EDITED BY NEERAJ VIJ

PULMONARY NANOMEDICINE DIAGNOSTICS, IMAGING, AND THERAPEUTICS

PULMONARY NANOMEDICINE



EDITED BY NEERAJ VIJ

PULMONARY NANOMEDICINE DIAGNOSTICS, IMAGING, AND THERAPEUTICS



Published by

Pan Stanford Publishing Pte. Ltd. Penthouse Level, Suntec Tower 3 8 Temasek Boulevard Singapore 038988

Email: editorial@panstanford.com Web: www.panstanford.com

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Pulmonary Nanomedicine: Diagnostics, Imaging, and Therapeutics

Copyright © 2012 Pan Stanford Publishing Pte. Ltd.

All rights reserved. This book, or parts thereof, may not be reproduced in any form or by any means, electronic or mechanical, including photocopying, recording or any information storage and retrieval system now known or to be invented, without written permission from the publisher.

For photocopying of material in this volume, please pay a copying fee through the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, USA. In this case permission to photocopy is not required from the publisher.

ISBN 978-981-4316-48-4 (Hardcover) ISBN 978-981-4364-14-0 (eBook)

Printed in the USA

To the fond memory of my parents, who taught me to seek enlightenment and knowledge and strive for excellence.

Dearest souls, although you have departed and moved far away, your perpetual memory in our hearts makes us feel that you are ever near us, with us.

—N.V.

Contents

Contributors				XV		
Pro	Preface					
Ac	Acknowledgments					
1.	1. Theranostic Applications of Nanotechnology in Chronic Obstructive Lung Diseases					
	Neer		nd Aakruti Gorde			
	1.1	onary Physiology and Pathogenesis of Chronic uctive Lung Diseases	1			
	1.2		cation of Nano-Based Systems in Treating Chroni uctive Lung Diseases	3		
		1.2.1	Therapeutic and Diagnostic Challenges in Chron Obstructive Lung Diseases	nic 6		
		1.2.2	Nanosystems to Overcome Challenges in Chron Obstructive Lung Diseases	ic 6		
	1.3 Nanotheranostics					
1.3.1 Theranostic Nanoparticles for Chronic Obstru						
			Lung Diseases	8		
		1.3.2	Perspective	9		
2. Multifunctional Tumor-Targeted Nanoparticles						
for Lung Cancer				15		
	Li Le	o Ma, M	a, Tomohisa Yokoyama, Justina O. Tam, Ailing W. Scott, Ianish Shanker, Jiankang Jin, Corbin Goerlich,			
			itts, Jack A. Roth, Konstantin Sokolov, Keith P. Johnston, oal Ramesha			
	2.1	Introd	luction	16		
	2.2	Bioma	arkers for Tumor Targeting	18		
	2.3	Nanot	echnology in Medicine	20		
		2.3.1	Development of Nanoparticles for Lung			
			Cancer and Other Medical Applications	20		
		2.3.2	Classes of Nanoparticles	23		
		2.3.3	Delivery Methods of Nanoparticles to			
Targeted Regions						

viii Contents

			2.3.3.1	Systemic Administration	26	
			2.3.3.2	Local Administration via Inhalation	27	
			2.3.3.3	Toxicity of Nanoparticles	28	
	2.4	EGFR-	Targeted	Hybrid Plasmonic Magnetic		
		Multif	unctional	Nanoparticles	29	
		2.4.1	Structur	e of Nanoparticles	29	
		2.4.2	Therape	eutic Function of EGFR-Targeted		
			Nanopa	rticles	30	
			2.4.2.1	Inhibition of EGFR signaling pathway	30	
			2.4.2.2	Induction of DNA damage	32	
		2.4.3	Diagnos	tic Function of EGFR-Targeted		
			Nanopa	rticles	33	
	2.5	Conclu	usions		34	
3.	Nas	al and	Pulmona	ary Delivery of Macromolecules		
				ry and Nonrespiratory Diseases	45	
	Durg	ja Patur	i, Mitesh P	atel, Ranjana Mitra, and Ashim K. Mitra		
	3.1	Introd	luction		45	
	3.2	Nasal	Drug Delivery			
		3.2.1	Nasal Aı	natomy	47	
		3.2.2	Mechan	isms of Nasal Absorption	48	
		3.2.3	Factors	Affecting Nasal Absorption	50	
			3.2.3.1	Physiological factors	50	
			3.2.3.2	Pathological conditions	50	
			3.2.3.3	Biochemical changes	52	
			3.2.3.4	Physicochemical properties of		
				the permeant	52	
			3.2.3.5	Properties of the formulation	53	
			3.2.3.6	Drug distribution	54	
			3.2.3.7	Device-related factors	54	
		3.2.4	Strategi	es to Enhance Nasal Absorption	55	
			3.2.4.1	Cyclodextrins	56	
			3.2.4.2	Fusidic acid derivatives	56	
			3.2.4.3	Phospholipids	56	
			3.2.4.4	Bile salt derivatives	56	
			3.2.4.5	Peptidase and protease inhibitors	57	
		3.2.5	Nasal Formulations			

			3.2.5.1	Nasal drops	59
			3.2.5.2	Nasal sprays	59
			3.2.5.3	Nasal powders	60
			3.2.5.4	Nasal ointments and emulsions	60
			3.2.5.5	Nasal gels	61
			3.2.5.6	Liposomes	62
			3.2.5.7	Nanoparticles	63
			3.2.5.8	Microparticles	65
		3.2.6	Nasal De	elivery of Vaccines	66
		3.2.7	Intranas	al Gene Delivery	67
	3.3	Pulmo	onary Dru	ig Delivery	69
		3.3.1	Anatom	y of the Lungs	70
				ary Absorption	72
		3.3.3	Barriers	in Pulmonary Drug Delivery	73
		3.3.4	Formula		74
			3.3.4.1	Micelles	74
				Liposomes	75
				Microparticles	76
			3.3.4.4	Nanoparticles	77
			3.3.4.5	Microemulsions	79
		3.3.5	Inhalati	on Devices	82
			3.3.5.1		
				inhaler (pMDI)	83
			3.3.5.2		84
				Dry powder inhalers	85
				Affecting Pulmonary Deposition	85
			Vaccines		86
			Nucleic		87
			Oligonu	cleotides	91
	3.4	Conclu	usions		92
4.				Diagnosis of Pulmonary Disorders	4.00
	Using Nanotechnology 1				103
	Indrajit Roy				
	4.1	Introd	oduction		
	4.2	Nanop	oarticles		104

x Contents

		4.2.1	Quantum Dots	105
		4.2.2	Rare Earth-Doped Nanophosphors	105
		4.2.3	Dye-Doped Silica/ORMOSIL Nanoparticles	106
		4.2.4	Gold Nanoparticles	106
		4.2.5	Iron Oxide Nanoparticles	107
		4.2.6	Carbon Nanotubes	107
	4.3	In vitr	o Diagnosis, Techniques, and Challenges	108
		4.3.1	Flow Cytometry	108
		4.3.2	Multiplexed Microarray ELISA	110
		4.3.3	Molecular Beacon Technology	110
		4.3.4	Plasmonic Biosensing	111
		4.3.5	Magnetic Biosensing	112
		4.3.6	Electrochemical Biosensing	112
	4.4	In vivo	Diagnosis, Challenges, and Techniques	112
		4.4.1	1 8 8, 1 8	
			Confocal Endomicroscopy	113
			Magnetic Resonance Imaging	114
			Radiographic Imaging	115
		4.4.4	0 0	115
	4.5	-	ic Examples of Lung Disorders	116
		4.5.1	,	117
		4.5.2	Pneumocystis Pneumonia	118
			Cystic Fibrosis	118
		4.5.4	Tuberculosis	119
			Lung Cancer	121
	4.6	Toxico	ological Studies Using Nanoparticles	122
	4.7	Conclu	usions	123
5.	Nan	oparti	cles for Targeting T Cells in Allergy and	
	Infl	ammat	tory Airway Conditions	135
	Adha	ım Bear,	, Laura B. Carpin, Conrad R. Cruz, Rebekah A. Drezek,	
	and	Aaron E.	Foster	
	5.1	Introd	luction	135
	5.2	Role o	f T Cells in the Pathogenesis of Asthma	136
	5.3	Treatr	nent Strategies for Asthma	139
		5.3.1	Nanosteroids for the Treatment of Asthma	139

		5.3.2	2 Nanocarrier Vaccines as Immune Modulators			
			to Promote T _H 1 Responses			
	5.4	Potent	ial T Cell-Targeted Strategies for			
		Nanop	article-Based Therapies			
	5.5	T Cell-	Targeting Ligands			
		5.5.1	Large Targeting Ligands			
			5.5.1.1 Antibody conjugates to target			
			T cell surface molecules	148		
			5.5.1.2 TCR-targeted strategies	151		
		5.5.2	Small Targeting Ligands	152		
			5.5.2.1 Aptamers	152		
			5.5.2.2 Peptides	153		
	5.6	Altern	ative Approaches	154		
		5.6.1	Chemokine Receptor-Targeted Strategies	154		
	5.7	Summ	ary	155		
6.	Mul	tifunct	tional Chitosan Nanocarriers for Respiratory	7		
•••			ene Therapy	167		
Shyam S. Mohapatra, Subhra Mohapatra, Gary Hellermann, and Rhonda R. Wilbur						
						6.1
		6.1.1 What Are Chitosan Nanoparticles? Therapeutic Effects and Safety of Chitosan in				
	6.2					
		Human Disease				
		6.2.1	Chitosan as Gene Therapy	175		
		6.2.2	Toxicity and Safety of Chitosan Gene Therapy	177		
	6.3	Safety	and Efficacy Studies in Dogs	178		
	6.4	Safety	Safety of Chitosan-Gene Nanocomplexes in Nonhuman Primates			
		Nonhu				
	6.5	Respir	ratory Disease Applications	182		
		6.5.1	Examples of Chitosan Nanoparticle			
			Applications to Treat Allergic Disease	183		
			6.5.1.1 Food allergy and anaphylaxis	183		
			6.5.1.2 Experimental asthma	183		
	6.5.1.3 RSV infection			184		
		6.5.2	Nano-Immunotherapy for Allergies	185		
	6.6	Future	e of Immunotherapy	186		
	6.7	Concluding Remarks				

7.	Targ	geted I	Delivery t	to the Pulmonary Endothelium	193
	Yifei	Zhang, j	liang Li, Xi	ang Gao, and Song Li	
	7.1	Introd	uction		193
	7.2	7.2 Pulmonary Endothelium as a Target for			
		Drug I	Delivery	C C	194
		7.2.1	Physiolo	ogical Functions of Lung ECs	194
		7.2.2		ary Endothelium as a Drug	
			Delivery	' Target	195
			7.2.2.1	Passive targeting	195
			7.2.2.2	Active targeting via surface antigens	196
		7.2.3	Physiolo	Physiological Barriers for Intravenous Drug	
			Delivery	to the Pulmonary Endothelium	199
			7.2.3.1	<i>In vivo</i> barriers	200
			7.2.3.2	Cellular barriers	201
	7.3	Target	ing the P	ulmonary Endothelium for Imaging	
and Therapeutic Applications				c Applications	206
		7.3.1	Imaging	Applications	206
		7.3.2	Therape	eutic Applications	207
			7.3.2.1	Targeted delivery of protein	
				therapeutics	207
			7.3.2.2	Targeted gene delivery to the	
				pulmonary endothelium	212
	7.4	Conclu	usion		218
8.	Nan	osyste	ms for So	elective Epithelial Barrier	
	Targ	geting	in Chron	ic Airway Diseases	235
	Heat	her A. P	arsons, Rad	chel L. Damico,	
	and	Venkata	ramana K.	Sidhaye	
	8.1	Introd	uction		235
	8.2	Obstru	active Lui	ng Diseases	238
		8.2.1	Airway l	Inflammation in COPD	240
		8.2.2	Airway l	Inflammation in Asthma	242
		8.2.3	Role of t	he Airway Epithelial Barrier	242
			8.2.3.1	Epithelial barrier in asthma	243
			8.2.3.2	Epithelial barrier in COPD	244
	8.3	-			

	8.3.1 Local Delivery	244
	8.3.2 Existing Studies for the Treatment of	
	Chronic Airway Diseases	246
8.4	Toxicity of NPs	248
8.5	Conclusions and Future Directions	250
	ential Respiratory Health Risks of Engineered	l 259
-	es C. Bonner, Jeffrey W. Card, Stavros Garantziotis, Darryl C. Zeldin	
9.1	Introduction	259
9.2	Immune Cell Interaction with CNTs	261
9.3	Fibrogenic Reactions to CNTs	262
9.4	CNTs and Preexisting Allergic Asthma	263
9.5	CNTs and LPS-Induced Airway Inflammation	266
9.6	Effects of CNTs on Other Organ Systems	266
9.7	DNA Damage and Aneuploidy Caused by CNTs	267
9.8	Pleural Toxicity of CNTs	268
9.9	Conclusions	269

Contributors



James C. Bonner received his PhD in physiology from Mississippi State University in 1987, completed his postdoctoral training at the National Institute of Environmental Health Sciences (NIEHS) in 1990, and served as a principal investigator at NIEHS and at the Hamner Institutes for Health Sciences. He joined the Department of Environmental and Molecular

Toxicology at NC State University as an associate professor in 2007.

Dr. Bonner has over 20 years of experience in respiratory toxicology and lung disease pathogenesis. He has published more than 80 peer-reviewed research articles on environmental lung disease, numerous review articles, and several textbook chapters on respiratory toxicology.

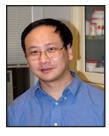
He is the lead author of Chapter 9, on the potential respiratory health risks of engineered carbon nanotubes.



Aaron E. Foster received his BA in biology from the University of Puget Sound in Tacoma, Washington, in 1994 and his PhD in chemical engineering from the University of Sydney, Australia, in 2003. Currently, he is an assistant professor at the Center for Cell and Gene Therapy at Baylor College of Medicine.

Dr. Foster's research interests include cancer vaccine development, immune modulation, and gene therapy applications using cytotoxic T lymphocytes (CTLs) as anti-tumor effector cells or as carriers for *in vivo* delivery. In collaboration with Dr. Rebekah Drezek in the Department of Bioengineering at Rice University, he is also studying the development and use of multifunctional nanoparticles for the treatment of cancer and infectious disease.

Dr. Foster is the main author of Chapter 5, on the use of nanoparticles to treat airway inflammation.



Song Li received his MD in 1985 and PhD in tumor immunotherapy in 1991 from the Fourth Military Medical University, China. He worked with Dr. Leaf Huang at the University of Pittsburgh School of Medicine as a post-doc for two years and then as a research faculty for another four years. Dr. Li joined the faculty of the School of Pharmacy at the University of Pittsburgh in June 2000 and

is currently an associate professor of pharmaceutical sciences. His major research interest is focused on the development of lipidand polymer-based nanodelivery systems for targeted delivery of various types of therapeutics including nucleic acids (genes, siRNA, and peptide nucleic acids), proteins, and small molecules (e.g., anticancer agents and antioxidants).

Dr. Li is the main author of Chapter 7, on targeted delivery to the pulmonary endothelium.



Ashim K. Mitra received his PhD in pharmaceutical chemistry in 1983 from University of Kansas. He joined the University of Missouri-Kansas City in 1994 as chairman of Pharmaceutical Sciences. He is also vice provost for Interdisciplinary Research, Curators' Professor of Pharmacy, and director for Translational Research at University of Missouri–Kansas City, School of

Medicine. Dr. Mitra has over 25 years of experience in ocular drug delivery and disposition and has authored or co-authored over 250 refereed articles and 30 book chapters in this field. He holds 8 patents and has made well over 450 presentations, including abstracts, at national and international scientific meetings. This work has attracted over 6 million dollars in funding from government agencies such as the National Institutes of Health (NIH) and Department of Defense (DOD) and from pharmaceutical companies.

Dr. Mitra is also a recipient of several research awards from AAPS, AACP, and various pharmaceutical organizations and serves on numerous editorial boards. According to Biomed Experts (during the past 10 years), he co-authored the third-highest number of publications in the world in the area of "Prodrugs." In April 2010, he was ranked fifth in the world among AAPS's Top Ten Researchers. In February 2012, his article "Ocular Drug Delivery" was again ranked as one of the top 5 downloaded articles in the *AAPS Journal*. Currently, he is chairman of the USP Council of Experts, General Chapter

<771> *Ophthalmic Preparations* Expert Panel, U.S. Pharmacopeia. His current research interests are focused on two main areas: delivery and targeting of antiviral agents and development of noninvasive delivery systems for peptide and protein drugs.

Dr. Mitra is the senior author of Chapter 3, which discusses the use of nasal and pulmonary delivery of macromolecules to treat respiratory and nonrespiratory diseases.



Shyam S. Mohapatra is a Distinguished USF Health Professor and director of the Division of Translational Medicine, Nanomedicine Research Center at the Morsani College of Medicine, University of South Florida. He also directs the Signature Program in Allergy, Immunology and Infectious Diseases at the college. A PhD graduate of the Australian National University, Prof.

Mohapatra is a recipient of two international awards: the Alexander von Humboldt research fellowship (1984, Bonn, Germany) in genetics and Pharmacia Allergy Research Foundation Award (1992, Paris) for his contributions to the field of allergy and immunology.

Prof. Mohapatra's research program focuses on the molecular mechanisms underlying inflammation in respiratory diseases, cancers, viral infections, and traumatic brain injury. He has used nanotechnology approaches to advance translational research in these disease areas.

Prof. Mohapatra is the senior author of Chapter 6, which discusses the application of multifunctional chitosan nanocarriers in respiratory gene therapy.



Rajagopal Ramesh received his PhD in molecular biology in 1994 from the All India Institute of Medical Sciences, New Delhi, India. He completed his postdoctoral fellowships at Tulane University School of Medicine, New Orleans, in 1998 and later joined the faculty at M. D. Anderson Cancer Center in Houston, USA. Currently, Dr. Ramesh is a professor in the Department of Pathology and

director of Experimental Therapeutics and Translational Cancer Medicine at the University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA. He holds the Jim and Christy Everest Endowed Chair in Cancer Developmental Therapeutics and the title of the Oklahoma TSET Cancer Research Scholar. Dr. Ramesh's research is focused on investigating new cancer therapies with an emphasis on lung cancer. His laboratory has been conducting applied translational cancer research in leading areas such as cancer gene therapy, nanotechonology, and molecular targeted therapy. Research in his laboratory has led to four clinical trials for the treatment of cancer. He has published more than 86 articles in leading scientific journals and 17 textbook chapters on cancer therapy and drug development. His research is funded by the National Cancer Institute and other national granting agencies.

Dr. Ramesh is the senior author of Chapter 2, which discusses the use of multifunctional tumor-targeted nanoparticles for lung cancer.



Indrajit Roy received his MSc and PhD degrees from the University of Delhi, India, in 1997 and 2002, respectively. Following that, he completed postdoctoral research at the State University of New York (SUNY) at Buffalo, as well as at the Johns Hopkins School of Medicine. His research interests include the use of various nanoparticles for applications in targeted drug

delivery, nonviral gene delivery, photodynamic therapy (PDT), and multimodal diagnostic imaging.

Dr. Roy has published more than 50 articles in leading scientific journals and holds 3 U.S. patents. In 2005, he was presented with the Visionary Innovator Award by the technology transfer office at SUNY, Buffalo. From 2005 to 2009, he served as a research assistant professor in the Institute for Lasers, Photonics and Biophotonics (ILPB) at SUNY, Buffalo. At present, he is an associate professor of chemistry at the University of Delhi.

Prof. Roy is the author of Chapter 4, on *in vitro* and *in vivo* diagnosis of pulmonary disorders using nanotechnology.



Venkataramana K. Sidhaye received her bachelor's in biomedical engineering in 1995 and her MD in 1998 at Northwestern University. She then did her residency in internal medicine and was a chief resident at Northwestern before coming to Johns Hopkins in 2002 for fellowship training in pulmonary and critical care medicine. She joined the Hopkins Pulmonary faculty in

2006. Dr. Sidhaye's research interest in is epithelial barrier function,

with a focus on the airway epithelium. She is interested in the crosstalk between the epithelial barrier and cell–cell contacts and the role of the epithelium in innate immunity, and this is modified by luminal exposures. More recently, she has been interested in epithelial responses to inspired nanomaterials.

Dr. Sidhaye is the senior and corresponding author of Chapter 8, on epithelial barrier targeting in chronic airway diseases.



Neeraj Vij received his PhD in biotechnology from the Indian Institute of Technology in 2001 and was also a recipient of international fellowship at the Institute of Genetics, Biological Research Center (Centre of Excellence of the European Union), Hungary, in same year. He subsequently completed his postdoctoral research at the University of Heidelberg,

Germany, and The Johns Hopkins University School of Medicine (JHU SOM). Dr. Vij is currently an assistant professor at the Department of Pediatric Respiratory Sciences and Institute of NanoBiotechnology, JHU SOM. He serves on the editorial boards of several nanomedicine journals, including *Journal of Nanomedicine & Nanotechnology, Expert Opinion in Drug Delivery, International Journal of Nano Studies & Technologies*, and so forth. He has been invited to help organize several nanotechnology conferences and seminars, such as NanoBiotech 2009, and the nanotechnology postgraduate course at American Thoracic Society (ATS). He is also frequently invited to serve as a reviewer for various nanomedicine journals and grant review study sections, including NIH, USA. He is a life member of the American Society for Nano Medicine (ASNM) and several other international scientific societies. Dr. Vij has received several research awards and recognition for his scientific contributions.

The primary research focus of Dr. Vij's laboratory is identification of molecular pathways leading to chronic disease pathophysiology, with an aim to identify novel therapeutic sites. His laboratory is interested in applied and pre-clinical translational research and concentrates on the identification of novel therapeutic strategies including design and development of nano-based delivery systems for theranostic applications in chronic obstructive lung diseases.

Dr. Vij is the editor of this book and senior author of Chapter 1, which discusses the theranostic applications of nanotechnology in chronic obstructive lung diseases.

Preface

Nanotechnology has revolutionized medicine over the past decade. The unique physicochemical characteristics of engineered nanoparticles (ENPs) enable novel therapeutic and diagnostic (theranostic) applications, particularly in pulmonary diseases. The research over the past decade has provided insights into biological properties and application of NPs in pulmonary medicine.

This book provides a comprehensive review on the pulmonary applications of NPs and aims to enlighten the readers about novel nano-based theranostic strategies for treating pulmonary disorders. Each chapter discusses strategies to overcome the technological and disease-specific pathophysiological barriers to develop novel nanobased diagnostics, imaging, and therapeutic tools for treatment of various airway diseases.

In summary, the book is focused on emerging cutting-edge applications of nanotechnology in pulmonary medicine and aims to synchronize the efforts of pulmonary biologists, nano-chemists, and clinicians to develop novel nano-based theranostic systems for treatment of airway diseases.

This book has been compiled with the goal to serve both academic institutions and industry for education, training, and research. It is written to educate graduate and postgraduate students on emerging theranostic applications of ENPs in treating various pulmonary diseases. It will also serve as a guide for both clinicians and researchers in developing novel theranostics while closely monitoring the health effects of next-generation ENPs.

Overall, this is a wikipidea of pulmonary nanomedicine that discusses the scope of both current and future nanotechnologies for pulmonary applications.

> Neeraj Vij, MS, PhD Baltimore, MD April 2012

Acknowledgments

I express my sincere thanks to all authors and reviewers, who are experts in their respective fields, for their exceptional contribution and support. This book came into its present form with the earnest efforts of all authors, who helped me ensure that therapeutic and diagnostic strategies of novel pulmonary nanomedicine were discussed to help lead the advancement of the emerging scientific field of pulmonary nanomedicine. I am extremely grateful to Stanford Chong (Director) and Sarabjeet Garcha (Editorial Manager), of Pan Stanford Publishing Pte. Ltd., for their outstanding support and perceptiveness. Sarabjeet was especially instrumental in providing the much-needed editorial support for the swift collation of the book.

Neeraj Vij