While the incidence of most cancers in the United States has declined, the incidence of thyroid cancer has been increasing at an annual rate of 5.5% and 6.6% in men and women, respectively. Two transcription factors, Runx2 and TRβ have been implicated in thyroid tumorigenesis. Thyroid Hormone Receptors (TRs) are ligand-dependent transcription factors encoded by the TRα and TRβ genes and have been reported to inhibit cell transformation, proliferation, and inhibit tumor progression. Activation or increased expression of Runx2 induces an array of genes associated with cell adhesion, invasion, and survival. Inhibition of Runx2 expression is associated with either a reversal or a less aggressive phenotype in breast cancer cells implicating Runx2 as a key regulator of tumorigenesis. In the context of the onset of thyroid cancer, a compelling question is whether there is coordinated expression of TRβ and Runx2 and if TRβ tumor suppressor activity is mediated in part through modulation of Runx2. The focus of this project is on the expression of TRβ and Runx2 in benign and malignant thyroid cell lines following various treatments of Thyroid Hormone (T3). T3 exposure induced a time and concentration dependent decrease in Runx2 protein levels in both benign and malignant thyroid cells. The discovery of this TRβ-Runx2 signaling pathway provides a novel target for therapeutic intervention.