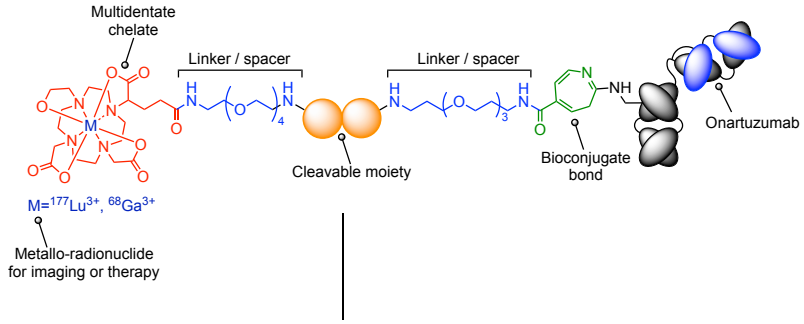
Metabolisable linkers as a strategy to reduce non-target uptake of radiolabelled antibodies

Stanislav Prytuliak, Cesare Berton, Fan Liu, Jason P. Holland

University of Zurich, Department of Chemistry, Winterthurerstrasse 190, CH-8057, Zurich, Switzerland
stanislav.prytuliak@chem.uzh.ch

Radioimmunotherapy (RIT) is a fast-emerging field of nuclear medicine. Successful preclinical applications and the subsequent approval of ^{90}Y-ibritumomab tiuxetan (Zevalin®, Bayer, Leverkusen, Germany) and ^{131}I-tositumomab (Bexxar®, GSK, Brentford, UK) opened the door for the development of numerous antibody-based radiopharmaceuticals. Currently, more than 60 radiolabelled antibodies or antibody fragments are reported to enter different phases of clinical trials.[1] Monovalent antibody onartuzumab was used in several studies for imaging of the C-Met receptor, which is significantly overexpressed in several malignancies.[2,3] It shows high affinity to the target receptor and good tumour retention. However, its high uptake into the kidneys hinders its usage as a therapeutic agent.[3]



In this work, we tried to reduce the non-target uptake of onartuzumab by including a cleavable moiety between the radiolabelled chelate and the antibody. Several target enzymes were identified in the kidney, and their corresponding substrates were tested as possible metabolisable linkers in order to accelerate the release of the radioactivity from the kidneys by enabling the fast renal excretion pathway.

[1] Rondon A, Rouanet J, Degoul F. Radioimmunotherapy in Oncology: Overview of the Last Decade Clinical Trials. *Cancers (Basel)*. **2021**, 13(21), 5570

[2] Pool M., Terwisscha van Scheltinga A. G. T., Kol A., Giesen D., de Vries E. G. E., Lub-de Hooge M. N. ^{89}Zr-onartuzumab PET imaging of c-MET receptor dynamics. *Eur J Nucl Med Mol Imaging*. **2017**, 44, 1328–1336

[3] Klingler S., Fay R., Holland J. P. Light-Induced Radiosynthesis of 89Zr-DFO-Azepin-Onartuzumab for Imaging the Hepatocyte Growth Factor Receptor. *J Nucl Med*, **2020**, 61 (7), 1072-1078