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Towards the labelling of heat-sensitive biomolecules with terbium radionuclides: Chelation studies of DOTA-NHS with natural Tb and 161Tb

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Introduction: Targeted radionuclide therapy using 161Tb is a promising approach for β- and Auger electron therapy.1 Moreover, the availability of the diagnostic radionuclides 152/155Tb is of interest in a theranostic setting.2-4 Heat-sensitive biomolecules (e.g. antibody fragments, etc.) are increasingly being used as carriers in radiometal-based radiopharmaceuticals. These molecules, however, require mild radiolabeling conditions. In this study, we evaluated DOTA-NHS as potential bifunctional chelator for mild Terbium radiolabelling.

Methods and results: Cold complexation studies were performed with DOTA-NHS (1 eq.) and natural $TbCl_3$ (0.5 eq.) in 0.1M acetate buffer, pH 4.7 at 25 ℃. The complexation was evaluated using high-resolution mass spectrometry (UV-HRMS-ESI-TOF, Bruker Maxis Impact). Complexation was complete after 60 minutes. The hydrolysed complex resonance is observed in the mass spectrum at m/z 561.1081 (theoretical mass calculated for $C_{16}H_{25}N_4O_8$ $[M+H]^+$: 561.0999). Radioactive tests were performed using 161Tb that was produced and purified at SCK·CEN (production in the BR-2 reactor: $^{160}Gd(n,\gamma)^{161}Gd \rightarrow {}^{161}Tb$). In these tests, 1.3 MBq $^{161}TbCl_3$ was added to 0.1, 1, 5 or 10 µM DOTA-NHS in a total volume of 1 mL and incubated at 25 or 40℃. Radiochemical yields were determined at different time points using instant thin layer chromatography (iTLC) eluted with acetonitrile;water (75:25 *v/v*) which were counted in a gamma counter. At 25 ℃, 161Tb was easily complexed using 5 µM of DOTA-NHS resulting in near-quantitative yields (96%) after 60 min. At 40 ℃, near-quantitative yields (97%) were obtained using 1 µM of DOTA-NHS after 60 minutes.

Conclusion: DOTA-NHS is a suitable candidate for future radiolabelling studies of heat-sensitive biomolecules. Other chelators of interest will be evaluated and in vitro and in vivo stability of the Terbium-complexes will be assessed.

References

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