



Engineering RNA for Targeted siRNA Delivery and Medical Application [☆]

Peixuan Guo ^{a,*}, Oana Coban ^a, Nicholas M. Snead ^b, Joe Trebley ^c, Steve Hoeprich ^b, Songchuan Guo ^c, Yi Shu ^a

^a Department of Biomedical Engineering College of Engineering/College of Medicine, University of Cincinnati, Cincinnati, OH 45221, USA

^b Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN 47907, USA

^c Kylin Therapeutics, Inc.

ARTICLE INFO

Article history:

Received 6 September 2009

Accepted 3 February 2010

Available online 15 March 2010

Keywords:

Viral DNA packaging motor

RNA dimer

Trimer

Hexameric ring

DNA translocation

Bacteriophage phi29

pRNA

Procapsid

Viral assembly

siRNA

Targeted delivery

Gene therapy

RNA nanotechnology

Nanobiotechnology

Nanomedicine

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.

© 2010 Elsevier B.V. All rights reserved.

Contents

1. RNA molecules with potential for diagnosis, prevention and treatment of human disease	652
2. Ribozymes	652
3. Antisense RNA	652
4. Small interfering RNA (siRNA).	652
5. Aptamers	652
6. MicroRNAs	652
7. Challenges of siRNA in therapy	653
8. Chemical stability.	653
9. Backbone modification	653
10. Sugar modification	653
11. Nucleobase modification	654
12. Terminal modification	654
13. Size and pharmacokinetics	654
14. Biodistribution and uptake	654
15. Potential therapeutic applications of siRNA for treatment of cancer	655
16. Target genes regulating apoptosis and cell cycle	655

[☆] This review is part of the *Advanced Drug Delivery Reviews* theme issue on "From Biology to Materials: Engineering DNA and RNA for Drug Delivery and Nanomedicine".

* Corresponding author. Vontz Center for Molecular Studies, 3125 Eden Ave., Rm# 1436, College of Engineering/College of Medicine, University of Cincinnati, Cincinnati, OH 45267, USA. Tel.: +1 513 558 0041; fax: +1 513 558 6079.

E-mail address: guop@purdue.edu (P. Guo).

17.	Target genes involved in signalling transduction	655
18.	Target genes involved in angiogenesis.	655
19.	Target genes involved in drug resistance	655
20.	Potential therapeutic applications of siRNA for treatment of viral infections	655
21.	Principles and approaches in engineering RNA for conjugation and bottom-up assembly	656
22.	Non-viral carriers for siRNA delivery	656
23.	Nucleic acid-based vectors	656
24.	Liposomes	656
25.	Cationic polymers (polyplexes)	657
26.	Polyethyleneimine	657
27.	Cyclodextrin-based polyplexes	657
28.	Chitosan	658
29.	Dendrimers	658
30.	Dynamic polyconjugates	658
31.	Protein-based siRNA vectors	658
32.	SiRNA conjugates to metallic core nanoparticles	658
33.	Ligand-targeted siRNA delivery	658
34.	Small molecules (carbohydrates, folate and cholesterol) as targeting ligands.	658
35.	Peptides, proteins and antibodies as targeting ligands	659
36.	Peptides	659
37.	Transferrin.	659
38.	Antibodies	659
39.	Aptamers as targeting ligands.	659
40.	Targeted delivery using phi29 pRNA nanocarriers	660
40.1.	Unique features of phi29 pRNA-derived nanocarriers	660
41.	Construction of pRNA monomers harbouring a therapeutic agent, a targeting ligand or a delivery marker	660
42.	Stabilisation of pRNA	660
43.	pRNA/siRNA	660
44.	pRNA/hammerhead ribozyme.	660
45.	pRNA/receptor-binding aptamers	660
46.	pRNA conjugated to drugs, folate or other chemical moieties	661
47.	Assembly of polyvalent dimeric, trimeric and hexameric pRNA complexes.	661
48.	Delivering siRNA using phi29 pRNA dimers	661
49.	Delivering imaging probes using pRNA multimers	662
50.	RNA for nanotechnology and tissue engineering	662
51.	Potential adverse side effects of siRNA therapy.	662
52.	SiRNA-mediated induction of immune responses.	662
53.	Sequence-dependent off-target effects of siRNA	662
54.	Saturation of endogenous silencing pathways	663
55.	Conclusion.	663
	Acknowledgements	663
	References	663

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.

Download English Version:

<https://daneshyari.com/en/article/2071489>

Download Persian Version:

<https://daneshyari.com/article/2071489>

[Daneshyari.com](https://daneshyari.com)