G protein coupled receptors (GPCR) on airway smooth muscle (ASM) cells are critical regulators of the airway hyperresponsiveness (AHR) and airway remodeling that occurs with asthma. Therefore, agonists or antagonists of GPCRs expressed on ASM cells are used to treat asthmatics. Gq signaling in ASM involves activation of phospholipase C that converts phosphoinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3). While IP3 leads to increases in [Ca2+]i, phosphorylation of MLC20 and ASM contraction, DAG directly activates PKC family members and Ras guanyl nucleotide-releasing protein. Gs signaling on the other hand involves generation of cyclic AMP and activation of PKA which phosphorylates multiple intracellular targets to initiate ASM relaxation. Studies in our laboratory are focused on identifying multiple modes of regulating ASM functions via GPCRs. This includes identifying novel receptors expressed on ASM cells, intracellular signaling machinery involved in receptor desensitization and establishing mechanisms of signaling/functional compartmentalization in ASM cells. The findings from these studies will not only advance the basic science of ASM biology and biochemistry, but also identify novel therapeutic targets whose manipulation can be exploited for developing a novel asthma therapy that addresses both AHR and airway remodeling.