Biological evaluation of dual-targeted radioconjugates carrying TPP and PSMA-binding moieties on prostate cancer models

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The development of new theranostic radiopharmaceuticals that target the prostate-specific membrane antigen (PSMA), which is commonly overexpressed in prostate cancer (PCa), is an area of active research. One successful approach involved the complexation of the beta minus emitter 177Lu with PSMA-617, a macrocyclic chelator containing a PSMA-binding moiety. The resulting radioconjugate (177Lu-PSMA-617) has been recently approved by the U.S. Food and Drug Administration (FDA) as a radiopharmaceutical for treating metastatic castration-resistant prostate cancer (mCRPC). However, beta minus emitters have limitations, including nephrotoxicity and resistance to beta radiation. Auger electron (AE) emitters, such 111In, have been suggested as an alternative to overcome these limitations.
In order to increase selectivity and efficacy, while minimizing adverse health effects, we have designed dually-targeted 111In radioconjugates specifically directed to the mitochondria of PCa cells. Our strategy involved the incorporation in the PSMA-617 structure of a moiety (the triphenyl-phosphonium (TPP) group) that specifically targets this organelle, which is highly sensitive to ionizing radiation.
All new compounds were fully characterized by high-performance liquid chromatography (HPLC) and electrospray ionization-mass spectrometry (ESI-MS). Biological evaluations were carried out in the LNCaP, PC3 PIP and PC3 Flu cell lines and included the assessment of stability, cellular uptake and PSMA-inhibitory activity.
The 111In complexes were stable in physiologic conditions, demonstrated high uptake in PSMA-positive cells (PC3 PIP) and low internalization in PSMA-negative cells (PC3 Flu). The inhibitory activity of the “cold” compounds was confirmed using PSMA extracted from LNCaP cells.
Our preliminary results showed that the novel dually-targeted 111In-complexes exhibit properties that make them good candidates for Auger therapy of PCa.

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