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Identification of Oxytocin Receptor (OXTR) as a Specific Theranostic Target in Ileal Neuroendocrine Tumors

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Background: G protein-coupled receptors (GPCR) have emerged as candidates for molecular targeting in neuroendocrine tumors (NETs) and their ligands show promise as theranostic agents, where a single compound is used for both diagnosis and therapy. *We hypothesize that peptides targeting OXTR can be radiolabeled with Ga-68 for diagnostic PET imaging and Y-90 for targeted therapy of OXTR-positive ileal NETs.*

Methods: Fresh tumor and adjacent normal tissue was obtained at surgery from patients with ileal (16) and pancreatic (10) NET. Specimens were immediately preserved in RNA-later and frozen for isolation of RNA and conversion to cDNA. GPCR expression was quantitated for tumor and normal tissue. Expression level of OXTR in ileal and pancreatic NET was confirmed by immunohistochemistry. A library of oxytocin analogs, predicted to have OXTR agonist or antagonist activity, was synthesized using solid-phase chemistry and conjugated with fluorescein. Agonist/antagonist activity of synthetic peptides was measured by calcium influx assays in cell lines expressing OXTR.

Results: GPCR expression data demonstrate overexpression of OXTR in ileal with little or no expression in pancreatic NET. A library of peptides was generated to target OXTR; fluoro-oxytocin bound to ileal but not pancreatic NETs. Oxytocin induced a positive response in calcium influx assays using PC3 cells that express OXTR.

Conclusions: We have identified OXTR as a specific and highly expressed target in ileal NET. Preliminary studies demonstrate binding of fluoro-oxytocin in OXTR expressing ileal NETs as well as oxytocin-induced calcium flux in OXTR expressing cell lines.

Future directions: Peptides in the oxytocin library will be used to characterize affinity, specificity, and agonist/antagonist activity for OXTR. Leading candidates will be tested as PET imaging agents and therapeutic radiopharmaceuticals in a mouse model of NET. GPCR targeted imaging and therapy is a powerful new THERANOSTIC tool in development of personalized treatment for patients with neuroendocrine tumors.