Preclinical Evaluation of MT1-MMP-Targeting Bicyclic Peptides for Radiotheranostic Applications

Abstract #

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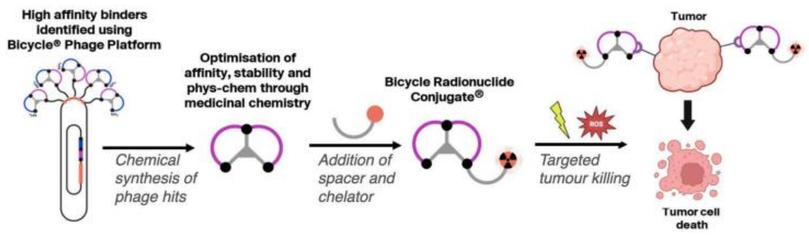
INTRODUCTION

- Membrane type 1 matrix metalloproteinase (MT1-MMP) is a key protease involved in extracellular matrix degradation, playing a critical role in tumor invasion and metastasis.
- BCY0, a first-generation MT1-MMP-targeting Bicycle Radionuclide Conjugate™ (BRC), demonstrated feasibility for PET imaging and is currently undergoing clinical translation.
- This study focuses on generating next-generation MT1-MMP-targeted bicyclic peptides with optimised pharmacokinetics to significantly enhance tumour targeting and minimise non-specific uptake.

METHODS

- Bicycle's phage platform was used to identify and optimise high-affinity MT1-MMP-binders
- Bicyclic peptides — BCY0, BCY1, BCY2, BCY3, and BCY4 (BCYx) — were radiolabelled with either ^{68}Ga or ^{177}Lu and tested for logD and specific binding/internalization potential in MT1-MMP$^+$ HT1080 cells
- MT1-MMP$^+$ HT1080 tumour-bearing BALB/c nu/nu mice underwent µPET/MR imaging up to 2 h post-injection (p.i., n = 1 each), and organ distribution studies 1 h p.i. (n = 3 each)
- BCY0 data from internal studies were used as a reference

Figure 1: Overview of the identification and design of Bicycle Radionuclide Conjugates®.



RESULTS

- Radiochemical yield >99%; logD = - 2.9 to -2.6
- High specificity of all BCYx to MT1-MMP and cellular internalization with negligible off-target binding (1–5%) (**Figure 2**)
- High *in vivo* tumour-to-background contrast was achieved in µPET/MRI within 0.5 h p.i. using BCY0, BCY1, BCY2, and BCY4 (**Figure 3**)
- Organ distribution confirmed high tumour uptake for all BCYx (12–25%ID/g) at 1 h p.i., with BCY1 and BCY4 showing the lowest off-target binding (6.3%ID/g and 6.1%ID/g, respectively, in kidneys), compared to BCY0's 8.6%ID/g tumour uptake and higher kidney retention (18%ID/g) (**Figure 4**).

Figure 2: Internalisation of [^{177}Lu]Lu-BCYx in MT1-MMP$^+$ HT1080 cells at 37 °C. Blocking with an excess of non-labeled compound (10 µM).

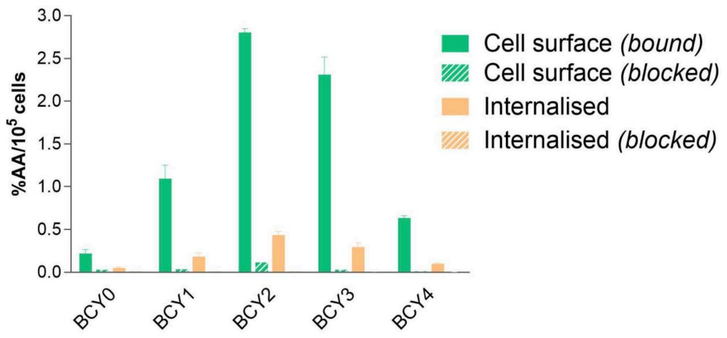


Figure 3: Whole-body maximum intensity projections of 150 pmol [^{68}Ga]Ga-BCYx in HT1080 xenograft (right flank) 1 h p.i. (A) and 2 h p.i. (B), obtained from small animal PET/MR imaging.

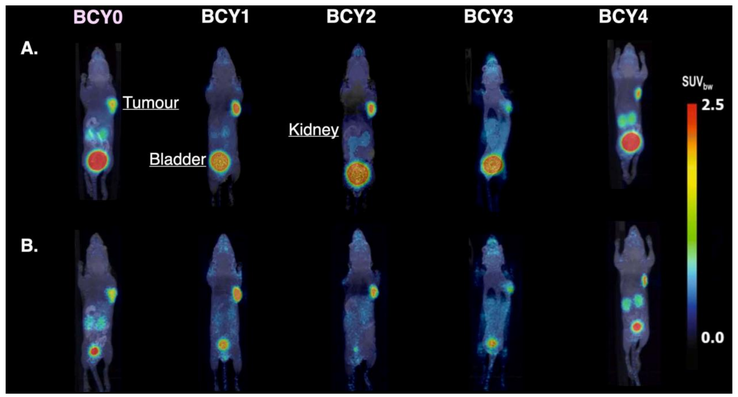
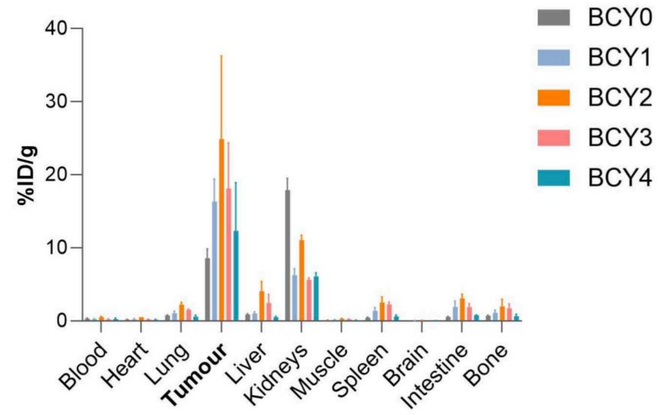


Figure 4: Biodistibution of 150 pmol [^{177}Lu]Lu-BCYx at 1 h p.i. in HT1080 xenografts.



CONCLUSIONS

- BCY1 and BCY4 demonstrated substantial improvements over BCY0, with up to a **90% increase in tumour uptake** and a **~66% reduction in kidney retention.**
- Their selective tumour targeting, low off-target accumulation, and favourable clearance profiles support their potential for radiotheranostic use.
- Further translational research is needed to fully explore their potential for PET imaging and patient treatment.

REFERENCES

1. Yana I, Seiki M. MT-MMPs play pivotal roles in cancer dissemination. Clin Exp Metastasis. 2002;19(3):209-15. doi: 10.1023/a:1015527220537. PMID: 12067201.
2. Eder M, Pavan S, Bauder-Wüst U, van Rietschoten K, Baranski AC, Harrison H, Campbell S, Stace CL, Walker EH, Chen L, Bennett G, Mudd G, Schierbaum U, Leotta K, Haberkorn U, Kopka K, Teufel DP. Bicyclic Peptides as a New Modality for Imaging and Targeting of Proteins Overexpressed by Tumors. Cancer Res. 2019 Feb 15;79(4):841-852. doi: 10.1158/0008-5472.CAN-18-0238. Epub 2019 Jan 3. PMID: 30606721.

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