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Preclinical Evaluation of [^{18}F]F-[^{nat}Lu]Lu-/[^{19}F]F-[^{177}Lu]Lu DOTA-rhCCK-18, a Radiohybrid-Based Minigastrin Analog With High Target Affinity and Tumor Accumulation: First Steps Towards Clinical Translation

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Aim/Introduction: In comparison to a recently introduced radiohybrid-based minigastrin analogue, [^{177}Lu]Lu-(R)-DOTAGA-rhCCK-16 ([^{177}Lu]Lu-(R)-DOTAGA-dap(SiFA)-(D-γ-Glu)$_6$-Ala-Tyr-Gly-

Trp-Asp-Nle-Phe-NH_2), the novel [^{177}Lu]Lu-DOTA-rhCCK-18 ([^{177}Lu]Lu-DOTA-dap(SiFA)-(D-γ-Glu)$_8$-Ala-Tyr-Gly-Trp-Asp-Nle-Phe-NH_2) revealed a significantly increased CCK-2R affinity (~4-fold improved IC_{50}) by a simple DOTA-for-(R)-DOTAGA substitution. In this study, we investigated the human serum albumin (HSA) and plasma protein binding and in vivo properties of [$^{18/19}$F]F-[$^{nat/177}$Lu]Lu-DOTA-rhCCK-18 to pave the way for a first evaluation in humans. ***Materials and Methods:*** All compounds were synthesised via automated Fmoc-based solid phase peptide synthesis (SPPS). ^{177}Lu-labelling was performed at 90°C within 15 min (1.0 M NaOAc buffer, pH = 5.5). ^{18}F-labelling was conducted at 60°C within 5 min (ammonium formate in DMSO) using previously dried [^{18}F]fluoride with subsequent purification by cartridge. Human serum albumin (HSA) and plasma protein binding was determined via an ultrafiltration method (3200 rpm, 40 min). Biodistribution studies were carried out at 1 and 24 h post-injection (p.i.) in AR42J tumor-bearing CB17-SCID mice. ***Results:*** Automated SPPS with concomitant purification via RP-HPLC yielded 5-20% peptide precursor. ^{177}Lu-labelling resulted in high radiochemical purity (RCP, >95%) and molar activity of A_m = 40 GBq/µmol. ^{18}F-labelling proceeded in radiochemical yields of 10-30%, RCP >95% and molar activities of A_m ~85 GBq/µmol. High HSA (62±3%) and plasma protein (95±1%) binding in vitro was determined for [^{19}F]F-[^{177}Lu]Lu-DOTA-rhCCK-18. In vivo at 1 h p.i., [^{18}F]F-[^{nat}Lu]Lu-DOTA-rhCCK-18 revealed high activity levels in the tumour and the kidneys (31.2 and 146 %ID/g, respectively) but a low bone uptake (<1.7 %ID/g), underlining the high stability of the Si-^{18}F bond in vivo. Apart from high activity accumulation in the kidneys overall background was low in non-target tissues. At 24 h p.i., [^{19}F]F-[^{177}Lu]Lu-DOTA-rhCCK-18 exhibited high activity retention in both the AR42J tumour xenograft and the kidneys (25.4±4.7 and 134±18 %ID/g, respectively), while further off-target retention was low, leading to superior tumour-to-background ratios for [^{19}F]F-[^{177}Lu]Lu-DOTA-rhCCK-18 compared to the reference compound [^{177}Lu]Lu-DOTA-PP-F11N ([^{177}Lu]Lu-DOTA-(D-Glu)$_6$-Ala-Tyr-Gly-Trp-Asp-Nle-Phe-NH_2). Based on these encouraging results, clinical translation of [^{18}F]F-[^{nat}Lu]Lu-DOTA-rhCCK-18 has already been initiated. Apart from the general pharmacokinetics it will be investigated whether the unfavourable high kidney uptake is obtained in humans as well. ***Conclusion:*** [$^{18/19}$F]F-[$^{nat/177}$Lu]Lu-DOTA-rhCCK-18 demonstrated favourable in vitro and in vivo properties, particularly high tumor accumulation and retention. A first-in-human application using either [^{18}F]F-[^{nat}Lu]Lu-DOTA-rhCCK-18 or [^{19}F]F-[^{68}Ga]Ga-DOTA-rhCCK-18 will elucidate if elevated kidney uptake observed in animals is reflected in humans. If not, the radiohybrid-based DOTA-rhCCK-18 could be a viable theranostic agent for positron emission tomography imaging and radioligand therapy of medullary thyroid cancer.