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Advances in the Radiolabeling of Antibodies with Astatine-211: Toward Simplified Procedures and Improved Radiochemical Yields

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Background and Objectives: Current protein astatination protocols most often rely on reactions that were developed several decades ago. Yet these methods are generally suboptimal. However, given the quite low availability of the alpha emitter ^{211}At, there is a need for new methodologies to limit the loss of radioactive material in each step. This can be achieved by improving reactions radiochemical yields (RCY) and/or purification processes. In this context, our aim was to improve these two critical steps of the astatination of an antibody, namely the prosthetic group radiolabeling step and the bioconjugation step.

Methods: Regarding the astatinated prosthetic group synthesis, we explored the potential of nucleophilic astatination of aryliodonium precursors instead of the conventional electrophilic demetallation of arylstannane compounds. 2 We then payed attention to the bioconjugation step, which usually consist in the conjugation of the ^{211}At-prosthetic group to lysines of proteins via an activated ester. Such approach cannot provide quantitative coupling yields since the activated ester degrades in the required conditions for bioconjugation. To solve this issue, we turned our attention to bio-orthogonal approaches that are known to be highly compatible with biological media.

Results and Discussions: We observed that aryliodonium salts were highly reactive with astatine, more than expected from extrapolation of other halogens reactivity, 1 and that the purification was simplified resulting in more than a doubling of the RCY for the astatination of the antibody (an anti-CD138 mAb for targeting multiple myeloma) in comparison with arylstannane chemistry. To solve the bioconjugation issue, we synthesized clickable astatinated prosthetic groups based on azide or tetrazine functionalities for ligation by 5 different modalities to pre-modified antibodies with the complementary bio-orthogonal handles. By this approach, the bioconjugation step yield was nearly quantitative, and in the best case (the tetrazine/trans-cyclooctene ligation) the coupling time was reduced from 30 min to few seconds which contributed significantly to improving the overall process RCY and duration. 3 Additionally, the lower antibody concentration required in this

approached allowed the increase of the specific activity of the resulting radio-immunoconjugate. In vitro evaluation showed that it preserved its binding ability, similar to the conventional approach.

In conclusion, the application of recent chemical technologies allowed us to improve the production efficiency of astatinated antibodies in terms of RCY and robustness. Further in vivo studies should confirm the usefulness of these approaches. Overall, these results should facilitate the development of astatinated radiopharmaceuticals and accelerate their transfer to the clinic.

Reference:

[1] Guérard et al, Chem. Eur. J. 2016, 22, 12332. 2 Guérard et al, Bioorg. Med. Chem. 2017, 25, 5975. 3 Navarro et al, Bioorg. Med. Chem. In revision.

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