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# Poly-L Lysine based Approaches for Pretargeted Radioimmunotherapy with Astatine-211

Pretargeted radioimmunotherapy (PRIT) has the potential to increase activity uptake in tumors relative to normal tissue compared with conventional radioimmunotherapy. In pretargeting there is preferably a three step administration of agents with different properties. Firstly the pretargeting molecules (usually antibody conjugates) are administered allowing for maximum tumor targeting during the course of several hours. Secondly, a clearing agent is injected in order to clear unbound pretargeting molecules from the blood circulation. When administering antibody-based pretargeting molecules systemically, they will exhibit a relatively slow clearance from the blood why the clearing agent reduce the absorbed dose to normal tissue and thereby maximize the absorbed dose to the tumors. Thirdly, a radiolabeled effector molecule with high affinity for the pretargeting molecule is administered. The effector is a small molecule that therefore exhibits rapid circulation and blood clearance allowing more of the injected radioactivity to reach the tumor compared with conventional radioimmunotherapy. In addition the small effector molecule also distribute faster within the tumor, rendering a more homogenous activity distribution compared with directly radiolabeled antibodies.

Homogenous activity distribution is especially important within Targeted Alpha Therapy where particles ranges in tissue are short (< 100μm). One of the best alpha particle emitters for curative therapies is astatine-211 that have a 7.21 h half-life and one alpha emission per decay.

Several different pretargeting approaches exists where two of the most important ones are the biological (strept)Avidine(SA)<->Biotin system and the chemical Tetrazine (Ttz)<->Tetracyclooctane (TCO) system. In either case the pretargeting molecule is functionalized with one of the ingoing components in each system while both the clearing agent and the effector molecule is functionalized with the other. Poly-L Lysine is a versatile scaffold that can be modified in order to function both as effector molecule and as clearing agent in either one of the mentioned pretargeting systems.

In this work, different approaches using Poly-L Lysine within pretargeted radioimmunotherapy with astatine-211 are explored. For use as clearing agent, Poly Lysine is functionalized with galactose amine to steer clearance to the liver and succinic anhydride for charge modification. Charge modification is also necessary for use as effector molecule where the poly Lysine in addition is functionalized with a molecule e.g. N-succinimidyl-3-(trimethylstannyl)benzoate, in order to allow for incorporation of the radionuclide, astatine-211. Poly-L Lysine is also available in different chain-lengths in order to change circulation and clearance properties.

## Email Address

emma.aneheim@radfys.gu.se

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**Primary author:** Dr ANEHEIM, Emma (University of Gothenburg, Sweden)

**Presenter:** Dr ANEHEIM, Emma (University of Gothenburg, Sweden)