Rapid photoradiosynthesis and preclinical evaluation of theranostic radioimmunoconjugates using Lutetium-177

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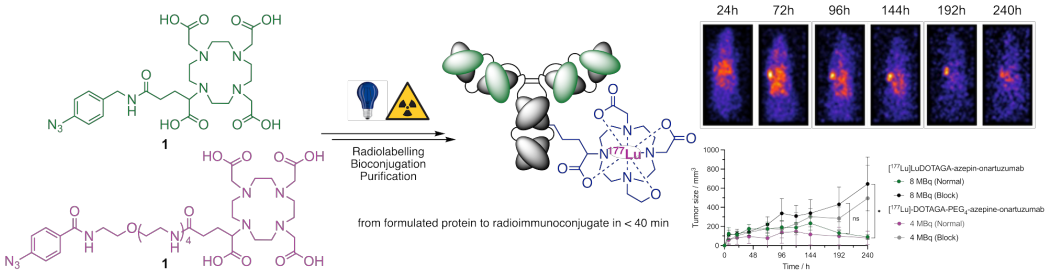
The conventional radiosynthesis of ^{177}Lu-radiopharmaceuticals makes use of analogues of the *aza*-macrocyclic chelate DOTA. The radiolabelling of such compounds typically requires heating to achieve efficient radiolabelling in short reaction times, good radiochemical yield (RCY), radiochemical conversion (RCC) and molar activity.[1] However, high temperatures are incompatible with proteins such as monoclonal antibodies (mAbs). We recently developed a fast photoradiochemical process which can produce ^{89}Zr-radiolabelled mAbs under mild conditions in less than 15 minutes, starting from clinical-grade protein samples with full formulation.[2,3] Here, we adapt the photoradiochemical process for the work with ^{177}Lu to access potential theranostic radiotracers.

The radiolabelling of the photoactivatable chelates DOTAGA-ArN_3 (**1**) and DOTAGA-PEG_4-ArN_3 (**2**) were achieved with RCYs >99% at 70 °C for 15 min before photochemical bioconjugation to proteins was performed at ambient temperature. Photochemical conjugation reactions on protein samples including human serum albumin (HSA), and the monoclonal antibodies trastuzumab (formulated as Herceptin) and onartuzumab (formulated as Met-mAb) and gave RCYs between 47-54% for HSA and 20-32% for the preparation of ^{177}Lu-labelled mAbs in formulation. The entire two-step process, including radiosynthesis, purification and formulation, can be completed in

[^{177}Lu]LuDOTAGA-azepin-onartuzumab and [^{177}Lu]LuDOTAGA-PEG_4-azepin-onartuzumab were administered to mice bearing subcutaneous MKN-45 tumours and the pharmacokinetic profile of the tracers were studied by temporal *in vivo* g-ray imaging up to 10 days and by *ex vivo* biodistribution studies at 3 and 10 day after administration and showed high uptake of 25.3 ± 3.9 and 21.66 ± 2.0 %ID/g respectively. The tumours showed a significant decrease in size at 10 days after treatment versus the blocking group.

DOTAGA aryl azides **1** and **2** grant access to a fast and reliable radiosynthetic route for ^{177}Lu-radioimmunoconjugates without exposing the protein to heat or other extreme conditions. The tracers produced following this procedure have been tested *in vivo* and showed selective accumulation in target tissue and indicated their efficacy against this model of gastric adenocarcinoma.



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