Contribution ID: **118** Type: **not specified**

A Novel Reaction for "Click"-based 211At-Astatination

Purpose & Introduction

The α-emitter 211At is a highly promising radionuclide for targeted alpha therapy (TAT). High linear energy transfer renders alpha particles highly radio-toxic to adjacent cells, making TAT a efficient treatment option for cancer.[1]

211At is the only alpha emitter used in therapy that allows for covalent labeling, thus preventing the use of chelating ligands. In general, astatinations are carried out utilizing stannyl-precursors and oxidative conditions. Due to the low abundance of this element, the chemistry of astatine is rather unexplored. The availability of other straight forward radio-astatination procedures would extend the variety of accessible 211At-TAT agents, leading to more options in clinical research and the treatment of malignant disease.

Methods & Results

Within this contribution a novel methodology for introduction of 211At into small molecules is presented. In this multi-component labeling reaction, an azide-moiety (A), an alkyne-moiety (B), and 211At are combined using base and metal catalysis. The product formed consists of a 1,2,3-triazole (T) bearing both structural motifs (A and B) with the astatine located at the formed triazole system (A-T(211At)-B). The reaction, which has shown to be unaffected by high starting activities, was optimized towards reaction time and radiochemical yield (RCY), finally providing >70% RCY within 10 min.
The reaction is highly tolerant considering the structural motifs A and B, as shown in a related study applying 125I as radioisotope.[2] This allows a high degree of structural variation, enabling straight-forward tuning of pharmacokinetic properties. We chose to use a biotin-azide as A and a tetrazine-alkyne as B, giving rise to a 211At agent that is suitable for biotin/streptavidin or tetrazine/trans-cyclooctene (TCO) based labeling and pre-targeting studies. The structure of the product was verified by binding experiments to TCO and streptavidin modified beads. Stability of the formed astatine-triazole bond was investigated by incubation of formed 211At-Beads in plasma for 300 min, showing 88% intact substance. Stability was further increased to 99% by click-assembly of a PEG-corona to the bead, using the tetrazine moiety of this multifunctional agent.

Discussion & Conclusion

To the best of our knowledge we have developed a new, high yielding, fast and versatile labeling system for astatine-211. Applying this chemistry we were able to prepare the first 211At-labeled 1,2,4,5-tetrazine that furthermore bears a biotin functional motif. This agent is capable of binding to TCO and/or streptavidin in a highly efficient manner, thus providing a tool for pre-targeted alpha radiotherapy (pTAT) and macromolecule labeling. We are convinced that this new astatination-strategy is a step forward towards broader application of TAT by expanding the variety of 211At based therapeutic agents.

[1]Elgqvist et al, Front Oncol. 2013.
[2]Yan et al J. Am. Chem. Soc., 2013

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Presentation Type

Contributed Oral

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