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Engineering RNA for Targeted siRNA Delivery and Medical Application ☆

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ABSTRACT

RNA engineering for nanotechnology and medical applications is an exciting emerging research field. RNA has intrinsically defined features on the nanometre scale and is a particularly interesting candidate for such applications due to its amazing diversity, flexibility and versatility in structure and function. Specifically, the current use of siRNA to silence target genes involved in disease has generated much excitement in the scientific community. The intrinsic ability to sequence-specifically downregulate gene expression in a temporally- and spatially controlled fashion has led to heightened interest and rapid development of siRNA-based therapeutics. Although methods for gene silencing have been achieved with high efficacy and specificity *in vitro*, the effective delivery of nucleic acids to specific cells *in vivo* has been a hurdle for RNA therapeutics. This article covers different RNA-based approaches for diagnosis, prevention and treatment of human disease, with a focus on the latest developments of non-viral carriers of siRNA for delivery *in vivo*. The applications and challenges of siRNA therapy, as well as potential solutions to these problems, the approaches for using phi29 pRNA-based vectors as polyvalent vehicles for specific delivery of siRNA, ribozymes, drugs or other therapeutic agents to specific cells for therapy will also be addressed.

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One research area in the emergent popular field of nanotechnology involves modification, engineering and/or assembly of organised materials on the nanometre scale [1,2], thereby forming conjugative or alternated supramolecular structures [3–5]. The modified materials can then be used as building blocks in nanomedicine or nanotechnology.

Biological macromolecules, including DNA, RNA and proteins, intrinsically have defined features at the nanometre scale and can serve as unique and powerful building blocks for the bottom-up fabrication of nanostructures and nanodevices. RNA is a particularly interesting candidate for nanotechnology applications due to its amazing diversity, flexibility and versatility in structure and function [6–9]. RNA molecules are polymers made up of four nucleotides: A, U, G and C. Thus, a 30-nucleotide (nt) RNA polymer can generate as many as 4^{30} (or 10^{18}) different RNA molecules. Three-dimensional RNA structures are of nanometre scale, and hence construction of RNA nanoparticles is feasible by a bottom-up approach. An example of one of the early applications of RNA bottom-up assembly is the construction of micrometre-scale RNA arrays derived from bacteriophage phi29 motor pRNA. For more details on pRNA-based nanostructures, please see Refs. [10] and [11].

RNA molecules can be designed and manipulated at a level of simplicity, characteristic of DNA [12,13], while possessing the flexibility in structure and function similar to that of proteins. For example, ribozymes are composed of RNA but have the enzymatic property of proteins. Likewise, RNA aptamers are similar to antibodies in that they can bind small molecules as specific biosensing and targeting moieties.

In addition to pure nanotechnology applications of RNA, the idea to silence target genes involved in disease using nanosized therapeutic RNA has generated much excitement in the scientific community. In particular, the mechanism of RNA interference (RNAi) has prompted the development of several therapeutic strategies. RNAi is a sequence-specific gene-silencing mechanism, typically involving short double-stranded RNAs (dsRNAs) called small interfering RNA (siRNA). The intrinsic ability to sequence-specifically downregulate gene expression in a temporally- and spatially controlled fashion has led to heightened interest and rapid development of siRNA-based therapeutics. Although methods for gene silencing with high efficacy and specificity have been achieved *in vitro*, effective delivery of nucleic acids to specific cells *in vivo* has been a hurdle for RNA therapeutics.

Here, we review different RNA-based approaches for diagnosis, prevention and treatment of human disease. This article is an extension of the earlier publication [10], at the same time focussing on the latest developments of non-viral carriers of siRNA for delivery *in vivo*. The applications and challenges of siRNA therapy, as well as potential solutions to these problems, will also be discussed. Approaches for using phi29 pRNA-based vectors as polyvalent vehicles for specific delivery of siRNA, ribozymes, drugs or other therapeutic agents to specific cells for therapy will also be addressed.

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