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# Molecular Targeting of G Protein-Coupled Receptors MC1R and VPAC1 for Positron Emission Tomography Imaging of Pancreatic Neuroendocrine Tumors

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**Background:** G protein-coupled receptors (GPCR) have emerged as candidates for molecular targeting in neuroendocrine tumors (NETs) due to their cell surface expression, exquisite specificity of ligand-receptor interactions, and key roles in NET signal transduction pathways. We hypothesize that the over-expression of MC1R and VPAC1 in pancreatic NETs 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. Unique, high affinity, stable peptide analogs of □melanocyte stimulating hormone ( □ MSH) and vasoactive intestinal peptide (VIP) 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:** Melanocortin (MC1R) and vasoactive intestinal peptide (VPAC1) receptors were identified as tumor specific GPCR targets in pancreatic NETs. Analogs of [redacted]MSH and VIP targeting MC1R and VPAC1, respectively, were synthesized and assayed for high affinity binding, metabolic stability, and stimulation of cAMP in vitro. Localization of MC1R-expressing xenografts was demonstrated in vivo using both fluorescence and PET imaging techniques.

**Conclusions:** GPCR TaqMan arrays have identified MC1R and VPAC1 as tumor specific molecular targets in pancreatic 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.