Synthesis of precursors for 211At-labelling of anti-PSMA HuJ591 mAb and stability comparison after in vitro cellular internalization

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Radiochemistry - other radionuclides and targetry

O-46 | Synthesis of precursors for ^{211}At-labelling of anti-PSMA HuJ591 mAb and stability comparison after in vitro cellular internalization

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Objectives

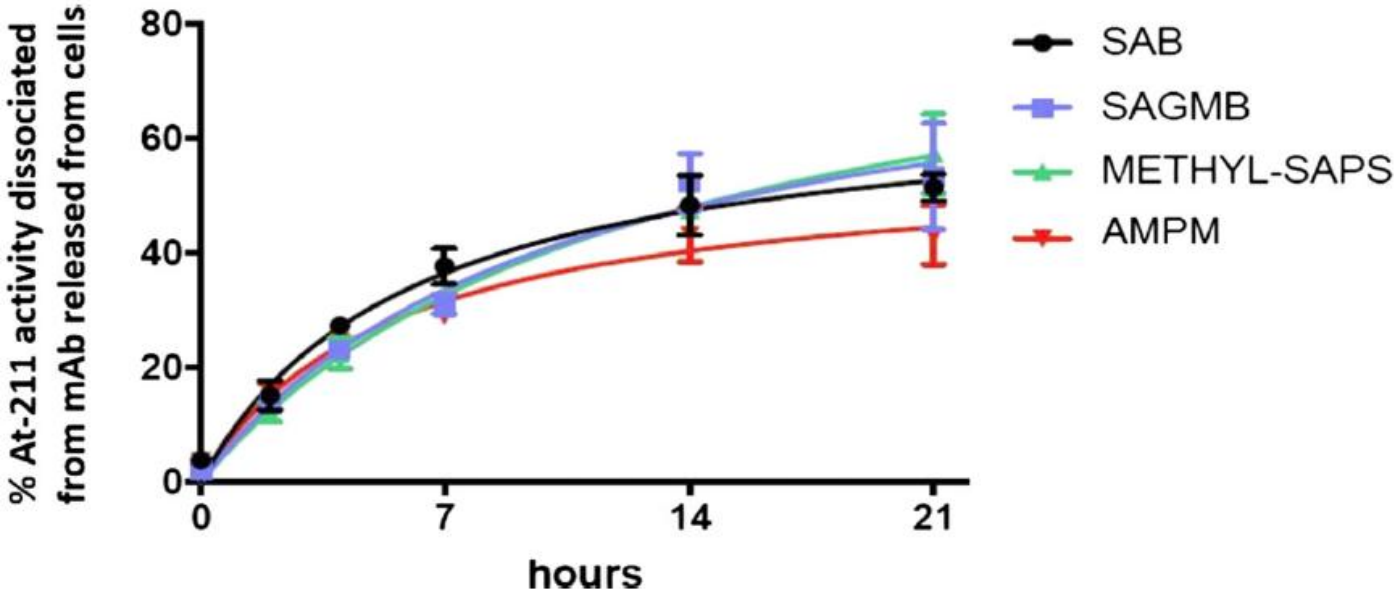
Radio-immunotherapy (RIT) is a promising approach for cancer treatment because curative doses of radiation can potentially be selectively delivered not only to the primary tumour but also to metastatic lesions spread throughout the body. A radionuclide of great interest for RIT is the heavy halogen ^{211}At because it decays by the emission of short-range, high-energy α-particles. Based on its electrophilic At^+ form, several approaches using the astatodestannylation reaction of aryl precursors have been developed in order to attach ^{211}At to biomolecules.[1] Many prosthetic groups have been synthesized for biomolecule labelling with ^{211}At, in order to reinforce the stability of ^{211}At-biomolecule bond.[2,3] Various improvements have been described but they all exhibit some in vivo instability when the radiopharmaceutical is rapidly metabolized or when it is internalized in the tumour cell. However, no direct comparison between these reported compounds has been reported. Thus, the aim of this work was to compare the stability of some of prosthetic groups coupled to antibodies by acylation of lysine amino group but also to study the influence of a maleimide function for addition to thiol functions. We report herein the comparison of four astatinated prosthetic groups that have been associated to internalizing anti-PSMA HuJ591 mAb through activated ester (NHS) or maleimide function and tested in the same in vitro test model.

Methods

Three NHS based precursors (MeATE, SPEMS and SGMTB) and a maleimide precursor (SMPM) were synthesized in order to compare the influence of the stability of the At-C bond or of the prosthetic group-Ab bound. They were radiolabelled with ^{125}I and ^{211}At and then coupled to the internalizing IgG anti-PSMA HuJ591 mAb via their NHS or maleimide function. To compare the stability of these four compounds, an in vitro cellular internalization assay was conducted with LNCaP-GFP cell line to measure the percentage of radioactivity dissociated from the IgG present in the extracellular medium after internalization.

Results

All precursors (MeATE, SPEMS, SGMTB, and SMPM) were synthesized and obtained with high purity. Radiolabelling of precursors with ^{125}I gave radiochemical yields (RCYs) for [^{125}I]SIB, [^{125}I]Methyl-SIP, [^{125}I]SGMIB, and [^{125}I]IMPM of 51, 63, 56, and 50%, respectively. Radiolabeling with ^{211}At gave RCYs for [^{211}At]SAB, [^{211}At]Methyl-SAPS, [^{211}At]SAGMB, and [^{211}At]AMPM of 48, 20, 14, and 31, respectively. Radiolabeling of J591 mAb with [^{125}I]SIB, [^{211}At]SAB, [^{125}I]Methyl-SIPS, [^{211}At]Methyl-SAPS, [^{125}I]SGMIB, and [^{211}At]SAGMB through the NHS function provided conjugation yields within the 45-60% range, providing the purified radiolabeled antibody with a >95% radiochemical purity.



Radiolabeling of J591 mAb with [^{125}I]IMPM and [^{211}At]AMPM through the maleimide function provided conjugation yields within the 80-90% range, providing the purified radiolabeled antibody with a >95% radiochemical purity. Internalization tests performed with either ^{125}I-radiolabeled compounds [^{125}I]SIB, [^{125}I]Methyl-SIPS, [^{125}I]SGMIB, and [^{125}I]IMPM, or ^{211}At-radiolabelled compounds [^{211}At]SAB, [^{211}At]Methyl-SAPS, [^{211}At]SAGMB, and [^{211}At]AMPM showed no significant differences even if we observed a little advantage to the maleimide coupling function.

Conclusion

Under the conditions of our experiment (with IgG HuJ591 and LNCaP-GFP cell line), all tested ^{125}I or ^{211}At radiolabelled compounds exhibited some instability after internalization but no significant differences where observed.

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REFERENCES

1. Guérard, F., Gestin, J.-F. & Brechbiel, M. W. Production of [^{211}At]-astatinated radiopharmaceuticals and applications in targeted α-particle therapy. Cancer Biother.Radiopharm. 28, 1–20 (2013).
2. Vaidyanathan, G., Affleck, D. J., Bigner, D. D. & Zalutsky, M. R. *N*-succinimidyl 3-[^{211}At]astato-4-guanidinomethylbenzoate: an acylation agent for labeling internalizing antibodies with alpha-particle emitting ^{211}At. Nucl. Med. Biol. 30, 351–359 (2003).
3. Talanov, V. S. *et al*. Preparation and in vivo evaluation of a novel stabilized linker for ^{211}At labeling of protein. Nucl. Med. Biol. 33, 469–480 (2006).