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

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Membrane type 1 matrix metalloproteinase (MT1-MMP) is crucial in extracellular matrix degradation, which facilitates cancer progression and metastasis. Previous studies have shown the feasibility of using phage display-derived radiolabelled bicyclic peptides for positron emission tomography (PET) imaging. This study aimed to identify and characterize novel MT1-MMP-binding bicyclic peptides with an improved pharmacokinetic profile.

Four novel MT1-MMP-targeting bicyclic peptides (BCY1, BCY2, BCY3, and BCY4) were radiolabelled with either gallium-68 or lutetium-177. We assessed various physicochemical properties, including binding affinity, serum stability, and logD values. Cell binding and internalization were evaluated using MT1-MMP-expressing HT1080 cells. In vivo performance was analyzed in MT1-MMP+ tumor-bearing nude mice via μPET/MR imaging up to 2 hours post-injection (p.i.), followed by an organ distribution analysis (n = 3 for each peptide).
Results
All peptides exhibited nanomolar binding affinity (4.1 - 9.8 nM), with radiochemical purity exceeding 99 %. They demonstrated high serum stability, and their logD values ranged from - 3.6 to - 2.6. In vitro studies confirmed high specificity and minimal off-target binding (1 - 4 %). High tumour-to-background contrast was achieved within 30 minutes p.i. for BCY1, BCY2, and BCY4. Organ distribution studies revealed significant tumor uptake (12 - 25 % injected dose per gram, %ID/g) of all bicyclic peptides at 1-hour p.i., with BCY1 and BCY4 exhibiting the lowest off-target binding, aside from kidneys (5.8 %ID/g and 6.1 %ID/g, respectively).
Conclusion
BCY1 and BCY4 demonstrated optimal pharmacokinetic profiles characterized by high tumor uptake, specificity, and rapid blood clearance. Further translational research is essential to evaluate their full potential for radiotheranostic applications.

Preferred type of presentation

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