RADIOPHARMACEUTICAL CHEMISTRY OF TARGETED RADIOPHARMACEUTICS. SYNTHESIS OF ^{211}At-LABELED RADIOPHARMACEUTICALS AT HIGH ACTIVITIES FOR CLINICAL USE†

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†This work was entirely made at the Radiopharmaceutical Chemistry Laboratory, Department of Radiology, Duke Univesity Medical Center.

Targeted α-particle radiotherapy is an appealing approach to cancer treatment because of the potential for delivering curative doses of radiation to tumor with minimal damage to normal tissue due to a range equivalent to only a few cell diameters. Compared with β-emitters they have significant advantages from a radiobiological perspective. The LET of ^{211}At α-particles is more than 400 times higher than the β-particles emitted by ^{90}Y, in addition the distance between ionizing events is almost the same as that between the two strands of DNA, yielding a high probability of creating non-repairable DNA damage. It gives the ability to kill cancer cells not compromised by hypoxia, dose rate effects or cell cycle position, enhancing their attractiveness for targeted radiotherapy.

However, translation of the concept to the clinic has been slow, many obstacles had to be surmounted before clinical studies could be initiated, the first clinical evaluation of a ^{211}At-labeled mAb was made in 2001(1). This study circumvents many of the challenges to entering clinical studies with ^{211}At. But several problems were encountered in maintaining efficient labeling with escalating radiation dose of alpha-particle likely related to radiolysis. The impact of the radiolysis produced by the α-particle over the labeling chemistry is much higher in comparison with typical β-emitters due to a deposition of energy in the solvent in a highly localized manner two orders of magnitude per unit volume higher than ^{90}Y or ^{131}I.

Due to these difficulties a comprehensive basic science study about the radiolytic effects of astatine alpha-particles over the synthesis of ^{211}At-labeled radiopharmaceuticals was carried out. Its main goal was overcoming the problem of the synthesis of ^{211}At-labeled radiopharmaceuticals at the high activities necessaries for therapy and also to extend the shelf life of astatine elutions. Briefly this study held several steps, the first one was to study the role of solvent-related radiolytic effects over the astatination precursors in several solvents and pH. On the second step we studied the effect of the radiolysis-mediated process on the nature of the labeled product generated and the yields of the astatinated molecule used to label the mAb (SAB) as a function of the radiation dose and pH. Afterward we explored the effect of radiation dose on the astatine species present before initiation of the labeling reaction based on the hypothesis that ^{211}At will react with highly reactive radiolytically generated species coming from the solvent, these studies were carried out only in methanol which the results from the previous two steps identificated as the optimal solvent for astatodestannylation.

The results of the studies showed that astatine chemistry critically depends on the solvent where the reaction is carried out. The α-particle-induced radiolytic effects mostly work through interaction with the solvent, consequently the mechanisms and kind of damage

accountable for the decreasing on the astatination reactions yield will strongly depend on the solvent. Of the three solvent used as model of the solvent groups mostly utilized on the past to do astatination, aromatics, halogenated and alcohols, we showed that methanol was the optimal solvent for astatodestannylation. In benzene the solvent itself is pretty stable but the astatine is mostly trapped in reaction with the aromatic molecules. In chloroform there is a fast decreasing of astatination precursor mainly due to competitive reactions with free radicals coming from radiolytic degradation of the solvent (chlorine radicals mainly). In methanol the tin precursor remains largely intact with increasing radiation dose, instead the radioisotope itself is the most affected. The result probed that the astatine chemical form does become altered and converted to a reduced species with increasing radiation dose deposition to the solvent, the reation is also pH dependent; solid experimental evidence lead us to hypothesize that the reduced astatine is most likely astatide. This reduction reaction turns out to be a main deleterious effects over astatination reactions at the high activities required for therapeutic purpose.

This study provided critical information to understand the chemistry of astatine and its microenvironment at high activities hence high radiation field. This information was used for studies focus on the stabilization of the astatine from the consequence of its own radiation field to make possible astatination reactions at the high activities that therapy requires.

(1) Zalutsky MR, Zhao X-G, Alston KL, Bigner DD. High-level production of α- particle-emitting ^{211}At and preparation of 211At-labeled antibodies for clinical use. J Nucl Med. 2001;42:1508 –1515.