Mitochondria-targeted Radiocomplexes for Auger Electron Therapy of Cancer

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Auger electron (AE) emitters hold great promise for targeted radionuclide therapy (TRT) of cancer, due to their high linear energy transfer (LET) over a nanometric range. When Auger emitters are internalized into highly radiosensitive organelles, such as the cell nucleus or the mitochondria, it is expected that the desired therapeutic effect is achieved with lower administered doses, thus minimizing the side effects. Nuclear DNA has been considered the most relevant target of Auger electrons to have augmented radiotoxic effects and significant cell death. However, the mitochondria are recognized as one of the most important cellular targets to trigger apoptotic reactions and recently are also being studied as a subcellular target for therapeutic AE-emitting radionuclides[1].

In this context, we have designed dual-targeted ^{111}In-DOTA complexes carrying a Prostate Specific Membrane Antigen (PSMA) inhibitor (PSMA617 derivative) and a triphenyl phosphonium (TPP) group to promote a selective uptake by prostate cancer (PCa) cells and their accumulation in the mitochondria, respectively. Conjugates bearing a cathepsin B cleavable linker between the PSMA617 moiety and the DOTA chelator were also synthesized, aiming at a further enhanced accumulation in the mitochondria upon enzymatic cleavage of the linker. In this way, we expected to obtain AE emitting radioconjugates suitable for a more selective TRT of metastatic castration-resistant prostate cancer (mPCa).

In this communication, we will report on the synthesis and characterization of novel DOTA-based bifunctional chelators functionalized with PSMA617 and TPP derivatives and on their respective indium complexes, obtained with ^{nat}In and ^{111}In. The preliminary biological evaluation of the radioactive ^{111}In-complexes was also performed to have a first insight on their potential usefulness for AE therapy of prostate cancer, and will be also presented. These biological studies included internalization and subcellular localization experiments in different cell lines (LNCaP, PC3 PIP and PC3 Flu), and the assessment of radiobiological effects based on the clonogenic survival assay.

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[1] D. Figueiredo et al., *Molecules*, **2021**, 26(2), 441.