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Preclinical evaluation of the theranostic 68Ga/177Lu-[DOTA-CXCR4-L] pair

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Background
The chemokine-4 receptor (CXCR4) is overexpressed in more than 23 types of human cancers that metastasize to distant organs. In the progression of breast cancer and its metastases, the overexpression of CXCR4 has been demonstrated in 90% of triple-negative breast cancer tumors
Objective
To prepare and evaluate the in vitro and in vivo ability of 68Ga-CXCR4-L and 177Lu-CXCR4-L ligands to target the CXCR4 protein in glioblastoma and triple-negative breast cancer cells.
Methodology
68Ga labeling was performed by adding 1 M acetate buffer (pH 4.0) and gallium-68 chloride obtained from a 68Ge/68Ga generator (ITG, Germany) to a lyophilized formulation containing the cyclo(D-Tyr-D-[NMe]Orn(HYNIC-DOTA)-Arg-NaI-Gly) ligand [DOTA-CXCR4-L] followed by incubation at 95℃ for 10 min. For 177Lu labeling, 1 M acetate buffer (pH 5.0) and lutetium-177 chloride (ITG, Germany) were added to a lyophilized vial containing the DOTA-CXCR4-L following by incubation at 95℃ for 30 min. The radiochemical purity was evaluated by reversed-phase HPLC and ITLC-SG analyses. Stability studies in human serum were performed by size-exclusion HPLC. In vitro and in vivo cell uptake was tested using human breast cancer cells (triple-negative DU-4475) and human glioblastoma cells (U87MG) with blocked and non-blocked receptors. Images were obtained in athymic mice with induced DU 4475 or U87MG pulmonary micrometastasis by using a micro-SPECT/PET/CT system.
Results and discussion
68Ga-DOTA-CXCR4-L and 177Lu-DOTA-CXCR4-L obtained with radiochemical purities of 95% and 99%, respectively, showed high stability in human serum and specific in vitro and in vivo recognition in glioblastoma and triple-negative breast cancer cells. Using pulmonary micrometastasis DU-447 and U87MG models, a clear uptake of both radiopharmaceuticals was observed.

Conclusions
The results obtained in this study warrant further preclinical studies to evaluate therapeutic efficacy of 177Lu-DOTA-CXCR4-L, as well as dosimetry and clinical studies to determine the specificity and sensitivity of 68Ga-DOTA-CXCR4-L to target the chemokine-4 receptor in different kind of tumors.
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