Contribution ID: **1055** Type: **Poster**

Development of 211At-Radiopharmaceuticals for Pretargeted Radioimmunotherapy of Disseminated Cancer

Thursday, 19 May 2022 17:33 (18 minutes)

Background: To enhance the therapeutic efficacy of radioimmunotherapy of cancer, several pretargeting strategies have been developed. In pretargeted radioimmunotherapy, the tumour is pretargeted with a modified monoclonal antibody that has affinity for both, tumour antigen and radiolabeled carrier. A big challenge in cancer treatment is the elimination of occult disseminated tumour cells, in this context the alpha emitter 211At has drawn attention due to its physicochemical characteristics. This project aims to design new molecules for pretargeting applications based on the Diels Alder click chemistry system (Tetrazine (Tz)/Trans-cyclooctene (Tco)) using 211At as radionuclide, and to evaluate these substances to optimize the pharmacokinetics.

Material and Methods: The effector molecule was synthesized attaching N-Succinimidyl-3-(trimethylstannyl)-benzoate, Tetrazine-NHS ester, and Succinic Anhydride to a poly(L)lysine (PL) scaffold (HTzPL and MeTzPL). A dry astatine residue was activated with N-iodosuccinimide followed by electrophilic substitution of the trimethyl-tin group on the TzPL, resulting in an astatinated product. Purification was performed eluting the product in PBS on illustra NAP-5 column. Radiochemical purity of the product was determined with radio-TLC using 100% ethanol as mobile phase and iTLC-SG as stationary phase. Finally, Tco-functionalized magnetic beads (Tco-mBeads) were used to assess the Tetrazine/Tco binding after radiolabeling.

Results: Astatinated TzPL resulted in > 80% of radiochemical yield and > 98% of radiochemical purity. Preliminary studies on Tco-magnetic beads have shown a binding > 90% already after the first minute to reach a value > 97% after one hour.

Discussion and Conclusion: A protocol for the synthesis and radiolabeling of the PL based tetrazine-effector molecule has been developed. High radiochemical yield and radiochemical purity can be obtained in the polymer astatination, resulting in a good binding to Tco-mBeads. H-Tetrazine is reported to react faster than the Me-Tetrazine with Tco, which would be a great advantage when administered in vivo, but it is also less stable. Comparative studies are thus being performed to assess the characteristics of each compound. Additional in vitro and in vivo studies will be carried out for the full evaluation and optimization.

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Session Classification: Radiopharmaceuticals

Track Classification: Radiopharmaceutical Chemistry, Labelled Compounds