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Development of Gallium-68 Labeled Neuropeptide Analogs for Imaging NET by Positron Emission Tomography

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Background: Gallium-68 (^{68}Ga) labeled analogs of somatostatin (sst) have been demonstrated to be effective for imaging NETs by positron emission tomography (PET) in European clinical studies. These radiopharmaceuticals are more reliable (and prepared more conveniently) than fluorine-18 (^{18}F) labeled glucose (^{18}F-FDG) and dihydroxyphenylalanine (^{18}F-DOPA); with superior image quality/sensitivity compared to indium-111 single-photon-emission computed tomography (SPECT). ^{68}Ga-sst analogs target upregulation of sst receptor subtype-2 (sst2) in NETs. However, upregulated sst2 in NET is not ubiquitous and alternative-receptor targets (e.g., G-protein coupled receptors) are needed. We examined [^{68}Ga]-labeled analogs of sst and neuropeptide-Y (NPY) for imaging xenograft NETs in rats.

Methods: Cells (BON, SKNBE, SHSY5Y) were cultured by standard techniques. Sst analog tyr^3-octreotide (TOC) and NPY derivative YPSKxRHYINLITRQRY (NxPY; targeting NPY receptor subtype 2; x = hexanoic acid) were conjugated to chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) by standard methods. Radiolabeling was performed at pH 3.5 (100˚C, 10-20 minutes). Competitive binding assays established receptor specificity. Tumors were induced by subcutaneous flank injection of cells in nude rats (~4 weeks). Radiochemical purity (RP) and specific activity (SA) were monitored by radioHPLC. Imaging was performed using a Phillips Mosaic microPET.

Results: Binding assays demonstrate receptor specific binding with low IC50's (nM range) for [^{68}Ga]-DOTATOC and [^{68}Ga]-DOTANxPY. Western blots confirmed receptor expression. Dynamic PET imaging of [^{68}Ga]-DOTATOC (15.6 MBq) revealed SKNBE2 tumor:background accumulated to a constant value of 7 (120 min. PI), while BON tumor activity increased for approximately 60 minutes and then decreased to a final value of 3.6 (120 min. PI). Static imaging of [^{68}Ga]-DOTANxPY (11.6 MBq) revealed a tumor(SHSY5Y):background of 2 at 60 min. PI. Radiolabeling results:

Conclusions: These results prepare us to move forward with [^{68}Ga]-DOTATOC for early phase PET imaging trials of NETs. [^{68}Ga]-DOTANPY is a promising radiopharmaceutical.