

**S004** From mouse to monkey, on the way to man:  
Systemic Delivery of siRNAs and Antagomirs

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The main obstacle to achieve *in vivo* gene silencing by RNAi technologies is delivery. We have taken two strategies to overcome this challenge. In the first approach, which is based on a chemical conjugation approach, (*Nature* 2004, 432, 173-178.) that cholesterol conjugated short interfering RNAs (siRNAs) have shown silence an endogenous gene encoding apolipoprotein B (apoB) after intravenous injection in mice. Administration of siRNA conjugate resulted in silencing of the apoB messenger RNA in liver and jejunum, decreased plasma levels of apoB protein, and reduced total cholesterol. Alternatively (*Nature* 2006, 441, 111-114.), using a liposomal formulation approach, we demonstrated systemic efficacy of siRNAs in non human primates using the same target. *APOB*-specific siRNAs were encapsulated in stable nucleic acid lipid particles (SNALP) and administered by intravenous injection to cynomolgus monkeys at doses of 1 or 2.5 mg kg<sup>-1</sup>. A single administration resulted in dose-dependent silencing of *APOB* mRNA expression in the liver 48 h after administration, with maximal silencing of >90%. Significant reductions in ApoB protein, serum cholesterol and LDL levels were observed as early as 24 h after treatment and lasted for 11 days at the highest siRNA dose, thus demonstrating a potent and lasting therapeutic effect of siRNA treatment. Furthermore, using the conjugation chemistry strategy, we demonstrated that cholesterol conjugated miRNA complement oligonucleotides, termed 'antagomirs', are efficient and specific silencers of endogenous miRNAs in mice. (*Nature* 2005, 438(7068), 685-689).