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Discovery of G Protein Coupled Receptor Tumor Signatures and Identification of Positron Emission Tomography Imaging Targets in Ileal and Pancreatic Neuroendocrine Tumors

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Background: G protein coupled receptors (GPCR) have emerged as candidates for molecular targeting in neuroendocrine tumors (NETs). GPCR characteristics that account for their success as drug targets include cell surface expression, exquisite specificity of ligand-receptor interactions, and key roles in NET signal transduction pathways. *We hypothesize that pancreatic and ileal NETs have distinct GPCR signatures that can be exploited to develop tumor specific Positron Emission Tomography (PET) imaging agents.*

Methods: Specimens of ileal and pancreatic NET plus adjacent normal tissue were obtained at surgery according to an IRB approved protocol. RNA was isolated from matched tissues, reverse transcribed, and applied to TaqMan Human GPCR arrays for quantitative PCR. Results were confirmed using genome wide EXON chip analysis. Data were analyzed using Relative Quantification Manager and StatMiner software. Octreotide and α-MSH were synthesized using solid phase chemistry, conjugated with DOTA, purified by HPLC, and radiolabeled with Gallium-68 for in vitro membrane binding and *in vivo* PET imaging.

Results: Tumor specific GPCR signatures were identified in pancreatic and ileal NETs. Pancreatic NETs over-express somatostatin (sst2) and serotonin (HTR1D) receptors. In contrast, ileal NETs over-express melanocortin (MC1R), opiate (OPRK1), ghrelin (GHSR), and calcitonin (CALCR) receptors. [^{68}Ga]-DOTATOC and [^{68}Ga]-DOTA-α-MSH targeting sst2 and MC1R, respectively, were synthesized and radiolabeled with high specific activity and radiochemical purity. High affinity binding of [^{68}Ga]-DOTATOC was demonstrated *in vitro* in NET cell lines. Localization of NET xenografts was demonstrated *in vivo* using [^{68}Ga]-DOTATOC PET.

Conclusions: GPCR TaqMan arrays have identified tumor specific molecular signatures for pancreatic and ileal NETs that are distinct from adjacent normal tissue. Development of receptor specific ligands as PET imaging agents will enable more sensitive, non-invasive identification of primary tumors as well as quantitative assessment of response to therapy. Molecularly targeted PET imaging may also pave the way for development of tumor specific radiotherapy.