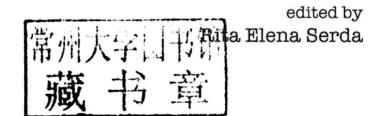


Mass Transport of Manocarriers



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.

Mass Transport of Nanocarriers

Copyright © 2013 by 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 978-981-4364-41-6 (Hardcover) ISBN 978-981-4364-42-3 (eBook)

Printed in the USA

Mass Transport of Nanocarriers

Preface

The journey of a nanocarrier from the site of entry to the site of action is filled with abundant sequential and concomitant obstacles, or barriers, designed to protect the host from foreign invaders. One of the major goals of nanomedicine research is the optimization of particle properties to achieve site-specific delivery of therapeutics to the target lesion(s). Nano- and microparticles possess intrinsic characteristics that influence their interactions with the surrounding milieu, which go beyond chemical composition, and include geometrical and chemical properties. These properties can be tailored to achieve particular tasks, creating nanoscale entities with macroscale capabilities.

Although barriers have a negative connotation in drug delivery, their unique traits within lesions can create opportunities for increased accumulation of therapeutics delivered through speciallydesigned carriers. For example, unique attributes of the tumor microenvironment, such as abnormal blood vessel morphology, vascular fenestrations, and unique vascular and cellular markers, or "zipcodes," can be used to enhance targeting by means of optimizing physical characteristics and surface chemistry of the particles. The route of administration dictates biobarriers encountered in route to the treatment site. Barriers exist from the macro- to the microscale. and this book explores barriers ranging from the level of endothelia. stroma, and mucosa to the level of cellular organelles. Cellular barriers include crossing the plasma membrane, escaping the endosome, and intracellular trafficking to the target organelle. The book also explores methods for nanocarrier fabrication and imaging techniques to track particles in vitro and in vivo. Several model types of nanocarriers and their biological applications are presented.

The majority of the authors who contributed to this book are researchers at the Texas Medical Center, with contributions from investigators at the University of Houston, the University of North Carolina, the University of New Mexico, and the University of Louisville. Each chapter is written by experts discussing their own research and providing an overview of the field.

Rita Elena Serda

Winter 2012

Contents

Preface			xvi
Part 1	Overvie	ew	1
		port: Barriers and Opportunities	
for I	rug De	livery	3
Rita	E. Serda		
1.1	Introdu	uction	4
1.2		Barriers: Journey to the Tumor	4
	1.2.1	Endothelial Barriers	4
		Epithelial Barriers	7
		Mucosal Barriers	10
		Cell-Based Transport Across Barriers	10
1.3		mor Microenvironment	12
		Vasculature	12
		Lymphatic Drainage	13
		Viscoelasticity	14
1.4		r Barriers	15
		Endocytosis	15
		Intracellular Trafficking of Nanoparticles	16
		Cellular Targeting	17
V 2001		Tools for Cellular Imaging	17
		Design Approaches	19
1.6	Summa	ary	20
Part 2	Macro 1	Barriers: Journey to the Tumor	25
2. Biol	ogical B	arriers: Targeting and Crossing the	
End	otheliui	m	27
Silvi	a Ferrati	i, Brenda Melendez, and Aaron Mack	
2.1	Introdu	uction	27
2.2	Biologi	ical Barriers to Transport	28
	_	Barriers at the Systems Level	28

			2.2.1.1	Mucus and epithelial barriers	28
			2.2.1.2	Blood circulation and RES	36
			2.2.1.3	Endothelial barrier	40
	2.3	Organ a	nd Tissue	e Level	42
	2.4	Cellular	Level		44
	2.5	The Mu	ltistage S	ystem	46
	2.6	Angioge			47
		2.6.1	VEGF		48
		2.6.2			49
			Angiopoi		50
				ironment	50
			Vasculatu		51
	2.9	-	_	ing the Tumor Vasculature	53
				Disrupting Agents	54
	27 0 101			nesis Inhibitors	55
- 2	2.10	_	ng Strateg	-	56
		2.10.1	Peptides		56
		0.400		Peptide synthesis	59
			Viral Vec		61
			_	splay Libraries	62
			RGD Pep		63 64
		2.10.5	Aptamer		65
				Thioaptamers	67
		2106	Antibodi	Aptamers for targeting	67
				Mimetics	68
		2.10.7	Antibouy	Millectes	00
3.	Stro	mal Bar	riers to I	Delivery	83
	Rosa	F. Hwan	g		
	3.1	Tumor	-Associate	ed Stroma	83
	3.2	Stroma	Contribu	ites to the Malignant Phenotype	84
				Promotes Tumor Progression	84
		3.2.2	Stroma (Contributes to Resistance to	
			Therapy		87
	3.3	Stroma		s to Delivery: Possible	
		Mechai	nisms	-	89
		3.3.1	Stroma a	as a Physical Barrier	89
		3.3.2	Tumor V	asculature Is Disorganized	90
		3.3.3	Нурохіа		90

	Contents vii	
3.3.4 Stroma-Derived Factors	91	
3.4 Conclusions	91	
4. Mucosal Barriers to Drug- and Gene-Loaded		
Nanoparticles	97	
Myung Soo Kim, Ying-Ying Wang, and Samuel K. Lai	7,	
4.1 Introduction	0.7	
4.2 Need for Engineering Nanoparticles That	97	
Overcome the Mucus Barrier	98	
4.2.1 Fate of Conventional, Mucoadhesive	90	
Nanoparticles	99	
4.2.1.1 Sustained and targeted dru		
delivery using mucus-	ь	
penetrating particles	101	
4.3 Composition of Mucus	103	
4.3.1 Mucins	103	
4.3.2 DNA	106	
4.3.3 Lipids	106	
4.3.4 Salts	106	
4.3.5 Proteins	107	
4.3.6 Cells and Cellular Debris	107	
4.4 Properties of the Mucus Barrier	108	
4.4.1 Luminal vs. Adherent Mucus Layers	108	
4.4.2 Thickness of Mucus Layers and		
Turnover Rate	109	
4.5 Diffusional Barrier Properties of Mucus	111	
4.5.1 Understanding Particle Diffusion in		
Mucus: Macrorheology vs.		
Microrheology	112	
4.5.2 Microstructure of Mucus	113	
4.5.3 Adhesive Trapping of Particles	114	
4.6 Engineering Mucus-Penetrating Particles	117	
4.6.1 Understanding Physiochemical		
Properties Necessary for MPP	117	
4.6.2 Learning from Viruses	118	
4.6.3 PEGylation	118	
4.6.4 Size	122	
4.6.5 Other Methods to Improve Mucosal		
Delivery	122	

Part	3 7	The Tu	mor Microenvironment	137
5.	Mod	eling th	e Tumor Microenvironment as a	
		-	n Cancer Nanotherapeutics	139
			Frieboes, Kenji Yokoi, Bhuvanesh Dave,	
			n, and Biana Godin	
		Introdu		140
			Multi-Scale Biobarriers	140
			Effect of Tumor Microenvironment on	
			Therapeutic Outcome	141
	5.2	Modeli	ng the Tumor Microenvironment	143
			Effect of Tumor Microenvironment on	
			Cancer Cell Survival	143
		5.2.2	In silico Modeling of the Tumor	
			Microenvironment	145
		5.2.3	Discrete, Continuum, and Hybrid Models	
			of the Tumor Microenvironment	146
		5.2.4	Modeling of Therapy to Overcome Sub-	
			Optimal Delivery of Agents in the Tumor	
			Microenvironment	146
		5.2.5	Cancer Nanotherapeutics: Design	
			Considerations	148
	5.3		ectors and Tumor Biobarriers	150
			Physiology of Tumor Vasculature	150
		5.3.2	Passive Accumulation vs. Molecular	
			Targeting in Delivery of	
			Nanotherapeutics: A Posse Ad Esse	153
			Gradients in Tumor Tissue	155
		5.3.4	Effect of Angiogenic Blood Vessels on	
			Transport of Nanotherapeutics	155
			5.3.4.1 Vascular topology	155
			5.3.4.2 Hemodynamics	156
			5.3.4.3 Vascular diffusivity	157
			Drug Release from a Nanovector	158
	5.4		ng Tumor Growth and Shrinkage in	
		1.00	nse to Therapy	159
			Modeling Tumor Growth	159
		5.4.2	The second secon	160
			5.4.2.1 Pharmacokinetic parameters	160
			5.4.2.2 Pharmacodynamic parameters	162

6.3.3 Biochemistry of HIF Activation

6.3.4 Tumor Angiogenesis

197

198

	6.3.5	Cell Survival and/or Death	198
	6.3.6	Metabolism	200
	6.3.7	Regulation of pH	201
	6.3.8	Metastasis	202
	6.3.9	Hypoxia, Oncogenes, and Tumor	
		Suppressor Genes	202
	6.3.10	Hypoxia, HIF, and Therapeutics	203
6.4	Pericyt	es	203
	6.4.1	Pericyte Involvement in Tumor	
		Angiogenesis and Metastasis	204
	6.4.2	Pericyte-Mediated Vessel Destabilization	204
	6.4.3	Endothelial Cell Growth	204
	6.4.4	Ang2/Tie Signaling	206
	6.4.5	Targeting Stromal Cells as Molecular	
		Targets in Models Against Cancer	
		(Pancreatic, Colon, and Lung)	208
		6.4.5.1 Pancreatic cancer	208
		6.4.5.2 Colon cancer	209
		6.4.5.3 Lung cancer	210
6.5	Conclu	sions	210
	Concid	310113	
Part 4 (r Barriers	221
	Cellula	r Barriers	
7. Imag	Cellula	r Barriers ols for Cellular Uptake and	221
7. Imag Intra	Cellula ging Too	r Barriers	
7. Imag Intra	Cellula	r Barriers ols for Cellular Uptake and	221
7. Imag Intra Jarea	Cellula ging Too	r Barriers ols for Cellular Uptake and or Trafficking	221
7. Imag Intra Jared 7.1	Cellula ging Too cellula	r Barriers ols for Cellular Uptake and or Trafficking ives	221
7. Imag Intra Jared 7.1 7.2	cellula ging Too cellula Burks Object Illumin	r Barriers ols for Cellular Uptake and or Trafficking ives	221223224
7. Imag Intra Jarea 7.1 7.2 7.3	cellula ging Too cellula Burks Object Illumin Detect Tube)	r Barriers ols for Cellular Uptake and or Trafficking ives nation ors (CCD Cameras and Photomultiplier	221223224
7. Imag Intra Jarea 7.1 7.2 7.3	cellula ging Too cellula Burks Object Illumin Detect	r Barriers ols for Cellular Uptake and or Trafficking ives nation ors (CCD Cameras and Photomultiplier	221 223 224 228
7. Imag Intra Jared 7.1 7.2 7.3	cellula ging Too cellula Burks Object Illumin Detect Tube) Filters	r Barriers ols for Cellular Uptake and or Trafficking ives nation ors (CCD Cameras and Photomultiplier	221 223 224 228 229
7. Imag Intra Jarea 7.1 7.2 7.3 7.4 7.5	cellula ging Too cellula Burks Object Illumin Detect Tube) Filters Autom	r Barriers ols for Cellular Uptake and or Trafficking ives nation ors (CCD Cameras and Photomultiplier	221 223 224 228 229 230
7. Imag Intra Jarea 7.1 7.2 7.3 7.4 7.5 7.6	cellula ging Too cellula Burks Object Illumin Detect Tube) Filters Autom	r Barriers ols for Cellular Uptake and or Trafficking ives nation ors (CCD Cameras and Photomultiplier	221 223 224 228 229 230 230
7. Imag Intra Jarea 7.1 7.2 7.3 7.4 7.5 7.6	cellula ging Too cellula Burks Object Illumin Detect Tube) Filters Autom The M Live Co	r Barriers ols for Cellular Uptake and or Trafficking ives nation ors (CCD Cameras and Photomultiplier nated Stages icroscope	221 223 224 228 229 230 230 231
7. Imag Intra Jarea 7.1 7.2 7.3 7.4 7.5 7.6 7.7	cellula ging Too cellula Burks Object Illumin Detect Tube) Filters Autom The M Live Co	r Barriers ols for Cellular Uptake and or Trafficking ives nation ors (CCD Cameras and Photomultiplier nated Stages icroscope ell Imaging	221 223 224 228 229 230 230 231 232
7. Imag Intra Jarea 7.1 7.2 7.3 7.4 7.5 7.6 7.7	cellula ging Too cellula Burks Object Illumin Detect Tube) Filters Autom The M Live Co 7.7.1 Fluore	r Barriers ols for Cellular Uptake and or Trafficking ives nation ors (CCD Cameras and Photomultiplier nated Stages icroscope ell Imaging Phototoxicity and Photostability	221 223 224 228 229 230 230 231 232 234
7. Imag Intra Jarea 7.1 7.2 7.3 7.4 7.5 7.6 7.7	cellula ging Toc cellula Burks Object Illumin Detect Tube) Filters Autom The M Live Co 7.7.1 Fluore	r Barriers ols for Cellular Uptake and ar Trafficking ives nation ors (CCD Cameras and Photomultiplier atted Stages icroscope ell Imaging Phototoxicity and Photostability escent Probes	221 223 224 228 229 230 230 231 232 234 235

2	Endo	ocytosis	241				
Э.							
		lie Sirisaengtaksin, Brandon S. Brown,					
		Andrew J. Bean					
	8.1	Clathrin-Mediated Endocytosis	243				
		8.1.1 Clathrin and Clathrin-Coated Vesicles	243				
		8.1.2 Receptor-Mediated Endocytosis	244				
		8.1.3 Pinocytosis	245				
	8.2	Caveolin-Mediated Endocytosis	245				
		8.2.1 Caveolae Formation	245				
	8.3	Actin-Mediated Endocytic Pathways:					
		Macropinocytosis and Phagocytosis	246				
		8.3.1 Macropinocytosis	247				
		8.3.1.1 Induction of macropinocytosis	247				
		8.3.2 Phagocytosis	248				
		8.3.2.1 Particle recognition, adhesion,					
		and phagosome formation	249				
		8.3.2.2 Phagosomal maturation	250				
		Nanoparticle Internalization	251				
		Early Endosome-Late Endosome Maturation	253				
	8.6	Mechanisms of Protein Sorting at the Late	WOLLD THE				
		Endosome	254				
	8.7	Role of Ubiquitination in Late Endocytic Protein					
		Sorting	256				
		Multivesicular Body Fusion with Lysosomes	257				
		Autophagy and the Endolysosomal System	258				
		Lysosomes	259				
		Secretion from Endosomal Organelles	260				
	8.12	Exosome Release from MVBs	261				
	8.13	Nanoparticle Trafficking in the Endo-Lysosomal					
		System	261				
9.	Cellu	ılar Barriers to Delivery	269				
	Chris	topher Dempsey, Elizabeth Carstens, Feiran Huang,					
		lunghae Suh					
	9.1	Introduction	269				
	9.2	Entrapment in Endolysosomal Pathway	271				
		9.2.1 pH-Sensitive Fusion	272				
		9.2.2 pH-Buffering Disruption	273				
		9.2.3 Peptide- and Polymer-Mediated					
		Disruption	275				

		9.2.4	Alternate	Location for Escape	276
	9.3	Cytopla	smic Tran	sport and Organelle Targeting	276
		9.3.1	Diffusive	Transport	277
		9.3.2	Active Tra	ansport	278
		9.3.3	Nuclear T	argeting	279
		9.3.4	Targeting	Other Organelles	279
	9.4	Cargo F	Release		280
		9.4.1	Reducible	e Polymers	282
				tive Polymers	283
		9.4.3	Photosen	sitive Polymers	284
	9.5		asmic Inst		285
		9.5.1	Nuclease	S	285
			Cellular E	5	285
			7.	ticle Aggregation	287
	9.6			ematical Models of Cellular	
		Barrier			287
				opic Modeling	288
				pic Modeling	289
				ture Overcomes Cellular Barriers	291
	9.8	Conclu	sion		292
10.	Nan	ovector	s Targetii	ng Cell Surface Receptors	299
	Srim	eenaksh	i Srinivasa	ın, Wouter H. P. Driessen,	
	Betti	ina Pron	eth, Jenoly	n F. Alexander, Renata Pasqualini,	
			and Biana		
	10.1	Introd	uction		299
		10.1.1	The Cell	Membrane as a Biological	
			Barrier		299
		10.1.2	Types of	Cell Surface Receptors and	
			(5) (5)	le in Intracellular Uptake	301
	10.2	Cell Su	rface Bion	narker Discovery	302
				leceptor Binding Strategies	303
			_	In vivo phage display	303
				Antibodies	306
				Oligonucleotide-based	
				combinatorial libraries	307
			10.2.1.4	combinatorial libraries Considerations for ligand	307
			10.2.1.4	combinatorial libraries Considerations for ligand selection	307 307
		10.2.2	10.2.1.4 Sequence	Considerations for ligand selection	

Contents	xiii
10.2.3 Proteomics 310	
10.3 Nanovectors-Modification Techniques for	
Targeting Cell Membrane Receptors 310	
10.3.1 Aptamers 311	
10.3.2 Proteins 313	
10.3.3 Peptides 315	
10.3.4 Other Ligands 315	
10.4 Cell Membrane Targeted Nanocarriers for	
Advanced Diagnostics and Therapeutics 318	
10.4.1 Cancer 319	
10.4.2 Cardiovascular Diseases 326	
10.4.3 Targeted Nanovectors in Endocrine and	
Metabolic Disorders 330	
10.4.4 Neural Diseases 331	
10.4.5 Infections and Inflammation 331	
10.5 Effect of Carrier Geometry on Cell Surface	
Receptor Binding and Cellular Uptake 334	
10.6 Conclusions 337	
Part 5 Novel Design Approaches 361	
3 11	
11. The Fabrication and Mass Transport of Polymer	
Nanocarriers 363	
Litao Bai, Jason Sakamoto, and Haifa Shen	
11.1 Introduction 363	
11.2 Polymeric Nanoparticles as Nanocarriers 366	
11.2.1 Preparation of Polymeric Nanoparticles 367	
11.2.1.1 Preparation of polymer	
nanoparticles by solvent	
evaporation 367	
11.2.1.2 Preparation of polymer	
nanoparticles by salting out 369	
11.2.1.3 Preparation of polymer	
nanoparticles by solvent displacement/diffusion	
method 369	
11.2.1.4 Preparation of polymer	
fluid 370	
nanoparticles by supercritical	

			11.2.1.5	Preparation of polymer	
				nanoparticles by	
				polymerization method	371
		11.2.2	Drug Loa	ding with Polymer	
			Nanopar	ticles	371
		11.2.3	Drug Rel	ease from Polymer	
			Nanopar	ticles	372
	11.3	Polyme	er-Drug Co	onjugates	372
		11.3.1	HPMA Co	polymer-Drug Conjugates	374
				mic Acid-Drug Conjugates	375
		11.3.3	Dextran-	Drug Conjugates	375
				g Conjugates	376
	11.4			es as Nanocarriers	377
			Introduc		377
		11.4.2		ion and Drug Loading of	
				c Micelles	379
				ease from Polymeric Micelles	381
	11.5		mer Nano		383
			Introduc		383
		11.5.2	0.770	of Dendrimers by Physical	
			Encapsul		385
		11.5.3	_	of Dendrimers by Chemical	
			Conjugat		387
		11.5.4		on of Multifunctional	ans to
				er Conjugations	388
	11.6	Conclu	sion and I	Prospects	388
12.	-		y Control	of Nanotextured Drug	
	Carr	iers			409
	Үе Ні	u and Ke	evin Lin		
	12.1	Introd	uction		409
	12.2	Porous	Silicon M	icroparticles for Drug	
		Deliver	ry		412
		12.2.1	Synthesi	s of Porous Silicon	412
		12.2.2	Vascular	Targeting and Margination	413
		12.2.3	Biodistri	bution	416
	12.3	Spheri	cal Silica I	Particles for Drug Delivery	417
		12.3.1		for Particle Synthesis	418
			12.3.1.1	Synthesis of M41S-based	
				delivery particles	418