

A minimal physiologically-based pharmacokinetic/pharmacodynamic mouse xenograft model to inform the evaluation of ²¹²Pb-based Radio-DARPin targeting DLL3

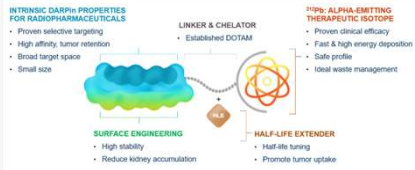
Sarah Minucci¹, Marc Presler¹, Josh Apgar¹, Josh Grant¹, Paul Baverel², Kyriaki Ioannou², Amal Saidi³, Amelie Croset², Andreas Bosshart², Julien Torgue⁴, and Michael T. Stumpp²

¹Certara Biosimulations, Sheffield, UK, ²Molecular Partners AG, Zurich-Schlieren, Switzerland, ³Orano Med Theranostics SAS, Paris, France, ⁴Orano Med Theranostics LLC, Plano, Texas, USA.

Background

- MP0712 is a novel radiopharmaceutical candidate composed of a Designed Ankyrin Repeat Protein (DARPin) vector, targeting DLL3, and the short-lived alpha particle-emitting radioisotope ²¹²Pb
- DLL3 is highly expressed on the tumor cell surface in neuroendocrine carcinomas such as small cell lung cancer (SCLC), with cytoplasmic localization in healthy tissues, allowing for selective delivery of radiation to tumors while reducing systemic exposure and minimizing damage to healthy tissues
- MP0712 has been evaluated in preclinical models for its biodistribution, efficacy and safety¹, and first clinical data are expected in H2 2025

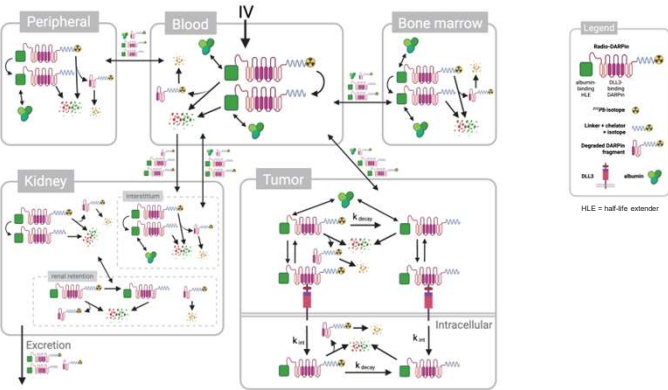
MP0712 drug features, incl. ²¹²Pb payload, an in-vivo generator of alpha particles



Methods: Model structure and development

A minimal physiologically-based PK/PD (PBPK/PD) mouse model of ²¹²Pb-MP0712 was developed to explore the impact of drug and target properties on the biodistribution of MP0712

Minimal PBPK/PD model schematic developed for ²¹²Pb-MP0712 in mice

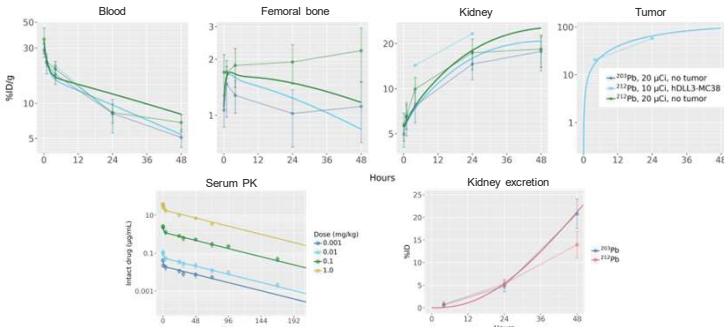


Model features include:

- Blood, peripheral, bone marrow, tumor and kidney compartments
- Binding of drug to DLL3, internalization and residalization in tumor
- DLL3 expression levels, evaluated in two preclinical tumor models in mice: hDLL3-MC38 for model calibration, and NCI-H82 (lower target expression) for model validation
- Albumin binding, explicitly modeled to recapitulate free drug and albumin-bound drug behaviors
- Disposition of the drug, described by first-order elimination rates representing the catabolic clearance of the DARPin and bi-directional intercompartmental transport in relevant tissues
- Trafficking into kidney and retention was modeled by incorporation of a transit compartment to reflect a delayed excretion mechanism
- Bone marrow radioactivity was inferred assuming drug evenly distributes throughout the bone
- Radioactive decays of ²¹²Pb-MP0712 and ²⁰³Pb-MP0712 were described with first-order rates representative of each radionuclide physical half-life (10.6 h for ²¹²Pb and 52 h for ²⁰³Pb), resulting in the formation of stable ²⁰⁸Pb and ²⁰³Tl respectively
- Daughter radionuclides of ²¹²Pb were not explicitly modeled
- First-order degradation of intact DARPin into a pool of fragments was assumed in all compartments

Model calibration and data used for model development

PBPK model calibration for radioactive ²¹²Pb-MP0712 across organs and serum PK of the vector



The minimal physiologically-based PBPK/PD mouse model of ²¹²Pb-MP0712 was calibrated based on several datasets:

- Mass-balanced data derived from serum exposure levels of non-radiolabelled MP0712 in mice
- Target expression levels obtained by flow cytometry in cell lines used in mouse xenografts (hDLL3-MC38 tumor-bearing mice data were used for model calibration)
- Literature data to inform initial model parameters^{2,3,4}
- Activity expressed in %ID/g (% injected dose per gram of tissue) in relevant organ tissues and excretion data obtained from several biodistribution studies in non-tumor bearing and xenograft mice

Acknowledgments: BioRender was used to generate the model schematic displayed in the Methods section.

Disclosures: All authors with affiliation 1) are employees of Certara; all authors with affiliation 2) are employees and stock owners of Molecular Partners; and all authors with affiliation 3) and 4) are employees of Orano Med Theranostics.

For any questions, please contact: info@molecularpartners.com / attention of Paul Baverel.

This poster was presented at PAGE 2025 (4-6 June, Thessaloniki, Greece).

Objectives

The objectives of this work were to develop a minimal PBPK/PD model:

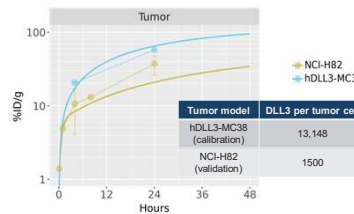
- To explore the biodistribution of MP0712
- To quantify ²¹²Pb % injected dose and activity profiles in relevant organs and identify determinants of tumor uptake to guide target compound profile

Key takeaways

- A minimal PBPK/PD model was developed for MP0712, a novel ²¹²Pb-based Radio-DARPin candidate targeting DLL3 and intended for treatment of relapsed/refractory SCLC patients
- The model showed good predictive features across xenograft mice models of varying expression of DLL3 and predicts that MP0712 has a favorable therapeutic index based on mouse data, with a tumor to kidney ratio >1, consistent with the observed data
- The model simulations showed:
 - Tumor uptake is nonlinearly associated with target expression
 - Affinity maturation for the target beyond a single digit nM affinity constant results in marginal improvements
 - Onset of tumor uptake is insensitive to target internalization rate, receptor density, and tumor size
- Additional translational work is currently ongoing to expand the model for dosimetry estimation of absorbed doses in target organs and tumors of SCLC patients
- Our quantitative framework aims to serve as a translational tool to guide future designs of DARPin-based radiopharmaceutical therapies for cancer patients

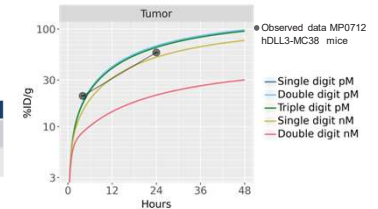
Model validation and impact of parameters on tumor uptake

External validation of the PBPK/PD model on tumor uptake data with lower DLL3 expression levels



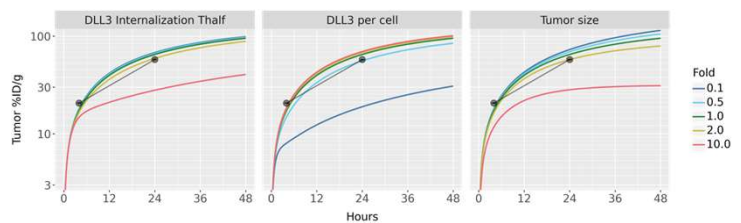
The model simulations showed a good match with the tumor biodistribution time-course data of ²¹²Pb-MP0712 in NCI-H82 cell lines, simply by varying the target expression level parameter

Affinity maturation on tumor uptake



Model simulations showed that higher affinity of MP0712 for DLL3 (low Kd) does not have a significant effect on tumor uptake beyond single digit nM range

Simulated tumor profiles of ²¹²Pb-MP0712 when varying DLL3 expression (internalization half-life, and receptor density), and tumor size



Model simulations showed that onset of tumor uptake was insensitive to DLL3 internalization rate, DLL3 receptor density per cell, and tumor size over a 0.1-10-fold range of initial parameter values

Model simulations to quantify activity in normal organs & tumors

Predicted activity levels of ²¹²Pb and therapeutic index of MP0712

Tumor model	Activity AUC per gram: AUC _{0-168h} (µCi·d/g)				Tumor : healthy tissue ratio	
	Blood	Bone marrow	Kidney	Tumor	Bone marrow	Kidney
NCI-H82	1.7	0.12	1.1	1.6	14	1.5
hDLL3-MC38	1.6	0.11	1	4.4	41	4.4

- A single IV dose of 20 µCi [0.01 mg/kg] ²¹²Pb-MP0712 was simulated in the hDLL3-MC38 and NCI-H82 xenograft models (mouse weight 35 g)
- AUC_{0-168h} estimates were calculated based on the total predicted radioactivity in the blood, tumor, kidney, and bone marrow
- The 9-fold increase in DLL3 expression in hDLL3-MC38 tumors (compared to NCI-H82) was associated with more than a 2-fold increase in tumor activity (AUC_{0-168h} = 4.4 vs. 1.6 µCi·day/g), with no change in activity predicted in healthy organs
- The model predicts a favorable therapeutic index of MP0712, with a tumor : kidney ratio above 1 in a clinically relevant tumor-bearing mice model (NCI-H82)
- These results warrants further investigation in cancer patients

References

- Croset A, et al. Cancer Res 2025;85(8, Suppl_1):346 (AACR 2025).
- Shah DK, Belts AM. J Pharmacokinet Pharmacodyn 2012;39(1):67-86.
- Bian W, Tang M, Jiang H, et al. Developmental Cell 2021;56(20):2902-19.
- Heuss SF, Ndaye-Lobry D, Six EM, Israël A, Logeat F. Proc Natl Acad Sci U S A 2008;105(32):11212-7.