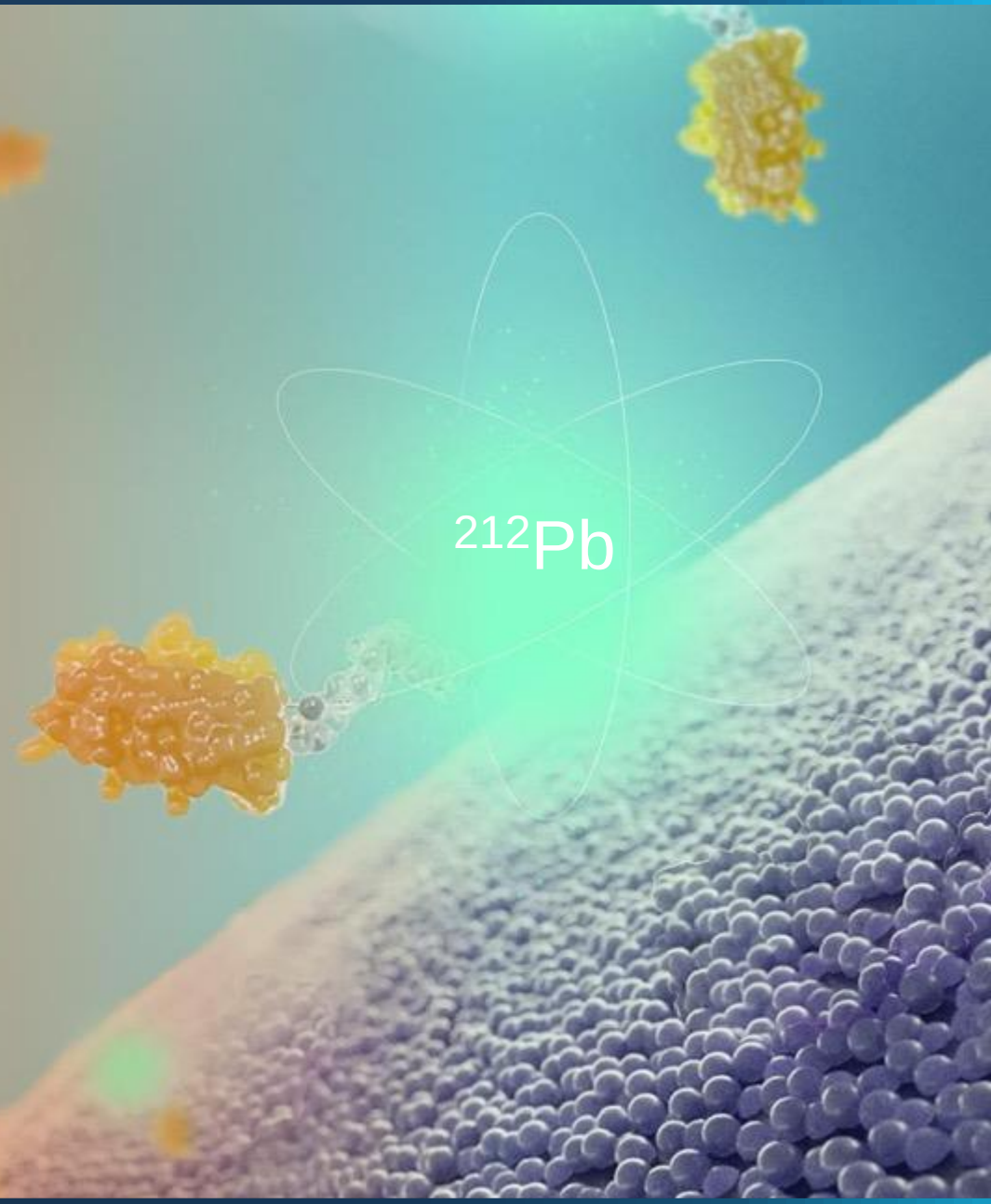
MOLECULAR partners

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



Christian Lizak, PhD

SNMMI, June 11th, 2024

Innovate. Illuminate.
June 8-11 2024 SNMMI ANNUAL MEETING CANADA TORONTO

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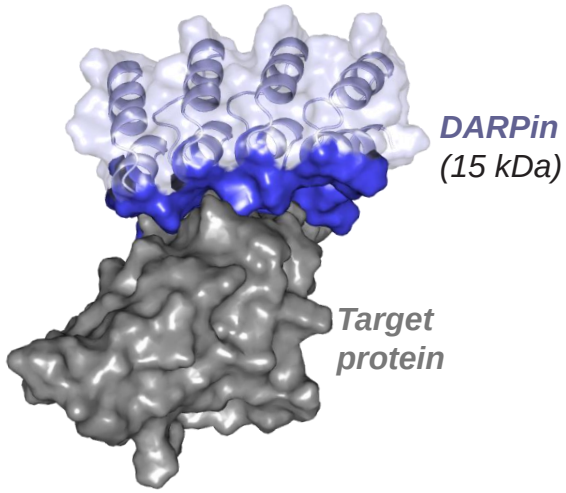
- All authors are employees of Molecular Partners and Orano Med
- Christian Lizak has ownership of stocks in Molecular Partners

DARPin Therapeutics: Opportunity in Nuclear Oncology?

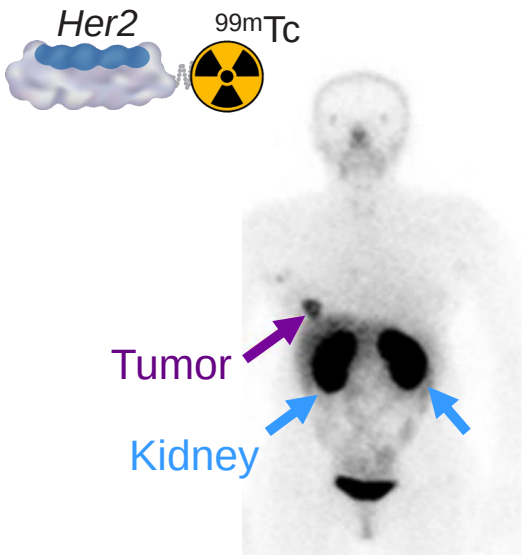
DARPins in Oncology & Beyond



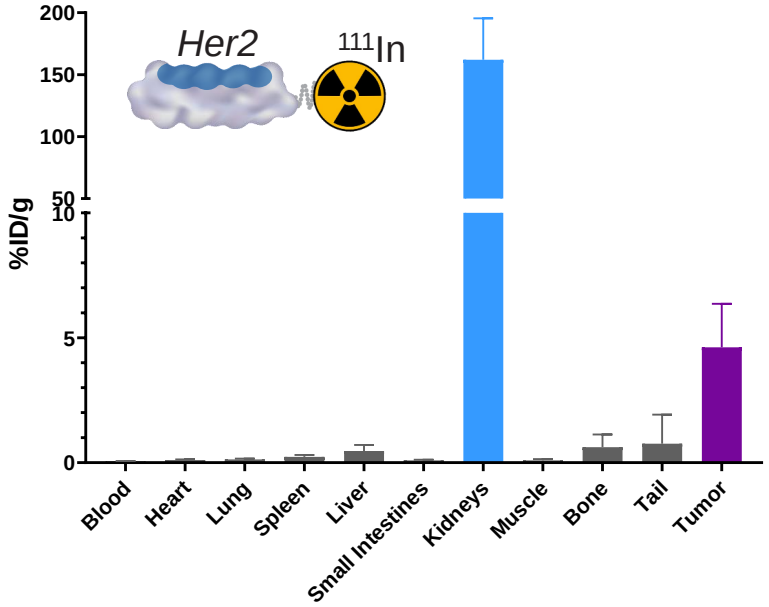
- Close the gap between small molecules & antibodies
- Broad target range, binders against >60 targets
- 7 clinical-stage compounds, >2500 patients treated

The Challenge for Radiotherapeutic Applications

Imaging of Breast Cancer



1st BioD in Tumor Mouse Model



Unlocking DARPins for Radiotherapeutic Applications

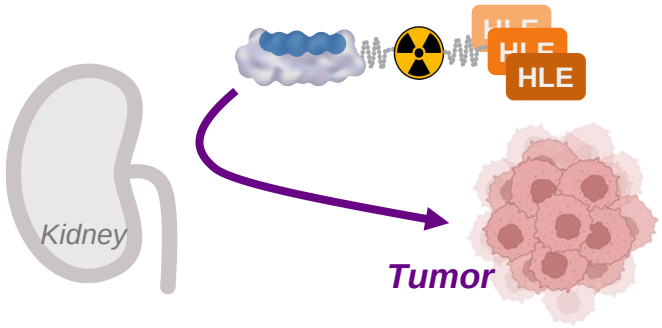
1) **Increase Tumor Uptake**
2) **Reduce Kidney Accumulation**

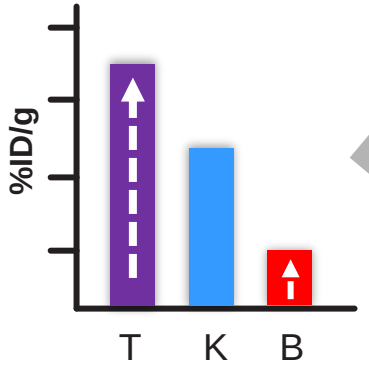
Adopted from Bragina *et al., J Nuc Med*, 2021

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

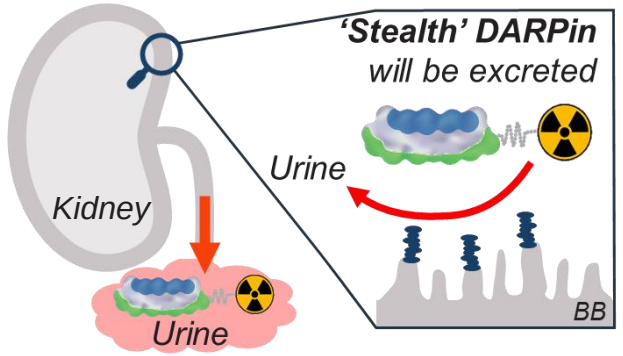
Radio-DARPin Platform Ready to Deliver Product Candidates

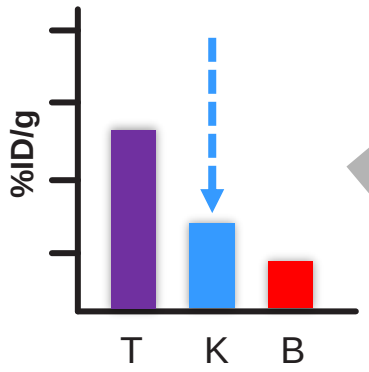
Increased Tumor Uptake
by half-life extension (*HLE*)*



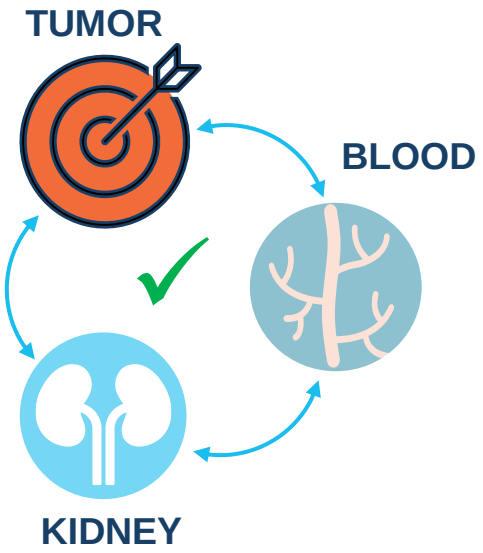


Reduced Kidney Accumulation
by surface engineering (*Stealth DARPin*)*





Optimized Biodistribution Properties



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*

MOLECULAR partners

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

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 pts**[3]

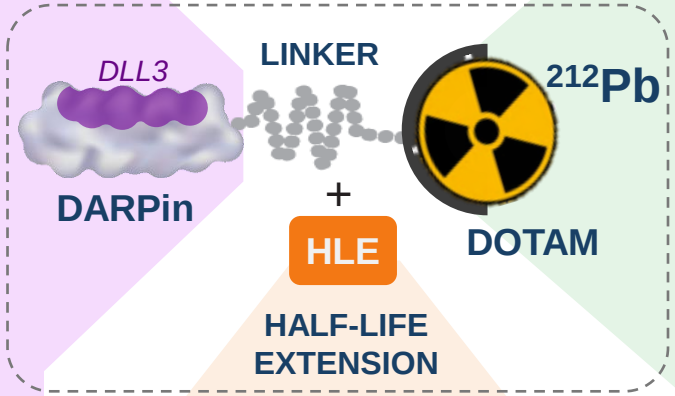
DLL3: A promising Target

- **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



Tunable albumin binding

^{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

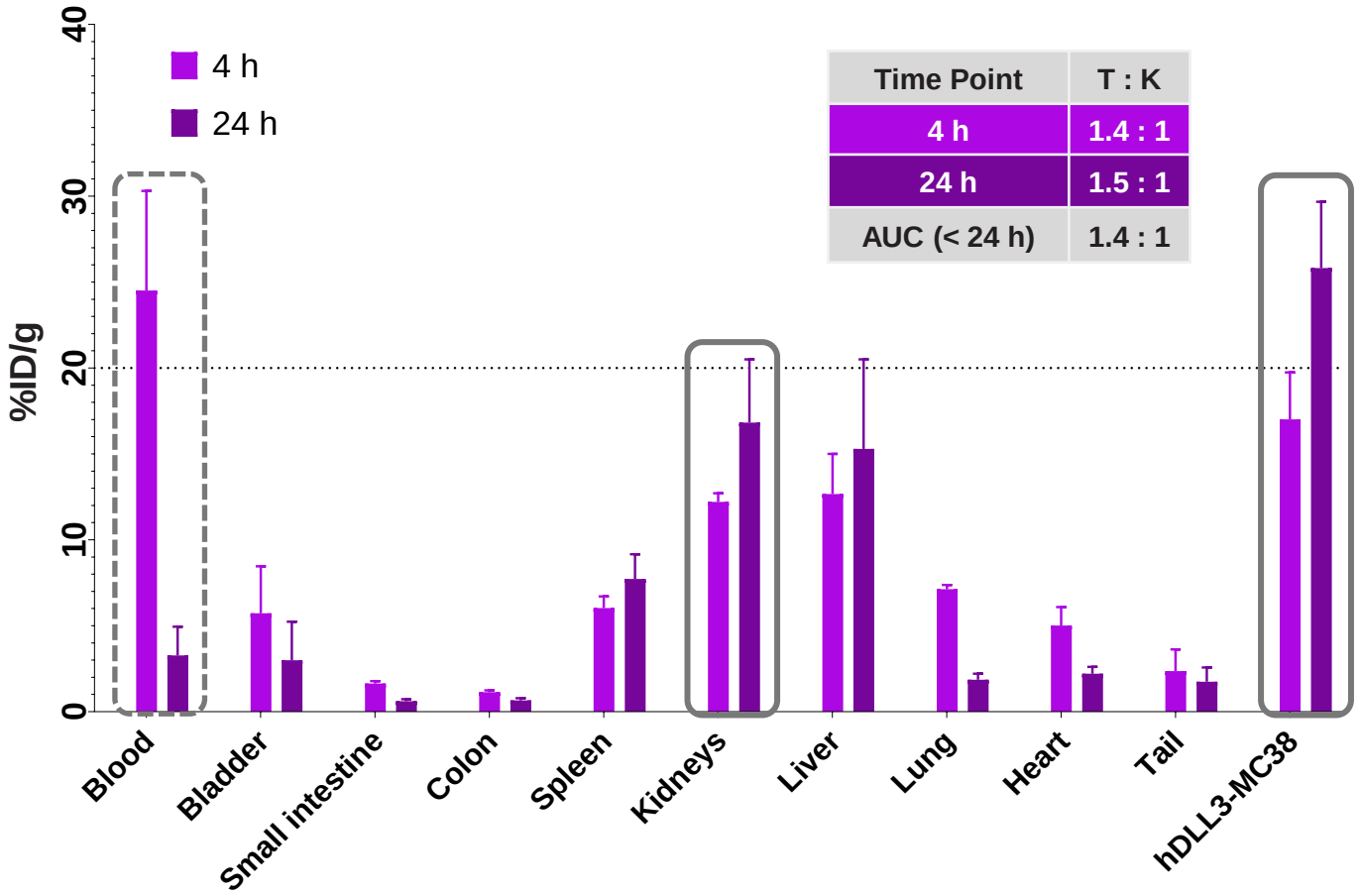
- The **leader for ^{212}Pb** & a committed partner
- **Reliable & scalable ^{212}Pb production**
- **Independent production** capacities (substantial inventory of purified ^{232}Th)

***ASCO**: Ph2 clinical data **^{212}Pb-DOTAMTATE** (AlphaMedix™) showed an **ORR of 55.6%** [4]*

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 presentation

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

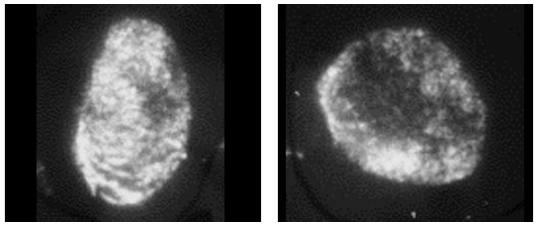
MC38-hDLL3 Model with Elevated DLL3 Expression Level *



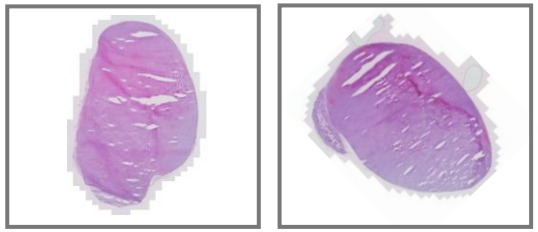
Time Point	T : K
4 h	1.4 : 1
24 h	1.5 : 1
AUC (< 24 h)	1.4 : 1

- 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)



Alpha Camera (1h)



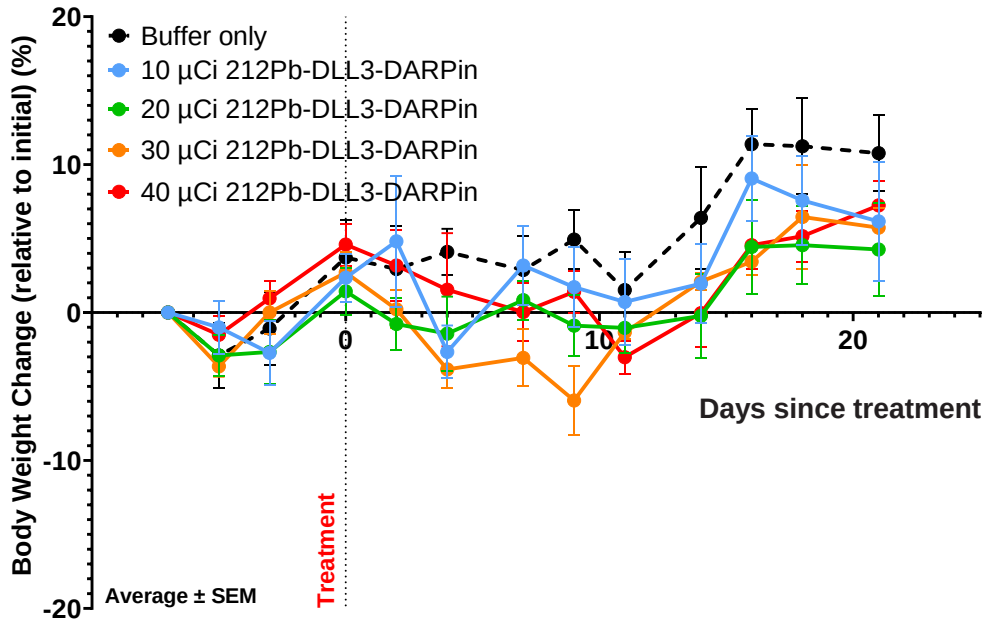
H&E Staining

Mice xenografted s.c. with hDLL3-MC38 (Biocytogen)
Dose: 10 µCi of ^{212}Pb at 0.01 mg/kg of DLL3 DARPin

** other healthy organs with levels ≤ 5%ID/g not shown*

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

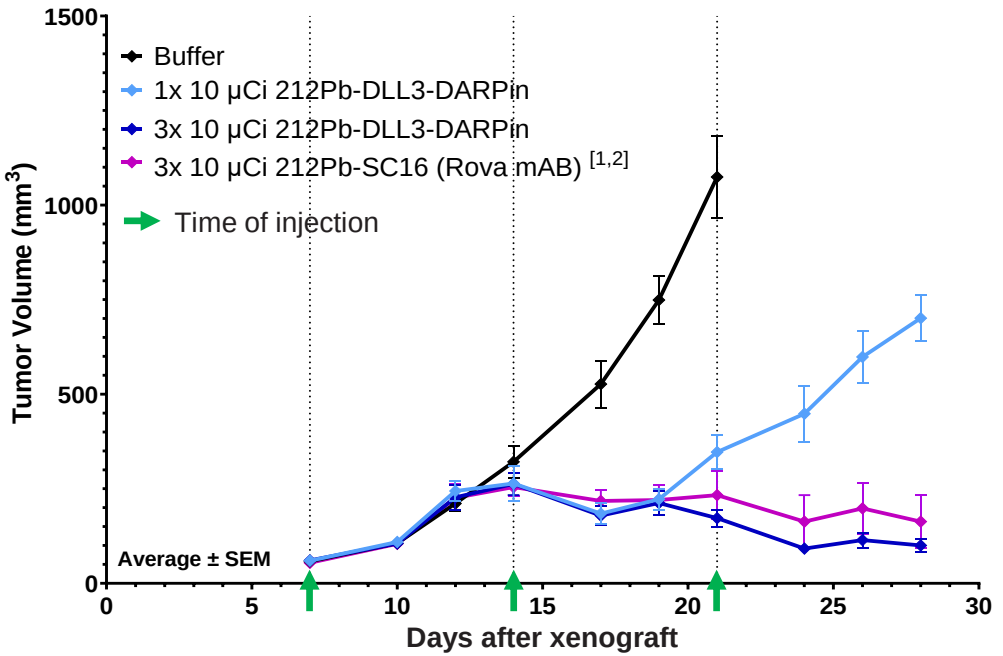
Dose Range Finding in wt Mice



- 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**

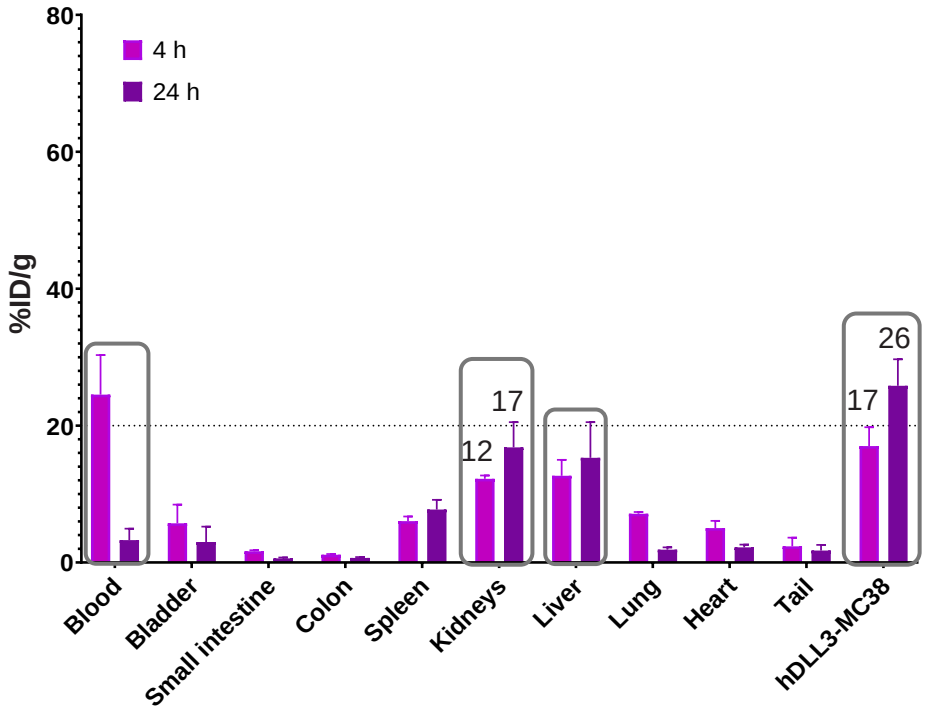
CD1 wt mice
Dose: 10 to 40 µCi of ^{212}Pb at 0.01 mg/kg of DLL3 DARPin

Mice xenografted s.c. with hDLL3-MC38 (Biocytogen)
Dose: 10 µCi of ^{212}Pb at 0.01 mg/kg of DLL3 DARPin

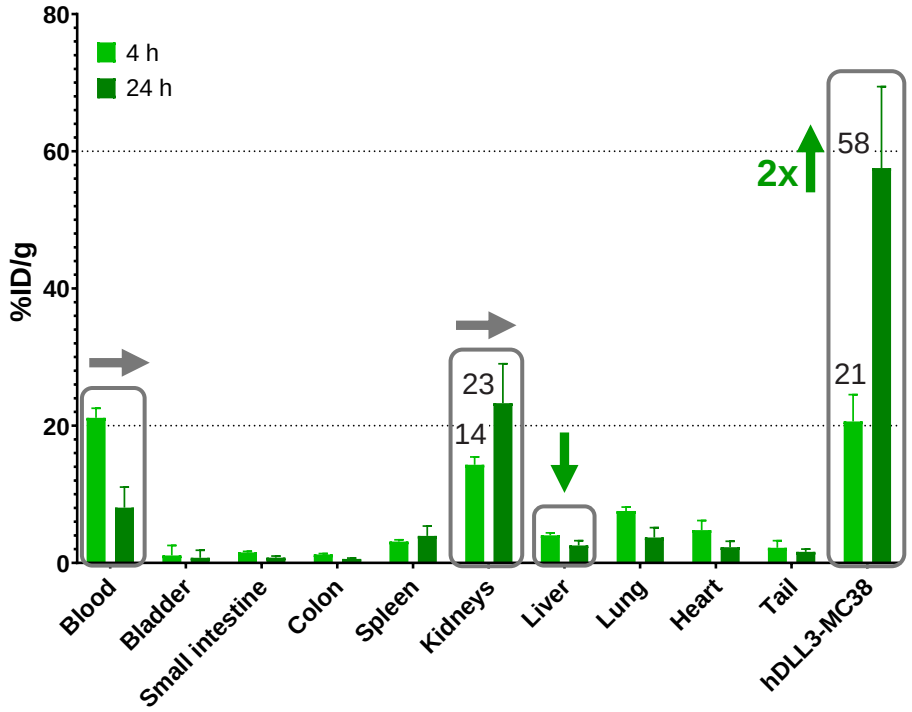
[1] Sharma *et al., Cancer Res*, 2017; [2] Korsen *et al., PNAS*, 2022

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**



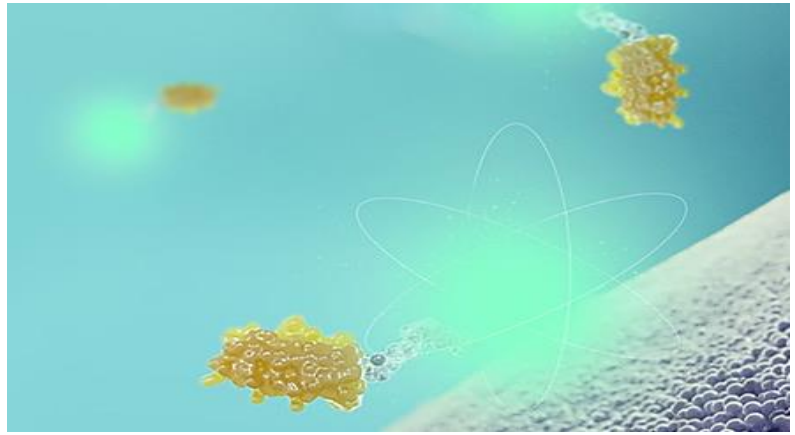
Time Point	T : K
4 h	1.4 : 1
24 h	2.5 : 1
AUC	2.1 : 1

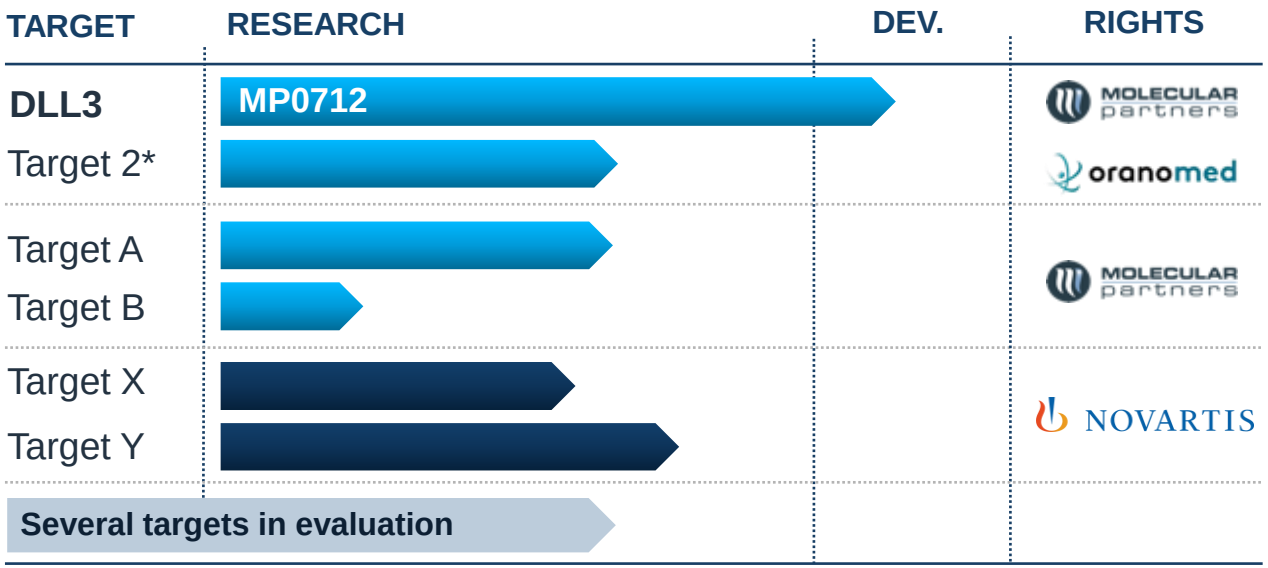
- **MP0712 Lead Candidate** shows encouraging BioD profile with **T:K Ratio >2** in MC38 model
- Similar profile in NCI-H82 model (patient relevant DLL3 expression) with T:K Ratio >1 (data not shown)

Mice xenografted s.c. with hDLL3-MC38 (Biocytogen)
Dose: 10 µCi of ^{212}Pb at 0.01 mg/kg of DLL3 DARPin

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**





Outlook:

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

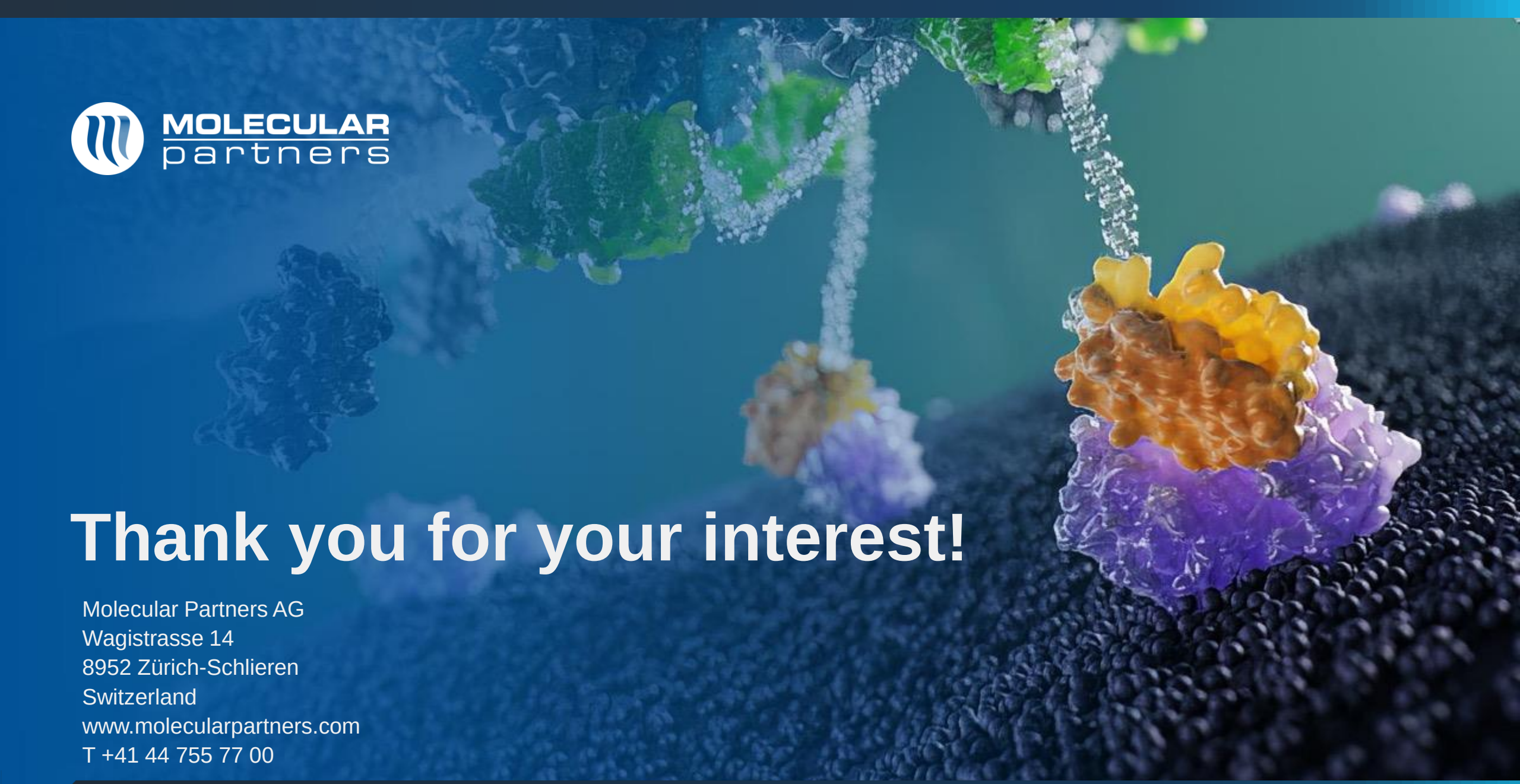
* The co-development agreement with Orano Med includes up to 3 potential oncology targets including DLL3 (Delta-like ligand 3)

Acknowledgments

Entire Team at Molecular Partners AG

Orano Med Team

Julien Torgue
Amal Saidi
Aaron Schatzmann
Tania Stallons
Amy Wong
Federico Rojas



Thank you for your interest!

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