

## “Integrative Computational Analysis to Drive Discovery of microRNA-mediated Regulatory Networks in Cancer”

### *Principal Investigator:*

- Christina Leslie, PhD, Memorial Sloan-Kettering Cancer Center

### *Co-Principal Investigators:*

- Olivier Elemento, PhD, Weill Cornell Medical College
- Christopher Mason, Weill Cornell Medical College
- Eric Holland, MD, PhD, Memorial Sloan-Kettering Cancer Center
- Chris Sander, PhD, Memorial Sloan-Kettering Cancer Center

Funding Category: A

**Abstract:** MicroRNAs (miRNAs) are small RNAs that regulate gene expression through post-transcriptional gene silencing and are now known to play an important role in the initiation and progression of cancer. Due to the availability of large tumor data sets containing multiple types of molecular profiling data, we now have the opportunity to computationally dissect the role of miRNAs in cancer. However, while many computational studies have identified cancer subtypes and expression signatures, few have attempted to construct the gene regulatory programs underlying these subtypes or model the contribution of miRNAs to these programs. In this study, we will develop novel integrative computational methods that exploit large tumor data sets - including mRNA and miRNA expression profiles and copy number data - to investigate both transcriptional and miRNA-mediated dysregulation of gene expression in cancer. We will combine regulatory sequence analysis with profiling data to infer common and subtype-specific regulators and use network analysis to identify dysregulated pathways. To validate and build upon our computational analysis, we will also generate and analyze new deep sequencing data from tumor samples and experimentally validate predicted miRNA regulators. We will use glioblastoma multiforme (GBM) and diffuse large B-cell lymphoma (DLBCL) as the main two case studies for the project, since our project team has strong experimental and computational expertise in these cancers. Our broader goal is to develop a systematic strategy for using computational analysis of multi-model data sets to drive experimental discovery. This strategy would be widely applicable in cancer genomics research.