

Matched Pair Theranostics with ^{99m}Tc and ^{188}Re -DETA-N-Onartuzumab for the c-Met Receptor.

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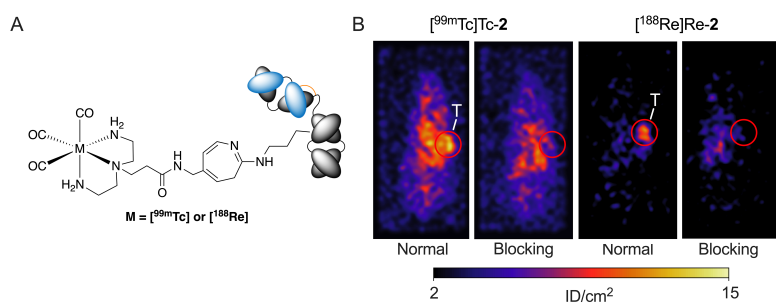
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Highly specific targeting vectors such as monoclonal antibodies (mAbs), enable a personalized radiotherapy that limits damage to the surrounding tissues.^[1] The linkage between a biomolecule and the radionuclide can be made by employing rapid photoreactions.^[2] The use of the matched pair ^{99m}Tc ($t_{1/2} = 6$ h, γ -ray = 141 keV [89%]) and ^{188}Re ($t_{1/2} = 17$ h, $\beta_{\text{max}} = 2.12$ MeV and γ -ray = 155 keV [15%]) have high potential for cancer therapy.

Herein, we report the synthesis, characterization, protein conjugation, and $^{99m}\text{Tc}/^{188}\text{Re}$ -radiolabeling studies on the cancer-specific mAb onartuzumab (MetMab), with the novel photoactivatable DETA-N ligand (Figure A). Photochemical protein ligation reactions with onartuzumab were performed in water under ambient conditions in 15 min. Planar γ -ray scintigraph imaging (γ -eye, Bioemtech, Greece) was performed on female athymic nude mice bearing subcutaneous MKN-45 xenograft between 0 h and 24 h post-radiotracer injection (Figure B). Biodistribution experiments were performed after 24 h and 72 h. The tumor specificity of $^{99m}\text{Tc}/^{188}\text{Re}$ -onartuzumab was assessed *in vivo* by competitive inhibition (blocking) studies.

The photoradiosynthesis of [$^{99m}\text{Tc}/^{188}\text{Re}$][Tc/Re(CO)₃(DETA-N)]-onartuzumab was accomplished by irradiating the reaction mixture with 395 nm light for 15 min. Purification by size-exclusion methods yielded the radiolabeled antibody in a RCP over 99% (^{99m}Tc and ^{188}Re) and an overall RCY of 17% (^{99m}Tc) and 18% (^{188}Re). Tumor uptake reached $20.20 \pm 4.05\% \text{ID g}^{-1}$ for ^{99m}Tc -onartuzumab and $22.13 \pm 3.11\% \text{ID g}^{-1}$ for ^{188}Re -onartuzumab after 24 h and $20.21 \pm 1.47\% \text{ID g}^{-1}$ for ^{188}Re -onartuzumab after 72 h in the normal groups. Blocking experiments confirmed tumor specificity with a reduction in tumor uptake of $\sim 70\%$ at the time points for ^{99m}Tc and ^{188}Re .

[$^{99m}\text{Tc}/^{188}\text{Re}$][Tc/Re(CO)₃(DETA-N)]-onartuzumab is a promising candidate for further use in theranostic studies of tumors presenting high expression of the c-MET receptor.



A: Structure of [$^{99m/188}\text{Re}$][Tc/Re(CO)₃(DETA-N)]-onartuzumab; B: Scintigraphs of the mice (left: ^{99m}Tc , right: ^{188}Re).

[1] J. Crudo, S. de Castiglia *et al.*, *J. Radioanal. Nucl. Chem.* **2004**, 261, 337-342.

[2] D. F. Earley, J. P. Holland *et al.*, *JACS Au* **2022**, 2, 646-664.