Background/Significance to NETS

The availability of **Peptide Receptor Radionuclide (Lutathera) Therapy** (PRRT) for neuroendocrine tumors and the possibility of developing peptide drug conjugates targeting the SSTR have encouraged us to develop strategies to increase SSTR expression. Increased SSTR expression has the potential to increase the efficacy of SSTR therapies by increasing available target. For the 175,000 people in the U.S. who are living with this diagnosis, increased expression and increased efficacy of therapies already shown to prolong survival could be of major benefit.

Material and Methods/Experimental Approach

We have examined a spectrum of neuroendocrine cell lines and have been able to demonstrate induction of the SSTR in a subset of cell lines, but not in all, including cell lines of lung and prostate origin. Specifically, using romidepsin, a histone deacetylase (HDAC) inhibitor approved by the FDA for the therapy of cutaneous and peripheral T-cell lymphoma, we have been able to increase the expression of SSTR2 and SSTR5 in neuroendocrine models. The increases occur quickly at nanomolar concentrations of romidepsin, making the observations clinically relevant. Note this is a strategy that looks to modulate gene expression not to induce cell death as has been the basis of epigenetic agent regulatory approvals to date. Consequently we have looked to induce expression of the SSTR at concentrations that are not or only minimally cytotoxic.

Results & Key Findings

With romidepsin increases have been observed at single digit nanomolar concentrations, begin within 24 hours of drug administration, and increase further with continued exposure up to 96 hours. The increase is sustained after the removal of drug for at least 48 hours. Increased SSTR expression confers increased sensitivity to an SSTR targeted agent but ongoing studies looking at target engagement have been designed to discriminate between greater toxicity from simple additivity of two cytotoxic agents as opposed to greater toxicity from increased SSTR expression and drug delivery with enhanced target engagement.

Conclusion/Next Steps

Our goal is to develop a regimen/strategy that allows us to use epigenetic agents including HDAC inhibitors, DNA methyltransferase (DNMT) inhibitors and Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit (EZH2) inhibitors for brief periods of time to induce a transient increase in surface expression of SSTR2, and in turn increase delivery of radiolabeled pharmaceuticals or peptide drug conjugates targeting the somatostatin receptor.