"Mechanisms of miRNA biogenesis and mRNA targeting and molecular interventions to modulate miRNA pathways in normal and disease states"

Principal Investigator:
- Thomas Tuschl, PhD, Rockefeller University

Co-Principal Investigators:
- Dinshaw Patel, PhD, Memorial Sloan-Kettering Cancer Center
- Eric Holland, MD, PhD, Memorial Sloan-Kettering Cancer Center
- Hakim Djaballah, PhD, Memorial Sloan-Kettering Cancer Center

Funding Category: A

Abstract: The long-term objective is to develop a detailed understanding of miRNA-regulated processes in mammals and to develop molecular tools to control these processes. We will establish a screening platform for identifying general and/or specific miRNA pathway inhibitors by exploiting tumor- or disease-associated miRNA expression in cell-based drug screens. Small molecule inhibitors of the RNAi process will advance biochemical and structural studies and will facilitate functional studies in animal models. Any small molecule drugs that control tumor-associated miRNA pathways may open new doors to cancer drug development, while the role of selected tumor-associated miRNAs will be explored using murine brain tumor models.
Specific aims are:
1. Perform biochemical and structural analysis of proteins and ribonucleoprotein complexes required for general miRNA biogenesis and function.
1.1. Solve crystal structures of the ribonucleoprotein complexes involved in miRNA maturation and miRNA-targeting.
1.2. Define the molecular network of miRNA and target mRNA interactions by biochemically immuno-precipitating (IP) miRNA-mRNA complexes to directly identify the miRNA-bound mRNA segments.
2. Perform small molecule drug screens to identify inhibitors for the entire miRNA pathway and/or specific repression of cancer-relevant miRNAs (miR-21, miR-17, miR-155). We will also define the specific targets and inhibited processes.
3. Analyze miR-21 as an oncogenic factor in murine glioma and medulloblastoma animal models. We will apply technology of miRNA target isolation to cell and tumor samples to assess the relevance of targeted mRNAs in controlling tumor growth. Test small molecule inhibitors of the general miRNA pathway and those specific for miR-21 in these tumor models.