

S003 Mechanisms and therapeutic application of RNA interference
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RNA interference (RNAi) has become a powerful tool for sequence specific down regulation of gene expression in eukaryotes. In mammals, it has been shown that the triggers for RNAi, small interfering RNAs (siRNAs) can direct both post-transcriptional gene silencing (PTGS) as well as transcriptional gene silencing (TGS). We have been studying the mechanisms of action of siRNAs as well as the therapeutic application of siRNAs for the treatment of HIV infection. We have developed a novel gel shift screen to identify potent siRNA/target combinations. We have also shown that siRNAs which are long enough to serve as substrates for the enzyme Dicer can be up to 100 times more potent than conventional 21 base duplexes. We hypothesize that this is the result of handing off the antisense strand to the effector components of the RNA induced silencing complex (RISC). In addition to PTGS, we have shown that siRNAs can trigger TGS by recruiting histone methyl transferases and altering chromatin structure. We have used siRNAs to silence the CCR5 promoter and find that Argonaute 1, TRBP and at least one of the Polycomb proteins are components of the silencing complex. Finally, we have developed a combinatorial RNA based strategy for the gene therapy treatment of HIV infection. We are using a lentiviral vector to deliver a combination of RNA based therapeutic genes to human hematopoietic progenitor cells. Progress of moving this into a therapeutic trial will be discussed.