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Preclinical Evaluation of Chemokine Receptor 4 Antagonists for High Grade NETs and NECs Theranostics

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BACKGROUND: Treatment strategies targeting Somatostatin receptor subtype 2 (SSTR2) achieve partial response or stabilize disease and improve quality of life for patients with grade 1 and 2 neuroendocrine tumors (NETs), but have little effect for G3 NETs and neuroendocrine carcinomas (NECs), suggesting a critical need for new target. Preliminary data has validated positive chemokine receptor 4 (CXCR4) expression in patients' specimens and NET cell lines together with 68Ga-Pentixafor (CXCR4 antagonist) PET/CT imaging in tumor-bearing mice. In this study, we determined CXCR7 expression which shares the same ligand as CXCR4 in NET cell lines, and further investigate known and newly designed CXCR4 antagonists for in vitro and in vivo evaluation to facilitate peptide-receptor radionuclide therapy in the future.

METHODS: The expression of SSTR2, CXCR4 and CXCR7 on cells, mice tumor xenografts and patient tissue microarray, is determined by immunohistochemistry and/or flow cytometry. CXCR4 antagonists were radiolabeled with 68GaCl3 for PET/CT imaging in mice followed by biodistribution. 90Y-, or 212Pb-antagonists were tested for in vitro binding and cytotoxicity (ongoing). Effect of antagonists on chemotaxis signal is determined by cell migration and invasiveness assay (ongoing).

RESULTS: Bon, GQP-1 and H727 cell lines express weak SSTR2 but moderate CXCR4 and CXCR7 by flow cytometry. H727 mouse xenograft expresses moderate CXCR4 while IMR32 the neuroblastoma xenograft expresses high CXCR4 by IHC

and PET imaging. 85% of poorly-differentiated NECs patients demonstrated high CXCR4 expression. 68Ga-CXCR4 antagonists showed high radiochemical purity as radiotracer for series of PET/CT imaging in tumor-bearing mice. Biodistribution displayed specifically tumor targeting, main kidney excretion and relatively high abdomen and blood retention. Radiolabeling antagonists with 90Y- or 212Pb- decreased their in vitro binding affinity.

CONCLUSION: 68Ga-CXCR4 antagonists are specific PET/CT radiotracers for high-grade NETs and NECs diagnosis. Radio-therapeutic antagonists need further investigation of their safely and efficacy in G3 NETs and NECs.