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Background
Because of its beta-negative (negatron) and beta-positive (positron) particle emissions, 64Cu is useful for PET imaging and therapy [1]. 99mTc-HYNIC-iPSMA has demonstrated high ability to target tumors over-expressing the prostate specific membrane antigen (PSMA) useful for SPECT imaging [2]. One critical aspect of this molecule is the presence of the HYNIC group acting as an additional lipophilic location for the coupling to the hydrophobic structure of the PSMA enzyme [3]. Taking the advantage of HYNIC-iPSMA to detect prostate tumors, in this research we added NOTA to the molecule to obtain a new 64Cu radiopharmaceutical with theranostic potential.
Objective
To synthesize and characterize biochemically 64Cu-DOTA-HYNIC-iPSMA as well as to evaluate in mice its potential as a PET imaging agent for PSMA-positive tumors.
Methodology
The p-SCN-Bn-NOTA (Macrocyclics, USA) was conjugated to the HYNIC-iPSMA ligand (molar ratio 0.95:1) by dissolving the compounds in 0.1 mL of 0.2M NaHCO3 (pH 9.5) and incubated at 37℃ for 1 h. After reaction, the sample was diluted to 50 mL using injectable grade water. The solution was filtered by membrane (0.22μm) and fractionated in sterile vials (2 mL and 100 μg of the conjugate per vial). Finally, samples were lyophilized and analyzed by HPLC. The lyophilized vials containing NOTA-HYNIC-iPSMA (purity of 95%) were reconstituted with 1 mL of acetate buffer (1M, pH 5.0) plus 0.5 mL of 64CuCl2 (pH 4) and incubated at 95℃ for 10 min. The in vitro evaluation of the obtained radiopharmaceutical was carried out in human serum (stability) and in human prostate LNCaP cancer cells (cancer cell uptake). For PET images a lung LNCaP micro-metastases model in athymic mice was used.
Results and discussion
HPLC analyses of NOTA-HYNIC-iPSMA showed a high yield of the reaction (99%). Only 5% of HYNIC-iPSMA remained as a chemical impurity. Radio-HPLC analysis showed the formation of 64Cu NOTA-HYNIC-iPSMA with a radiochemical purity of >98%. In vitro studies demonstrated high stability in human serum and a LNCaP cell uptake of 8.3±1.6 % (of the total activity) at 1 h. PET images showed a clear visualization of LNCaP metastases.

Conclusions
64Cu NOTA-HYNIC-iPSMA obtained from kit formulations showed high in vitro an in vivo stability in human serum and specific uptake in LNCaP cells with potential as a new theranostic radiopharmaceutical.
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