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RNAi-mediated inhibition of HIV-1

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HIV-1 replication can be effectively suppressed by stable expression of a potent antiviral short hairpin inhibitor (shRNA), but HIV-1 eventually escapes. When the non-essential nef gene is targeted, we reported a diversity of escape routes, from a single point mutation to complete deletion of the 19-nucleotide target sequence. We reasoned that deletion-mediated escape would not be possible when essential viral genes are targeted. We therefore selected potent shRNAs against the most conserved viral sequences. Indeed, no deletions were observed in these cases, but the virus still escaped through point mutation(s). Interestingly, silent codon changes were preferentially selected for some of these targets, indicating extreme pressure on the virus not to change the encoded protein domains. In analogy with the use of multiple antivirals in HAART to prevent viral escape, we designed strategies to express multiple antiviral shRNAs from a lentiviral vector system. Many problems were encountered (self-targeting, recombination on repeated promoter elements etc), but these could be solved by vector redesign. We constructed a lentiviral vector that co-expresses 4 potent shRNAs, and we observed durable virus suppression in stably transduced T cells. This construct was tested for safety and efficacy in the humanized immune system mouse (HIS mouse). We tested whether shRNA-transduced human $CD34^+$ precursor cells develop normally during haematopoiesis as a very sensitive toxicity screen. In addition, new approaches to attack viruses across the blood-brain-barrier will be presented.