

“A Multidisciplinary Approach to the Study of an Oncogenic microRNA Cluster”

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Abstract: In recent years miRNAs have gained considerable attention due to their ability to selectively regulate hundreds of genes in a precise temporal and spatial fashion. In addition to playing important roles in development, some miRNAs have been shown to act as oncogenes and tumor suppressors. In particular, several lines of evidence indicate that the polycistronic *miR-17~92* cluster, which encodes six distinct miRNAs, is an important human oncogene. Here we propose to investigate the function of *miR-17~92* in development and cancer. We will utilize mouse genetics, biochemistry, high-throughput sequencing and computational biology to identify the targets of the individual components of this important oncogene. There are two unique aspects to our approach. First, is the availability of an allelic series of knock-in mouse strains with targeted deletions of individual miRNA members of *miR-17~92*. These strains will enable us to define the relative contribution of each member of the cluster to development and cancer, and will form the basis for the functional validation of individual targets. The second innovative aspect of our proposal is the use of a genome-wide unbiased biochemical approach for identifying miRNA targets. The combination of these approaches will allow us to pin-point the relevant mRNA targets by which *miR-17~92* mediates its regulatory function and to establish a general framework for studying the functional role of other miRNAs in cancer and development. This proposal will provide key insights into the biology of an important oncogene, an essential step toward the development of novel therapeutic strategies.