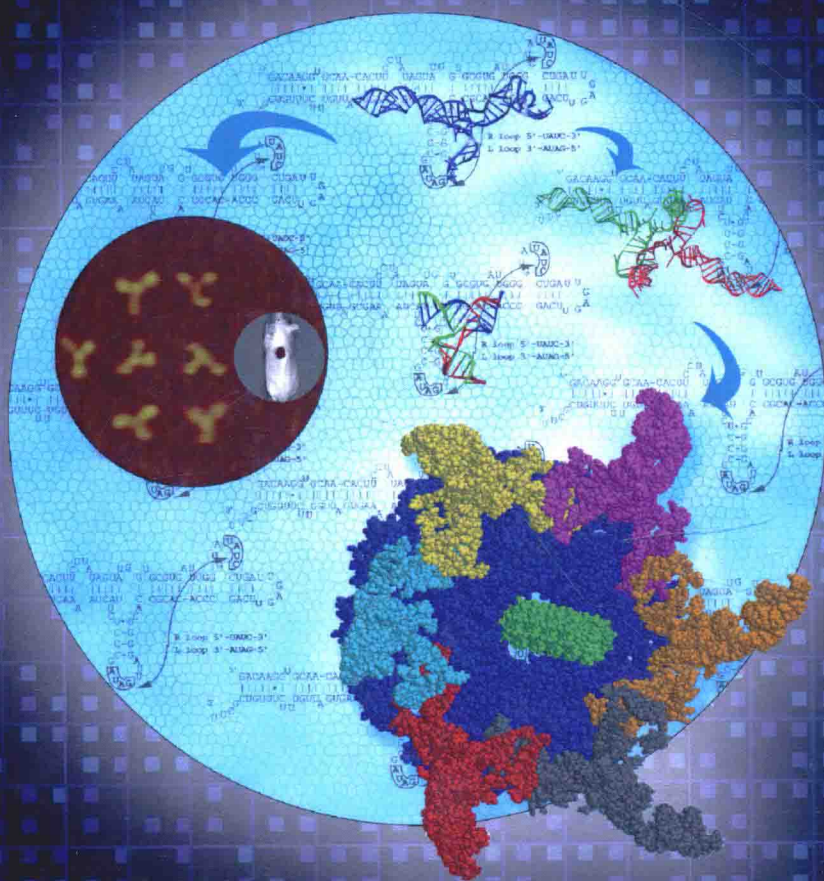


RNA Nanotechnology and Therapeutics



Edited by

Peixuan Guo
Farzin Haque



CRC Press
Taylor & Francis Group

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CRC Press

Taylor & Francis Group

Boca Raton London New York

CRC Press is an imprint of the
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CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

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Printed on acid-free paper
Version Date: 20130315

International Standard Book Number-13: 978-1-4665-0566-7 (Hardback)

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Library of Congress Cataloging-in-Publication Data

RNA nanotechnology and therapeutics / edited by Peixuan Guo and Farzin Haque.
p. ; cm.

Includes bibliographical references and index.

ISBN 978-1-4665-0566-7 (hardcover : alk. paper)

I. Guo, Peixuan, editor of compilation. II. Haque, Farzin, editor of compilation.

[DNLM: 1. Nanotechnology--methods. 2. RNA--therapeutic use. 3. Nanomedicine--methods. 4. Nanoparticles. QT 36.5]

QP619.A45
572.8'86--dc23

2013009491

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and the CRC Press Web site at
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Preface

Nanotechnology deals with the creation and application of materials at the nanometer scale, using either top-down approaches or bottom-up assembly. Macromolecules of DNA, RNA, and proteins have defined features and the perfect size to serve as powerful building blocks for the bottom-up fabrication of nanostructures and nanodevices. However, nanotechnology must fulfill certain criteria: (1) products should have a defined size and structure at the nanometer scale; (2) the nanoparticles can be purified to homogeneity or relatively homogeneous; and (3) the nanoparticles can be characterized or visualized by either chemical, physical, biophysical, or optical procedures. For example, molecular biology studies of DNA are not nanotechnology; however, the use of DNA as a nanomaterial to build homogeneous structures by bottom-up assembly to generate products with defined physical, chemical, and biophysical properties of the DNA structures is DNA nanotechnology, and this pioneering concept has created an unexpected paradigm of materials engineering and synthetic structural biology. As an alternative to DNA, RNA has recently been catapulted into place as a nanotechnology platform due to its diversity in both structure and function. RNA is unique in comparison to DNA by virtue of its higher thermodynamic stability, canonical and noncanonical base pairing ability, as well as a variety of single-stranded loops suitable for inter- and intramolecular interactions, base stacking, and distinct *in vivo* attributes. Previously, the sensitivity of RNA to RNase degradation had been the biggest hurdle in the production of RNA for use as a construction material. Recently, simple chemical modifications, such as that with 2'-fluorine, have led to the generation of certain RNAs resistant to degradation that have retained their folding property and even their function in certain cases. The robust production of stable RNA has now moved the dream of RNA nanotechnology into a reality. However, simply conjugating functional RNA modules to gold, liposome, dendrimer, or polymer-based nanoparticles does not constitute RNA nanotechnology; rather, RNA nanotechnology is a bottom-up approach to assemble nanometer-scale particles with its main constituent composed of RNA.

The studies on RNA structure and folding are dated decades ago. However, RNA nanotechnology is a unique, emergent field that is distinct from the classical studies of RNA structure and folding. Besides intramolecular interaction and folding, the special knowledge of intermolecular interaction is necessary. In 1998, the pioneering work of Peixuan Guo demonstrated that RNA dimer, trimer, and hexamer nanoparticles can be assembled using re-engineered RNA fragments derived from pRNA (packaging RNA), a vital component that gears the bacteriophage phi29 DNA packaging motor. This finding was published in *Molecular Cell* (Guo et al., 1998) and was featured in *Cell* (Hendrix, 1998), cementing the concept of RNA nanotechnology. Since then, pRNA nanoparticles have been used successfully as polyvalent vehicles to deliver a variety of therapeutic molecules, and for the construction of RNA arrays. Over the last few years, investigations into the folding and structure of RNA motifs, as well as advances in RNA 3D computation from the traditional intramolecular interactions to intermolecular interactions, have laid a solid foundation for further development in RNA nanotechnology.

RNA nanotechnology is a vigorous and rapidly progressing new field of science, as evidenced by the explosion of publications on RNA nanostructures that have been published over the last five years. These have come from diverse fields such as chemistry,

biochemistry, structural biology, microbiology, cancer biology, cell biology, biophysics, pharmacy, and nanomedicine. This innovative area of study is truly an interdisciplinary one that involves professionals with multiple backgrounds and skills. At this point in time, it is imperative to compile a book to serve as the first comprehensive collection of basic research that includes real-world applications pertinent to nanotechnology. The intended style of this book is one that can engage researchers from undergraduates all the way to postdoctoral researchers and professors, in engineering and other sciences, to further enhance this field. It is imperative that we work together to propel it to all that it can be and more.

This text strives to assemble information, engage its readers, and inspire scientists all over the world. It covers a wide range of topics, including the principles and fundamentals of RNA nanotechnology (Chapters 1 and 2); RNA folding, structure, and motifs in RNA nanoparticle assembly (Chapters 3 through 6); RNA computation and structure prediction for RNA nanoparticle construction (Chapters 7 and 8); nucleotide chemistry for nanoparticle synthesis, conjugation, and labeling (Chapters 9 through 11); single-molecule and biophysical techniques in RNA nanostructure analysis (Chapters 12 and 13); methods for the assembly of RNA nanoparticles (Chapters 14 through 16); and RNA nanoparticles for therapy and diagnostic applications (Chapters 17 through 29).

We would not have been able to accomplish our goal without the tremendous efforts of leading experts in the field who have taken the time to contribute a chapter. Foremost, we express our gratitude to them and the time that they have put into this text. We sincerely thank the staff at CRC Press/Taylor & Francis Group, LLC. In particular, we thank Michael Slaughter, the executive editor who convinced us to undertake this project; Laurie Schlags, the project coordinator; Ed Curtis, the project editor; and Amor Nanas, the project manager. Without their valuable contributions, this book would have never come to fruition. Finally, without the support of our devoted wives, this endeavor would never have been possible. We are delighted to present this book and hope that readers will find it very resourceful and as exciting as we do.

Peixuan Guo
Farzin Haque
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Editors



Dr. Peixuan Guo is the William Farish Endowed Chair of Nanobiotechnology and the director of the Nanobiotechnology Center at the University of Kentucky. He also directed one NIH National Nanomedicine Development Center from 2006 to 2011 and currently directs the National Cancer Institute (NCI) Cancer Nanotech Platform Partnership Program with a focus on RNA nanotechnology for cancer therapy.

He earned a PhD from the University of Minnesota in 1987 and a postdoctoral degree at NIH before joining Purdue as an assistant professor in 1990. He tenured in 1993, became a full professor in 1997, and has been honored as a Purdue Faculty Scholar since 1998. He moved to the University of Cincinnati's endowed chair in biomedical engineering in 2007 and moved to the University of Kentucky as endowed chair and center director in 2012.

He constructed the phi29 DNA packaging motor (*PNAS*, 1986), discovered phi29 motor pRNA (*Science*, 1987), assembled infectious dsDNA viruses (*J Virology*, 1995), discovered the pRNA hexamer (*Mol Cell*, 1998), and pioneered RNA nanotechnology (*Mol Cell*, 1998; *JNN*, 2003; *Nano Lett*, 2004, 2005; *Nat Nanotechnol*, 2010). His laboratory built a dual imaging system to detect single fluorophores (*EMBO J*, 2007; *RNA*, 2007) and incorporated the phi29 motor channel into a lipid membrane (*Nat Nanotechnol*, 2009) for single-molecule sensing with potentials for high-throughput dsDNA sequencing.

He received the Pfizer Distinguished Faculty Award in 1995; the Purdue Faculty Scholar Award in 1998; the Purdue Seed Award in 2004, 2005, and 2007; the Lions Club Cancer Research Award in 2006; the honor of being a COV Distinguished Alumni of the University of Minnesota in 2009; and the University of Cincinnati Distinguished Research Award in 2011. He is an editor or board member of five nanotech journals. His work has been reported hundreds of times on radio and television, such as in ABC and NBC, and has been featured in the newsletters or websites of NIH, NSF, MSNBC, NCI, and ScienceNow, among others. He was a member of two prominent national nanotech initiatives by NIST, NIH, NSF, and the National Council of Nanotechnology and a member of the NIH Nanomedicine Development Center Steering Committee from 2006 to 2010.



Dr. Farzin Haque is a research assistant professor in the University of Kentucky College of Pharmacy, Department of Pharmaceutical Sciences. He earned a BA in biochemistry and mathematics (2004) from Lawrence University and a PhD in chemistry (2008) from Purdue University. He held a postdoctoral appointment (2009–2011) at the University of Cincinnati with Professor Peixuan Guo. Dr. Haque's scholarly interest broadly focuses on nanoscience and nanotechnology in biology and medicine.

An excellent emerging scientist in the field of RNA nanotechnology, Dr. Haque has significant expertise in constructing RNA nanoparticles harboring functional modules for therapeutic and diagnostic applications (*Nano Today*, 2012; *Nat Nanotechnol*, 2011). In addition, he has expertise in a variety of fields, including lipid–lipid and lipid–protein interactions (*J Phys Chem B*, 2010; *Biophys J*, 2008), and protein nanopore development for single-molecule detection and sensing of chemicals and biopolymers (*ACS Nano*, 2012; *Nat Protoc*, 2013; *Nano Lett*, 2010).

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Contents

Preface.....	ix
Editors.....	xi
Contributors.....	xiii

Section I Introduction: Principles and Fundamentals of RNA Nanotechnology

1. The Emerging Field of RNA Nanotechnology	3
<i>Peixuan Guo</i>	
2. Uniqueness, Advantages, Challenges, Solutions, and Perspectives in Therapeutics Applying RNA Nanotechnology	23
<i>Peixuan Guo, Farzin Haque, Brent Hallahan, Randall Reif, Hui Li, and Shaoying Wang</i>	

Section II RNA Folding, Structure, and Motifs in RNA Nanoparticle Assembly

3. Kink Turn Structural Motif in RNA	59
<i>Peter Daldrop, Lin Huang, Kersten T. Schroeder, Jia Wang, and David M. J. Lilley</i>	
4. RNA Nanotechnology: Learning from Biologically Active RNA Nanomachines ...	73
<i>Neocles B. Leontis and Emil F. Khisamutdinov</i>	
5. Natural Selection and Structural Polymorphism of RNA 3D Structures Involving GNRA Loops and Their Receptor Motifs	109
<i>Takahiro Tanaka, Hiroyuki Furuta, and Yoshiya Ikawa</i>	
6. RNA Junction Motifs as Scaffolds for Construction of Multifunctional RNA Nanoparticles	121
<i>Farzin Haque and Peixuan Guo</i>	

Section III RNA Computation and Structure Prediction for RNA Nanoparticle Construction

7. Role of Dynamics in RNA Nanostructure Design	139
<i>Wojciech Kasprzak and Bruce A. Shapiro</i>	
8. RNA Three-Dimensional Structure Determination Using Experimental Constraints.....	159
<i>Feng Ding and Nikolay V. Dokholyan</i>	

Section IV RNA Chemistry for Nanoparticle Synthesis, Conjugation, and Labeling

9. Nucleotide Chemistry for RNA Nanoparticle Labeling, Conjugation, and Synthesis..... 179
Brian M. Laing and Donald E. Bergstrom
10. RNA Conjugations and Ligations for RNA Nanotechnology 197
Eduardo Paredes and Subha R. Das
11. Atom-Specific Mutagenesis of RNAs for Structure, Function, and Therapeutics Studies..... 213
Huiyan Sun and Zhen Huang

Section V Single-Molecule and Biophysical Techniques in RNA Nanostructure Analysis

12. Atomic Force Microscopy of RNA: Imaging and Beyond 237
Peter M. Schön, Luda S. Shlyakhtenko, and Yuri L. Lyubchenko
13. Single-Molecule Approach to Study RNA Nanoparticles 263
Hui Zhang, Chris Richards, Zhengyi Zhao, and Peixuan Guo

Section VI Methods for the Assembly of RNA Nanoparticles

14. Fabrication Methods for RNA Nanoparticle Assembly Based on Bacteriophage phi29 Packaging RNA Structural Features 285
Yi Shu, Bahar Seremi, and Peixuan Guo
15. Synthetic RNA–Protein Nanostructures and Their Potential Applications 303
Hirohisa Ohno, Eriko Osada, Tan Inoue, and Hirohide Saito
16. DNA Nanotechnology as Reference for RNA Nanotechnology 313
Zhen-Gang Wang and Baoquan Ding

Section VII RNA Nanoparticles for Therapy of Cancer, Viral Infections, and Genetic Diseases

17. Thermodynamically Stable RNA Three-Way Junction for Constructing Multifunctional Nanoparticles for Delivery of Therapeutics..... 363
Dan Shu, Yi Shu, Farzin Haque, Sherine Abdelmawla, and Peixuan Guo

18. Design and Construction of RNA Nanoparticles Targeting Prostate Cancer 389
Randall Reif and Peixuan Guo

19. Conjugation of RNA Aptamer to RNA Nanoparticles for Targeted Drug Delivery 399
Katherine Germer, Fengmei Pi, Peixuan Guo, and Xiaoting Zhang

20. Extracellular Membrane Vesicles and Extracellular Membrane Vesicle-Based Therapeutics for Brain Diseases..... 409
Jayden A. Smith, Clara Alfaro-Cervello, Chiara Cossetti, Nunzio Iraci, Matilde Stefanini, and Stefano Pluchino

21. Pharmacokinetics and Pharmacodynamics of RNA Nanoparticles 429
Markos Leggas

Section VIII RNA Nanotechnology for Diagnostic Applications

22. RNA Nanotechnology in Sensing, Detection, and Disease Diagnosis..... 439
Ping Lei and Guanxin Shen

23. Potentials of RNA Aptamers for Viral Detection and Treatment 449
Longxin Chen, Runtong Li, and Runlin Z. Ma

Section IX Application of RNA Aptamers in RNA Nanotechnology and Therapeutics

24. Application of RNA Aptamers in Nanotechnology and Therapeutics 467
Hua Shi

25. Aptamers Targeting a Subunit or a Conformation of Glutamate Ion Channel Receptors 487
Zhen Huang, William Jaremko, Chi-yen Lin, and Li Niu

Section X Application of miRNAs in RNA Nanotechnology and Therapeutics

26. Application of MicroRNAs in RNA Nanotechnology and Antiviral Therapeutics 513
Ye Qiu, Xin Ye, Maged Hemida, Mary Zhang, Paul Hanson, and Decheng Yang

27. MicroRNAs: Biology and Role in RNA Nanotechnology 533
Bin Guo and Daniel W. Binzel

**Section XI Application of siRNAs in RNA Nanotechnology and
Therapeutics**

28. Current Advances in Self-Assembly RNAi Nanoparticles.....545
Ka-To Shum, Jiehua Zhou, and John J. Rossi

29. Self-Assembly of siRNA Containing Nanoparticles559
Mengyao Zheng, Thomas Kissel, and Olivia M. Merkel

Index.....577

Section I

Introduction: Principles and Fundamentals of RNA Nanotechnology

