RNA INTERFERENCE

Breakthrough for systemic RNAi

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RNA interference (RNAi) has become a powerful research tool, yet progress in developing therapeutic applications of this technology has only recently started to gather momentum. In a major advance for this field, Zimmermann, MacLachlan and colleagues report in *Nature* the first demonstration of gene silencing in non-human primates after systemic delivery of small interfering RNA (siRNA).

RNAi-based therapeutics harness an endogenous cellular regulatory mechanism in which small double-stranded RNA molecules, or siRNA, bind to and mediate the destruction of specific mRNA molecules, preventing their translation into protein. Despite its great potential, moving siRNA forward into the clinic is beset by problems with siRNA stability and *in vivo* delivery.

Current siRNA-based drugs in clinical development rely on direct delivery to the diseased tissue (by injection, for example). Until now, few studies have reported successful systemic siRNA delivery even in rodent models, and strategies to achieve this are highly sought after. In this new study, researchers from Alnylam Pharmaceuticals and Protiva Biotherapeutics collaborated to target a clinically relevant gene, apolipoprotein B (ApoB), in a non-human primate using systemically delivered siRNA.

siRNA can target molecules that conventional therapeutics cannot reach. One such target is ApoB, a component of low-density lipoprotein (LDL), which is involved in cholesterol transport and metabolism, and linked with various coronary diseases. Although available drugs, including statins, have improved the management of these diseases, limitations exist, such as variable response and delayed efficacy. New strategies to reduce LDL are therefore in demand, making ApoB an important target.

Following previous work, in which ApoB was successfully silenced in rodents, the researchers set out to translate this strategy to a more clinically relevant model, the cynomolgus monkey. Importantly, to achieve selective and efficient delivery to the liver, where ApoB is synthesized, siRNA was encapsulated into small stable nucleic-acid–lipid particles, which remain stable in the bloodstream and are readily taken up by liver cells. Beginning as early as 24 hours after a single intravenous dose of siRNA, a drop in ApoB protein, LDL and cholesterol levels lasting at least 11 days was observed. This was associated with a 90% reduction in ApoB mRNA levels in the liver that was demonstrated to be mediated by RNAi. Interestingly, the gene-silencing effect was both stronger and longer-lasting than had been predicted from rodent studies — an early indication of some potentially useful therapeutic features of this agent.

Safety issues remain a major concern for therapeutic use of siRNA, with some studies reporting off-target effects on other mRNA molecules and proteins. In this study, no evidence of serious toxicity was observed; however, longer-term and more detailed safety evaluations will clearly be required before this technology can be transferred to the clinic. Nevertheless, this study represents a crucial step forward in the application of RNAi-based therapeutics, demonstrating the potential for siRNA to be delivered systemically and therefore opening up the range of diseases which could be tackled using this technology.

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ORIGINAL RESEARCH PAPER Zimmermann, T. S. *et al.* RNAi-mediated gene silencing in non-human primates. *Nature* 26 March 2006 (doi:10.1038/nature04688).