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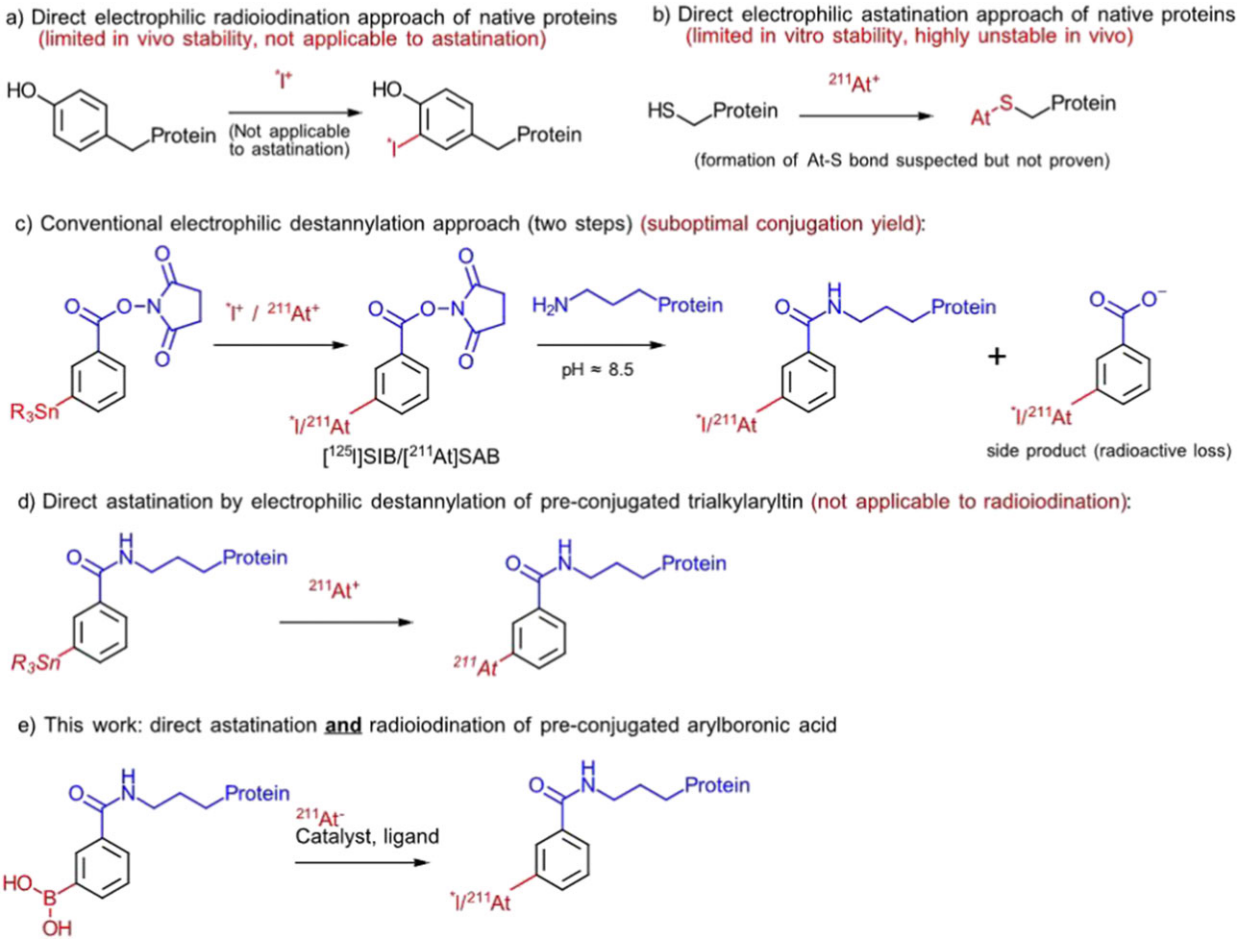
Marion Berdal[1]; Laurent Navarro[2]; Cyrille Alliot[4]; Michel Chérel[1]; Alain Faivre Chauvet[5]; Jean-François Gestin[1]; François Guérard[3]

[1] CRCINA, Inserm, CNRS, France; [2] CRCINA, France; [3] Université de Nantes, CRCINA, Nuclear Oncology group; [4] Arronax, France; [5] University of Nantes, France

Objectives

While astatine-211 and iodine radioisotopes are of high interest for radioimmunotherapy and nuclear imaging, available methods to bind them to carrier monoclonal antibodies (mAb) are still far from optimal. Direct radioiodination with electrophilic iodine (I^+) leads to substitution with mAb tyrosines with limited in vivo stability whereas electrophilic astatination do not lead to an At-tyrosine bond, but instead to a highly unstable and uncharacterized labeling. Consequently, to obtain sufficient stability, the formation of a stable bond with a prosthetic group (PG) conjugated to the mAb is thus mandatory. Ideally, the PG should be conjugated to the mAb before radiolabeling to avoid radioactive loss during the bioconjugation step that is observed when radiolabeling of PG is performed prior to conjugation.[1] If solutions have been reported for direct astatination of mAb, they are based on an electrophilic destannylation reaction that requires the electrophilic At^+ species which is unstable in solution and thus that do not guaranty consistent labeling efficiency.[2] Furthermore, such approach is not applicable to radioiodination since electrophilic labeling of tyrosine occurs competitively with the expected iododemetalation of the preconjugated prosthetic group. Thus to date, no common method is known for direct labeling of mAb with radioiodine and astatine. In this context, our objective was to investigate if nucleophilic approaches could be a solution to issues encountered in radioiodination and



astatination of mAb via electrophilic pathways, namely, the competitive reactivity of I^+ with tyrosine, and the instability of At^+.

Methods

The first step consisted in identifying the best class of precursors that could efficiently be radioiodinated and astatinated by nucleophilic approach in aqueous media (min 90% water) and at low temperature compatible with mAbs. For this, several compounds reported previously as efficient nucleophilic radiohalogenation reactions in organic medium were chosen from aryliodonium salts,[3] aryliodonium ylides,[4] arylsulfonium salts[5] and arylboronic acids or esters.[6] Then, we focused on the use of arylboronic acids with copper catalysis. On a model compound (4-chlorobenzeneboronic acid), labeling conditions in water were optimized (influence of pH, buffer salt nature and precursor, catalyst and ligand concentration) to make the reaction efficient with the lowest possible precursor and catalyst concentration. Optimal conditions were then transferred to the labeling of 2 mAbs (an anti-CD22 and our home made anti-CD138 mAb) pre-modified by conjugation to 3-carboxyphenylboronic acid NHS ester. Labeling efficiency and radiolabeled mAb integrity were then assessed.

Results

Of the precursors tested, only arylboronic acids in the presence of $Cu(OTf)_2Pyr_4$ catalyst and 1,10-phenanthroline ligand provided high radioiodination and astatination RCYs in aqueous solution at room temperature. Optimization of conditions with 4-chlorobenzeneboronic acid showed that a pH $\leq$ 6.5 was required to provide RCYs (> 90%) with low precursor concentrations ($\leq$ 250 μM). For use of this method with mAbs, the most compatible buffer in which the high RCYs were maintained and that prevented copper salt and/or mAb precipitation was found to be the TRIS buffer. Under these conditions, high radioiodination and astatination RCYs (> 80%) were also obtained with both mAbs tested with an excellent preservation of Immunoreactivity (94% for ^{125}I-anti-CD138 and 86% for ^{211}At-anti-CD138) which validated our concept.

Conclusions

This study proves for the first time the possibility to label mAbs in a single step with radioiodine and astatine-211 by a nucleophilic approach. Labeling efficiency and resulting immunoreactivity of labeled mAb were high which warrants further in vivo evaluation. Additionally, this is the first reported method that can be used for both radioiodination and astatination which should facilitate the development of theranostic tools based on these radionuclides.

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