

Drs. Lu and Cardoso

Tnrc6a proteins are essential for miRNA-mediated gene silencing, a fundamental mechanism required for proper development, homeostasis, and function of an organism. The function and mechanism of Tnrc6a (GW182) and its associated cytoplasmic granules, GW/P-bodies (GWBs) have been well studied in mammalian cells cultured in vitro. However, the significance for the formation of GWBs is unclear. Moreover, the expression, localization and function of Tnrc6a and GWBs during development in vivo are still poorly understood. To study Tnrc6a and GWBs in vivo, we have generated Tnrc6a mutant mice, and shown that Tnrc6a is required for miRNA-induced gene silencing. In this proposal, we will expand our studies to understand a subcellular localized miRNA mechanism that is associated with Tnrc6a and GWBs in multiciliated cells of airways. We have remarkable preliminary observations that Tnrc6a is highly expressed in multiciliated cells and Tnrc6a proteins are concentrated in GWBs that are closely associated with centrioles/basal bodies. Moreover, disruption of Tnrc6a expression leads to major defects in cilia formation. In Aim1, we proposed to determine how Tnrc6a regulates cilia formation and function by affecting key cellular events of ciliogenesis. In Aim 2, we proposed to rigorously characterize these unique multiciliated cell-specific GWBs, and determine the functional significance of formation and localization of Tnrc6a/GWBs in ciliogenesis. In Aim3, we will identify the miRNA program associated with these centriole associated GWBs that regulates ciliogenesis. Successful accomplishment of these studies will allow us to identify a novel subcellular localized miRNA mechanism in ciliogenesis that is associated with selectively enriched expression of Tnrc6a and the formation and localization of GWBs.