

## “Ago-miRNA Dysregulation in Primary and Metastatic Breast Cancer”

*Principal Investigator:*

- Robert Darnell, MD, PhD, The Rockefeller University

*Co-Principal Investigator:*

- Joan Massagué, PhD, Memorial Sloan-Kettering Cancer Center

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**Abstract:** We propose to explore miRNA-related dysregulation of mRNA expression in breast cancer. The Massagué lab has pioneered studies of cancer metastases, which are responsible for 90% of cancer deaths. Studies of primary and metastatic breast cancer have identified several miRNAs that contribute to breast cancer biology, but it has not been possible to systematically identify the mRNAs regulated by these miRNAs, nor the sites bound and regulated by these miRNAs, as miRNA action requires binding to only 6 nucleotide mRNA seed sequences. A robust means of identifying both the set of regulated mRNAs and their precise miRNA binding sites is possible with a new technology described in the last year by the Darnell lab. This method, HITS-CLIP, allows a genome-wide assessment of RNA-protein interactions in clinical tumor specimens. The method is general, and also can be used to assess the emerging role of miRNA co-factors. We will use HITS-CLIP to develop a comprehensive understanding of key miRNA-mRNA-protein interactions in primary and metastatic human breast tumors. Follow-up studies will explore the function and elimination of such RNA regulation using animal breast cancer models established by the Massagué lab. The work fits the RFA's Key Criteria: taking new methods in a previously unexplored direction, harnessing different skills-RNA biology and models of metastatic cancer-in a synergistic collaboration. It offers the potential to transform our understanding of the role of RNA regulation in cancer biology and to identify otherwise occult targets that may be exploited therapeutically.