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EDITORIAL

RNA interference-based therapeutics and diagnostics

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The 2006 Nobel Prize in Medicine and Physiology was awarded to Andrew Fire and Craig Mello only 8 years after their *Nature* publication showing small double-stranded RNA (siRNA)-mediated gene silencing by the process of RNA interference (RNAi). This remarkable recognition highlights the importance and immense implications of understanding and controlling cellular gene expression as a functional genomic study tool and its potential exploitation as a therapeutic modality. The discovery in 2001 by Thomas Tuschl's group that RNAi is found in mammals and exogenous synthetic siRNA introduced into the cell could silence genes fuelled initial excitement that small RNAs were a paradigm shift in therapeutics. Expectations were high because of the potential of these molecules to "silence" or "knock-down" any gene of interest to treat almost any disease by targeting otherwise "undruggable" targets such as molecules without ligand-binding domains or enzymatic function. A greater understanding of the RNAi mechanisms and rapid expansion of the field has resulted in the identification of a wide repertoire of RNAi triggers that engage at various levels of the RNAi cascade, collectively termed small interfering nucleic acids (siNA) that could be exploited as molecular medicines. MicroRNAs (miRNA), for example, are endogenous small non-coding RNA that control cellular gene expression whose deregulation can be associated with disease states, and as a consequence, have gained considerable attention as disease biomarkers and therapeutic drugs or targets.

Despite the promise, the clinical translation of siNA therapeutics has proven challenging. The main obstacle is delivery of these molecules to target sites and into cells at therapeutically relevant levels without toxicity. The expanding classes of siNA include mimics of endogenous microRNAs to suppress the expression of many genes, but with less efficient suppression of each one. The delivery requirements needed for conventional siRNA and imperfectly paired microRNA mimics are essentially the same although antagonizing endogenous microRNAs using single-stranded antisense oligonucleotides may be somewhat easier. When injected intravenously, siNA are rapidly cleared by renal filtration and are susceptible to degradation by extracellular RNases. The siNA circulatory half life can be increased—even to days—by chemical modifications to eliminate susceptibility to endogenous exonucleases and endonucleases and by incorporating the siNA into a larger moiety, above the molecular weight cutoff for kidney filtration. Intracellular entry is, however, a major hurdle due to the polyanionic nature and high molecular weight of siRNA. Although cells can endocytose many types of modified nucleic acids or nucleic acids-containing particles, another important bottleneck is getting these molecules efficiently out of the endosome into the cytosol where the RNAi machinery resides or into the nucleus for precursor miRNA or expression vectors for siNA.

Nucleic acid therapeutics has been extensively studied both in academia and in the pharmaceutical industry with high

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expectations as new therapeutic modalities especially in personalized medicine. The major hurdle that limits the translation of nucleic acids-based therapeutics and diagnostics from an academic concept to clinical use is the lack of efficient and safe delivery strategies.

This special DDTR issue *RNA interference-based therapeutics and diagnostics* addresses the fundamental biology of RNAi and its relevance in specific disease types with focus on miRNA in clinical diagnostics and therapeutics. The tutorial reviews and original manuscripts contained in this issue focus on state-of-the-art enabling delivery technologies for utilization of RNAi as a therapeutic modality and its clinical translation.

The application of RNAi-based treatments for inflammatory bowel disease highlights inflammatory bowel disease (IBD) as an example to show the benefits of an RNAi-based approach compared to conventional anti-inflammatory treatments. It addresses the underlying molecular basis for the disease crucial to identify the cellular and RNAi targets. Optimal siRNA designs that reduce nonspecific immune stimulation and maximize potency, and delivery solutions required for the clinical translation of RNAi-based IBD treatments are addressed. *Profiling of circulating microRNAs for prostate cancer biomarker discovery* reports genome-wide miRNA profiling of patient serum samples for identification of biomarkers as a prostate cancer diagnosis and prognostic tool. *A paradigm shift for extracellular vesicles as small RNA carriers: from cellular waste elimination to therapeutic applications* describes the biological role of membrane vesicles derived from multivesicular endosomes, termed exosomes, in cellular transport of RNAi molecules such as miRNA. The article focuses on utilization and advantages of exosomes as natural carrier systems for RNAi-based therapeutics and challenges for clinical translation. *miRNA delivery for cancer therapy* addresses the role of miRNA in cancer, extracellular and intracellular delivery requirements, and nonviral delivery solutions. Subsequent articles focus on delivery methods for RNAi therapeutics; *Multifunctional polyion complex micelle featuring enhanced stability, targetability, and endosome escapability for systemic siRNA delivery to subcutaneous model of lung cancer* addresses extracellular and intracellular delivery components that can be built into the nanoparticle design for delivery into tumors. *Hepatic RNA interference: delivery by synthetic vectors* focuses on hepatic targeting, optimal designs, disease targets, and preclinical studies. *Lipid nanoparticle delivery systems for siRNA-based therapeutics* describes the clinical application of lipid nanoparticles for delivery of siRNA with focus on treatment of liver diseases that are presently the main application for RNAi-based therapeutics in the clinic. *Gene silencing and antitumoral effects of Eg5 or Ran siRNA oligoaminoamide polyplexes* describes preclinical studies utilizing sequence-defined cationic oligomers for delivery of siRNA for antitumor activity. The clinical translation of RNAi-based therapies is dependent on safety as well as activity. *Toxicity profiling of several common RNAi-based nanomedicines: a comparative study* presents a comprehensive toxicity analyses of several RNAi-based delivery strategies with mechanistic insights into the different types of toxicities.

This issue has assembled global leaders in RNAi, nanomedicine, clinical diagnostics, and delivery science that reflect the broad nature of the field and the requirement for interdisciplinary research in order for RNAi-based therapeutics and diagnostics to reach their clinical potential.

Conflict of interest Kenneth Alan Howard declares no conflict of interest in this work. Dan Peer has financial interest in Quiet Therapeutics.