Vector-Based Strategies for RNAi Expression in Whole Mammals – *Kay*

Our efforts have been directed at establishing the scientific and clinical principles required for the therapeutic delivery of nucleic acids into mammals. We continue to pursue both recombinant adeno-associated viral vectors (rAAV) and a new type of DNA non-viral vector we refer to as minicircle DNA plasmids. Both of these vector systems have specific advantages and disadvantages. However, we have used rAAV vectors in a bench to bedside approach for treating hemophilia B (factor IX deficiency) in animal models and humans. The limitations of rAAV vectors include (1) the host immune system that can limit gene transfer and/or the persistence of gene expression in vivo, and (2) the ability to selectively transduce specific tissues at high efficiency. To circumvent these problems, we have developed an interspecies molecular evolution strategy to select for rAAV vectors with various infection parameters, including re-targeting properties. These vectors are now being tested in various gene transfer strategies.

A second area of interest has been to develop strategies to place RNAi expression sequences into gene expression vectors such as rAAV. We have used these RNAi-based vectors to inhibit the replication of human pathogenic viruses (HBV and HCV) as well as endogenous genes in animal models of disease. By combining the current technological advances in gene transfer vectorology with the recent advances in RNAi biology, new therapeutic applications are just beginning to be realized. I will present our recent advances in this area and what we need to do to achieve success in various clinical applications.