Molecular characteristics of MP0712, a clinical stage ^{212}Pb-based Radio-DARPin candidate for targeted anti-DLL3 radiotherapy of small cell lung cancer (SCLC)

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Introduction

- SCLC is an aggressive neuroendocrine malignancy with limited treatment options
- DLL3 is expressed on the cell surface of SCLC, while largely absent on healthy tissues, making it an attractive target for precision radiotherapy
- We developed MP0712, a clinical-stage DLL3-targeting alpha radioligand therapy combining a high-affinity designed ankyrin repeat protein (DARPin) with the therapeutic isotope ^{212}Pb
- MP0712 showed a favorable safety profile, biodistribution and antitumor efficacy in mice[1,2]
- First patient imaging data with ^{203}Pb from compassionate care showed robust tumor uptake of MP0712 that increased throughout the imaging period (116 h; Fig. 1A), while the washout from healthy organs, including kidney, was visible from 24 h onwards (Fig. 1B)[3,4]
- In this study, we describe the molecular characteristics that underpin the favorable biodistribution profile of MP0712

Initial SPECT/CT imaging demonstrates tumor uptake of ^{203}Pb-MP0712

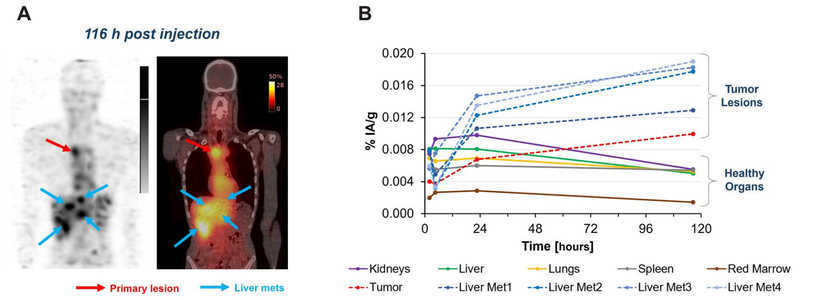
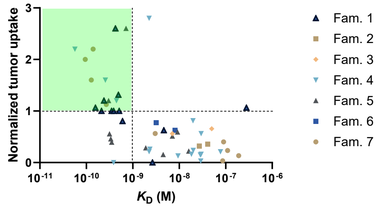


Figure 1: First-in-human data of MP0712 from a named patient access program under South Africa's Section 21 compassionate care framework in patients with SCLC and other DLL3$^+$ neuroendocrine cancers.[3,4] **A)** SPECT/CT imaging 116 h post injection and **B)** biodistribution profile of ^{203}Pb-MP0712 in a patient with metastatic SCLC.

Affinity is one key property driving tumor uptake of anti-DLL3 DARPins

Tumor uptake in NCI-H82 biodistribution studies

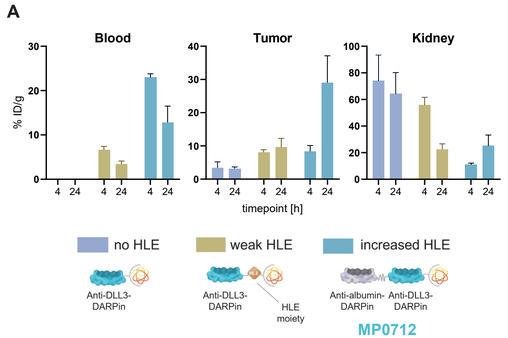


- Anti-DLL3 DARPins in picomolar affinity range are associated with enhanced tumor uptake

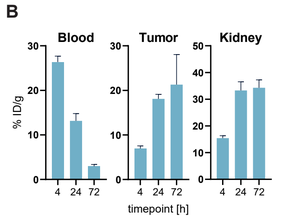
Figure 2: Tumor uptake of anti-DLL3 DARPins at 4 h (0.01 mg/kg, 0.37 MBq, ^{212}Pb, ATH mice, NCI-H82 s.c. tumors). Data from n=4 biodistribution studies, normalized to a reference DARPin (tumor uptake set to 1). Fam. = family. Green area depicts that DARPins with increased tumor uptake are associated with a higher affinity.

Half-life extension (HLE) sustains tumor uptake over time

Impact of half-life on biodistribution



MP0712 time course



DLL3 expression

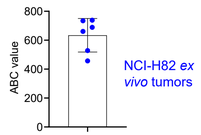


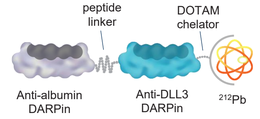
Figure 3: A) Biodistribution profile of anti-DLL3 DARPins with no, weak, or increased HLE at 4 h and 24 h (0.01 mg/kg, 0.37 MBq, ^{212}Pb). Weak HLE moiety contains a DOTA chelator, the other two DARPins contain DOTAM. **B)** Extended time course of MP0712 (0.1 mg/kg, 0.74 MBq, ^{203}Pb). For A and B: ATH mice, NCI-H82 s.c. tumors, mean + SD from 4–6 individual mice. **C)** Antibody binding capacity (ABC) determined by Flow Cytometry in NCI-H82 tumors.

Tumor uptake increases with blood levels

- Increased HLE boosts tumor uptake over time (Fig. 3A)
- Biodistribution in mice is generally consistent with initial patient imaging data[3,4], except for kidney: washout occurs after 24 h in patients, whereas murine kidney uptake persists up to 72 h (Fig. 3B)
- Notably, increased tumor uptake is achievable in a DLL3-low model (ABC values ~ 600, Fig. 3C) consistent with the upper range of DLL3 expression observed in SCLC tumors

MP0712 combines high DLL3 affinity and half-life extension

Molecular structure



Affinity (SPR)

B

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

Cell binding

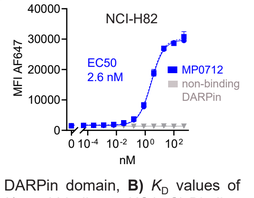
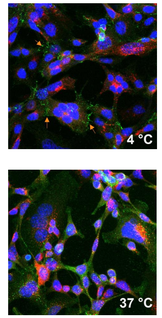
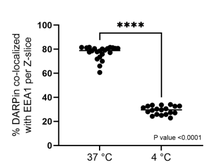


Figure 4: A) Design of MP0712 with one HSA-binding and one DLL3-binding DARPin domain, **B)** K_D values of MP0712 binding to hDLL3 in absence and presence of human serum albumin (HSA), and binding to HSA, **C)** Binding of MP0712 to NCI-H82 cells assessed by Flow Cytometry.

DLL3 recycling could support sustained tumor uptake of MP0712

Microscopy of internalized MP0712





Internalization kinetics

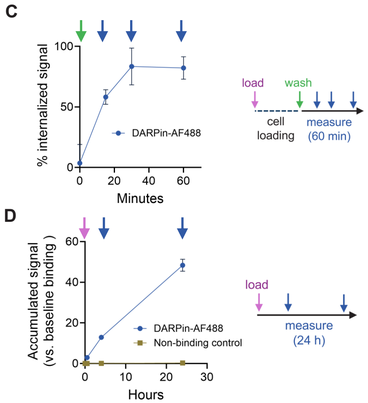


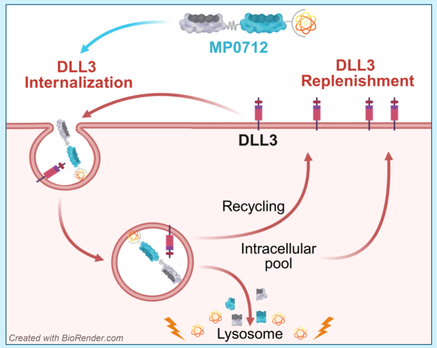
Figure 5: A) Staining of MP0712 after 3 h incubation at 4 °C or 37 °C on PFA-fixed cells, readout by confocal microscopy. **B)** Quantification of the co-localized signal of EEA1 (*Early Endosome Antigen 1*, marker of early endosomes) and MP0712 shown in A). **C)** Internalization kinetics of pre-bound MP0712, **D)** Internalization of DARPin provided in excess over 24h.

MP0712 internalizes rapidly *in vitro* and accumulates over time

- Upon internalization, MP0712 co-localizes with the endosomal compartment (Fig. 5A and B)
- Pre-bound MP0712 internalizes rapidly (Fig. 5C). In the presence of excess ligand, DLL3$^+$ cells accumulate several-fold more DARPin than the surface-bound fraction within 24 h, indicating multiple rounds of internalization and replenishment of DLL3 binding sites (Fig. 5D).

Discussion and Outlook

- Initial patient imaging shows robust tumor accumulation of MP0712[3,4], in line with our data from preclinical models[1,2]
- The data presented here suggest that HLE may offer a target-specific advantage: despite low surface density, repeated internalization-replenishment cycles of DLL3 could allow efficient tumor loading of MP0712 without saturating binding sites
- MP0712 is currently evaluated in a first-in-human phase I study in SCLC and other DLL3+ tumors (NCT07278479)



Conflict of interest disclosures: SR, FM, CR, NP, AE, MM, JR, MG and DS are employees and stock owners of Molecular Partners; ASa, ASc, TS, and AW are employees of Orano Med. JT was employee of OranoMed at the time the study was conducted.

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For any questions, please contact: info@molecularpartners.com / attention of Stefanie Riesenberg or Daniel Steiner.

References: [1]Croset et al., AACR 2025; [2]Saidi et al., manuscript in preparation; [3]Kabunda (NuMeRi) et al., TWC 2026; [4]Lizak et al., TWC 2026.