

B-9

Molecular Imaging of High-Grade Neuroendocrine Tumors Using Novel Peptide-Receptor Targeted Radiopharmaceuticals

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BACKGROUND: Grade-3 neuroendocrine tumors (NET) and neuroendocrine carcinomas (NEC) are highly aggressive and resistant to all current therapies. Somatostatin receptor type 2 (SSTR2) directed peptide-receptor radiotherapy (PRRT) has improved outcomes for patients with G1 and G2 NETs, but has had little effect on G3 NET or NEC. There is a critical need for novel approaches to diagnosis and staging of these aggressive NETs and NECs. Chemokine receptor 4 (CXCR4) is a G-protein coupled receptor (GPCR) that plays a crucial role in multiple malignancies by stimulating cell proliferation, angiogenesis, migration and metastasis of cancer cells through the PI3K/Akt/mTOR pathway. Studies have shown that SSTR2 expression decreases in high grade NETs, while CXCR4 expression increases. We hypothesize: (1) a CXCR4 antagonist, Pentixafor, will bind to CXCR4 with high specificity and affinity; and (2): ⁶⁸Ga-Pentixafor PET/CT will provide a new and highly-sensitive imaging technique for diagnosis and staging of G3 NETs and NECs.

METHODS: SSTR2 and CXCR4 gene expression was quantified by qPCR array assay and flow cytometry in high-grade cell lines (SKS; uterine carcinoma and IMR32; neuroblastoma). DOTATOC and Pentixafor were labeled with ²⁰³Pb- for SPECT/CT imaging and ⁶⁸Ga- for PET/CT imaging of tumor-bearing mice, followed by euthanasia and assessment of the biodistribution of the radiolabeled peptides.

RESULTS: IMR32 cells expressed high levels of SSTR2 and CXCR4 while SKS cells expressed a moderate level of CXCR4 and minimal SSTR2, as evidenced by both in vitro and in vivo tests. ^{203}Pb -DOTATOC and ^{68}Ga -DOTATOC targeted specifically to SSTR2-expressing tumor xenografts. PET/CT imaging using ^{68}Ga -Pentixafor demonstrated high uptake in CXCR4-expressing tumors (5.8%ID/g) with primarily renal clearance and partial distribution to digestive tract.

CONCLUSION: ^{68}Ga -Pentixafor is an excellent PET tracer targeting CXCR4 in tumor-bearing mice. ^{68}Ga -Pentixafor PET/CT has the potential to provide diagnostic and staging information in patients with Grade-3 NET or NEC.