Functional Analysis of Ectopic Germline Gene Expression in Cancer

Principal Investigator:
Gregory J. Hannon, PhD, Cold Spring Harbor Laboratory

Co-Principal Investigators:
- Gurinder Atwal, PhD, Cold Spring Harbor Laboratory
- Robert B. Darnell, MD, PhD, The Rockefeller University

Funding Category: A

Abstract: Considerable similarities between germ cell development and tumor progression have long been observed: Cancer cells, like germ cells, struggle in a complicated balance between genomic stability and flexibility; both are considered immortal; and analogous to the migration of germ cells, cancer cells metastasize. To ensure genomic stability, germ cells employ specialized RNA interference pathways that silence transposons. At the core of these pathways are PIWI proteins and their associated small RNAs. Recent studies revealed expression of PIWI pathway components outside of the germline in various cancers - strengthening earlier observations of ectopic germline gene expression in cancer. Such germline genes are potentially ideal targets for diagnosis, therapy, and vaccination due to their restricted physiological expression and unique immunogenic properties. Here, we propose to systematically investigate germline signatures and their functions in oncogenesis through a multidisciplinary approach combining computational, molecular and biomedical methodologies. First, we will assemble a compendium of functional germline gene-networks and characterize cancer/germline signatures computationally. Second, we will investigate the function and molecular mechanisms of piRNA pathways in cancer. Based on the importance of small RNA silencing pathways in development and disease and the vital function of piRNA pathways in the germline, we anticipate uncovering a novel layer of gene regulation in cancer. Third, we will elucidate the function of germline signatures in glioblastoma *in vivo* and evaluate their clinical potential. Overall, this work will provide comprehensive identification and characterization of functional germline signatures in cancer with the aim of identifying candidate vaccine antigens, diagnostic markers, and therapeutic targets.