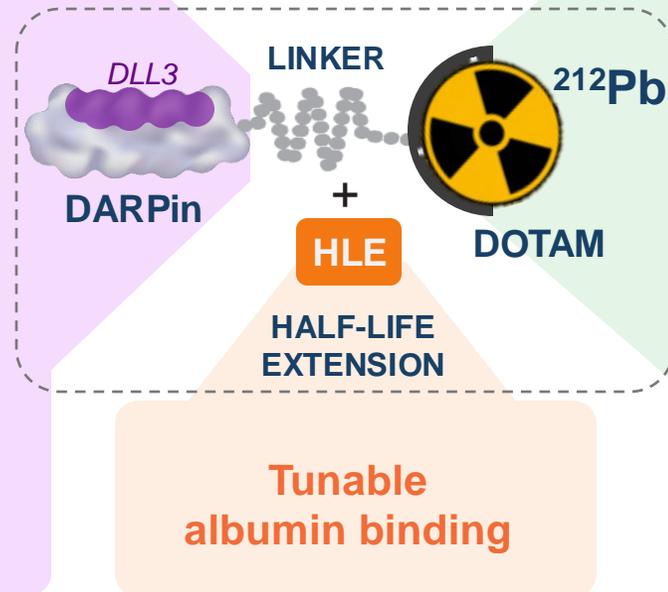
DLL3: A promising Target

- Homogeneous tumor expression, but low expression level in pts
- No expression in healthy tissues
- New treatments with room for improvement: Tarlatamab (AMGEN) for 2L+; ORR ~40%

Diverse set of DARPins against DLL3

- Good developability
- Specific binding with high affinity

PRODUCT COMPOSITION



^{212}Pb for Targeted Alpha Therapy

- Strong cytotoxicity (dsDNA breaks)
- Single alpha decay (limited free daughters)
 - Limited irradiation of healthy tissues
- Relatively short half-life (10.6 h)
 - Fast energy deposition (efficacy)
 - Easier waste management

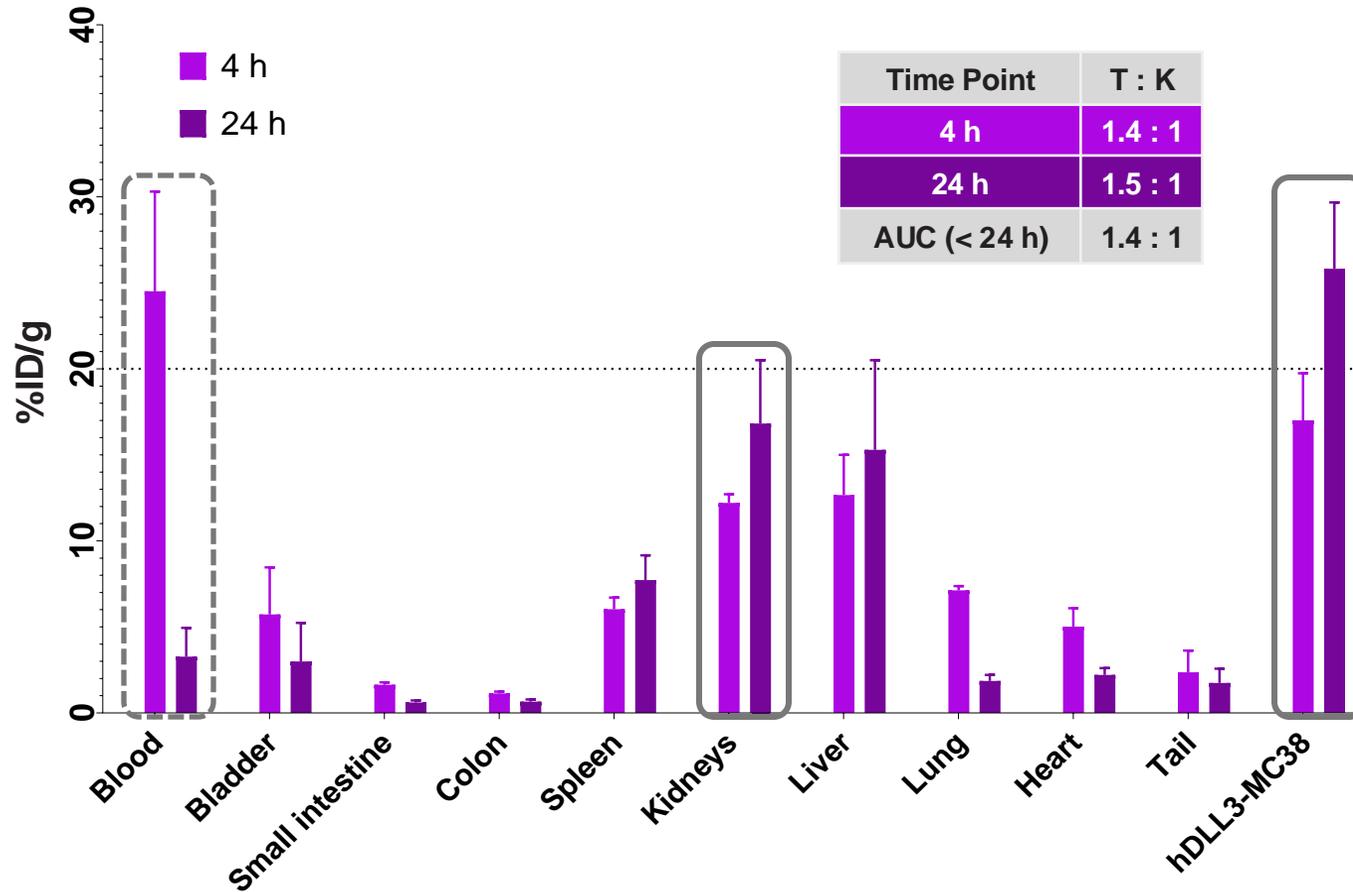
Co-Development with Orano Med

- The leader for ^{212}Pb & a committed partner
- Reliable & scalable ^{212}Pb production
- Independent production capacities (substantial inventory of purified ^{232}Th)

ASCO: Ph2 clinical data ^{212}Pb -DOTAMTATE (AlphaMedixTM) showed an ORR of 55.6%⁴

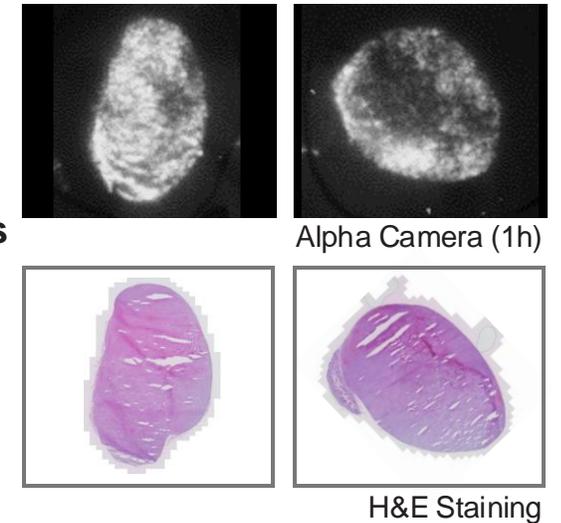
Promising Biodistribution Profile of ^{212}Pb -DLL3 RDT Candidate

MC38-hDLL3 Model with Elevated DLL3 Expression Level *



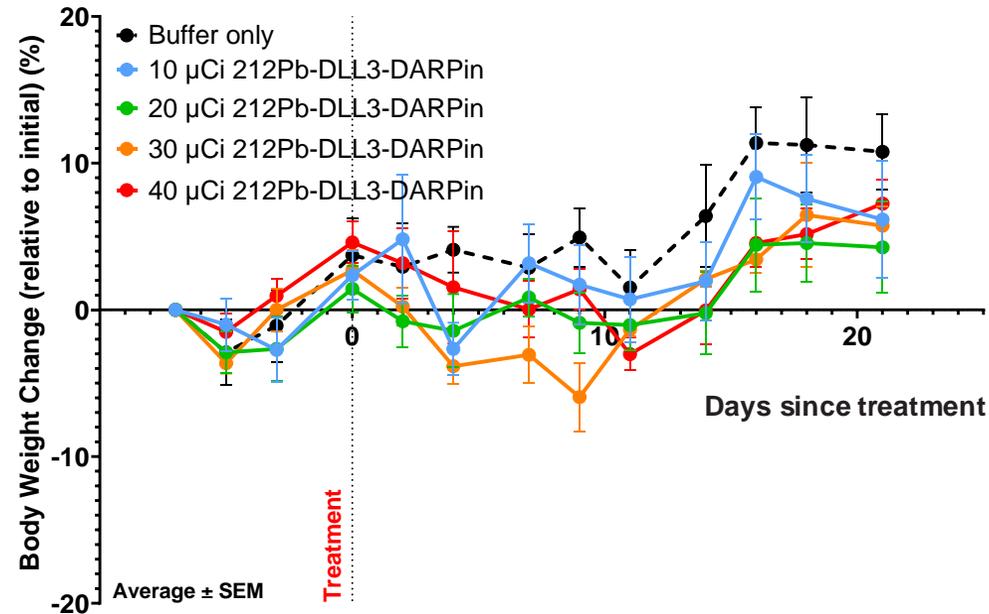
- Positive tumor to non-tumor ratio
→ **Tumor to kidney ratio of 1.4:1 (AUC)**
- Strong and homogenous tumor uptake** confirmed by alpha camera
- Elevated blood levels** (caused by half-life tuning) are **quickly decreasing**

Tumor Sections
(NCI-H82 model)



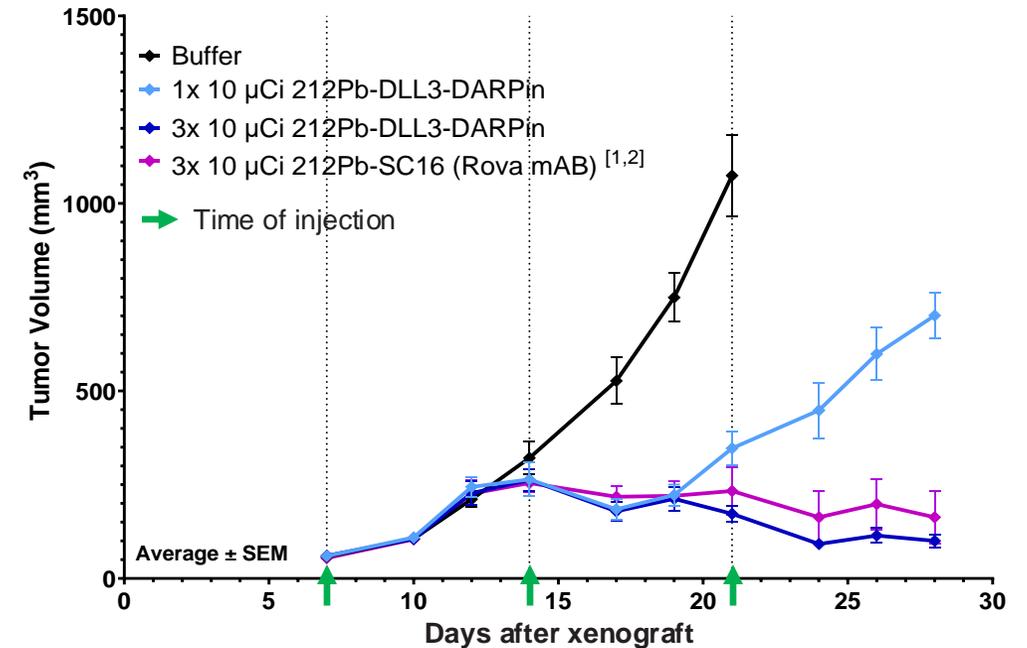
Favorable Safety & Potent Efficacy of ^{212}Pb -DLL3 RDT Candidate

Dose Range Finding in wt Mice



- All treatments up to 40 μCi were well tolerated
- Treatment shows a favorable safety profile suggesting its potential for clinical use

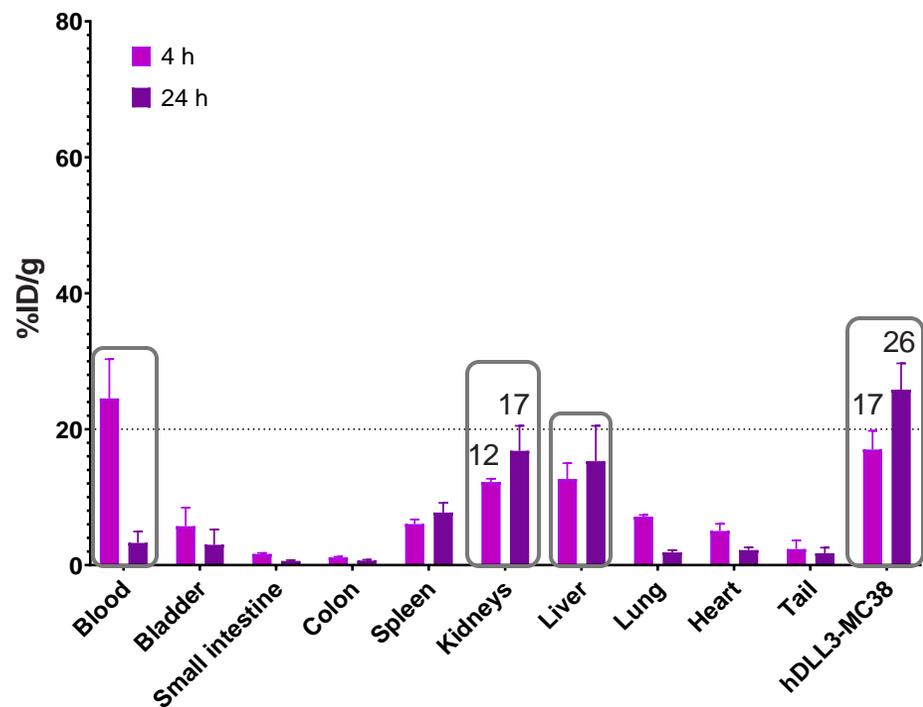
Efficacy in MC38-hDLL3 Model



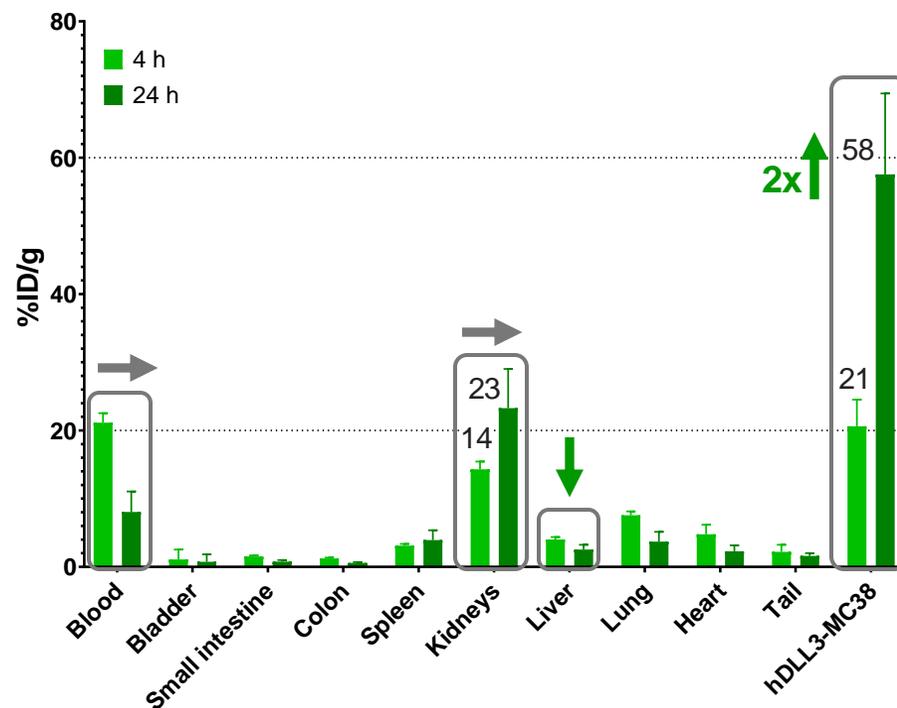
- Significant and durable inhibition of tumor growth (comparable to benchmark mAB)
- Treatment shows profound antitumor activity at clinically relevant dose

MP0712: ^{212}Pb -DLL3 Lead Candidate with Attractive BioD Profile

Reminder: BioD Profile of Previous DLL3 RDT Construct



NEW: Strongly Improved BioD Profile of RDT Lead Candidate



Time Point	T : K
4 h	1.4 : 1
24 h	2.5 : 1
AUC	2.1 : 1

- **MP0712 Lead Candidate** shows encouraging BioD profile with **T:K Ratio >2** in MC38 model
- Similar profile in NCI-H82 model (patient relevant DLL3 expression) with T:K Ratio >1 (data not shown)

Summary – Radio-DARPin Therapy (RDT)

- ✓ Successful RDT platform optimization for reduced kidney accumulation and increased tumor uptake
- ✓ **MP0712 selected as Lead Candidate for ^{212}Pb -DLL3 targeted Radio-DARPin Therapy**
- ✓ IND-enabling activities initiated with Orano Med; **FIH clinical data expected in 2025**



TARGET	RESEARCH	DEV.	RIGHTS
DLL3	MP0712		MOLECULAR partners
Target 2*			oranomed
Target A			MOLECULAR partners
Target B			
Target X			NOVARTIS
Target Y			
Several targets in evaluation			

Outlook:

- **Advance MP0712 and additional pipeline candidates**
- **Evolve RDT platform**
- **Progress collaboration projects with Orano Med and Novartis**

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Entire Team at Molecular Partners AG



Orano Med Team

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Aaron Schatzmann

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Thank you for your interest!

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