A First-in-Class Dual-Chelator Theranostic Agent Designed For Use With Imaging Therapy Pairs of Different Elements

*James L. Wood[a,b], Zachary H. Houston[b], Saikat Ghosh[b], Nicholas L. Fletcher[b], William Tieu, Michael P. Wheatcroft[c], Kristofer J. Thurecht[b], and Rachel Codd[b]**

[a]Centre for Advanced Imaging (CAI), Australian Institute for Bioengineering and Nanotechnology (AIBN) and ARC Training Centre for Innovation in Biomedical Imaging Technology
The University of Queensland
Brisbane, QLD, Australia
[b]School of Medical Sciences
The University of Sydney
Sydney, NSW, Australia
[c]Telix Pharmaceuticals
Melbourne, VIC, Australia
*j.wood1@uq.edu.au, rachel.codd@sydney.edu.au**

With the use of radiometals for imaging and therapy increasing and expanding in scope, there is a need for further optimisation of the delivery of these radiometals in a theranostic setting. One approach is to use two discrete chelators optimised for each radiometal, however, this may lead to difficulties in translating dosimetry information between modalities due to biodistribution differences. This work aimed to produce a single ligand with the capability of coordination of mixed-element radiometal pairs. Ligands DFOB (1) and DOTA (2) were grafted together to produce a single ligand capable of coordination of ^{89}Zr for imaging and ^{177}Lu for therapy. The differing coordination chemistries of ^{89}Zr and ^{177}Lu presented a unique opportunity to allow for regioselective coordination of the two radiometals, with DFOB offering selective coordination of ^{89}Zr and DOTA offering selective coordination of ^{177}Lu.

Regioselective coordination of the two metals was confirmed using the discrete chelator DFOB and a dual-chelator precursor, D2a, *via* {^{1}H}-^{13}C NMR spectroscopy analysis. The properties of the dual-chelator, D2, were then assessed, including antibody conjugation, radiolabelling and *in vitro/in vivo* performance in a murine HT-29 xenograft model. D2 was conjugated with an antibody yielding an antibody-chelate ratio between 1-2 and both [^{89}Zr]Zr-D2-mAb and [^{177}Lu]Lu-D2-mAb were progressed without need for further purification. [^{89}Zr]Zr-D2-mAb and [^{177}Lu]Lu-D2-mAb showed similar *in vitro* cell binding and internalisation to the matched DFOB and DOTA controls, which showed that the mAb was functional and the complex with D2 was capable of residualisation. *In vivo* immunoPET imaging analysis showed no significant difference in biodistribution between [^{89}Zr]Zr-D2-mAb and [^{89}Zr]Zr-DFOB-mAb. *Ex vivo* analysis showed similar biodistribution between the matched dose of [^{89}Zr]Zr-D2-mAb and [^{177}Lu]Lu-D2-mAb. The *ex vivo* biodistribution of [^{89}Zr]Zr-D2-mAb and [^{177}Lu]Lu-D2-mAb was also found to be similar to the matched controls of [^{89}Zr]Zr-DFOB-mAb and [^{177}Lu]Lu-DOTA-mAb. This suggested that the dosimetry information gained from administration of [^{89}Zr]Zr-DFOB-mAb could be more accurately translated to therapeutic application of [^{177}Lu]Lu-D2-mAb.

The results suggested that a dual-chelator containing DFOB and DOTA was capable of regioselective coordination of ^{89}Zr and ^{177}Lu. D2 displayed similar *in vivo* and *ex vivo* performance to the matched controls of DFOB and DOTA, displaying potential for D2 as a single ^{89}Zr-^{177}Lu theranostic agent.