

Contents

Foreword XVII

Preface XIX

About the Editors XXI

List of Contributors XXIII

Part I: Control of Cell/Film Interactions 1

- 1 Controlling Cell Adhesion Using pH-Modified Polyelectrolyte Multilayer Films** 3
Marcus S. Niepel, Kristin Kirchhof, Matthias Menzel, Andreas Heilmann, and Thomas Groth
 - 1.1 Introduction 3
 - 1.2 Influence of pH-Modified PEM Films on Cell Adhesion and Growth 5
 - 1.2.1 HEP/CHI Multilayers 5
 - 1.2.2 PEI/HEP Multilayers 16
 - 1.3 Summary and Outlook 24

Acknowledgments 25
 References 25
- 2 The Interplay of Surface and Bulk Properties of Polyelectrolyte Multilayers in Determining Cell Adhesion** 31
Joseph B. Schlenoff and Thomas C.S. Keller
 - 2.1 Surface Properties 33
 - 2.2 Bulk Modulus 38

References 42
- 3 Photocrosslinked Polyelectrolyte Films of Controlled Stiffness to Direct Cell Behavior** 45
Naresh Saha, Claire Monge, Thomas Boudou, Catherine Picart, and Karine Glinel
 - 3.1 Introduction 45
 - 3.2 Elaboration of Homogeneous Films of Varying Rigidity 48

3.3	Elaboration of Rigidity Patterns	52
3.4	Behavior of Mammalian Cells on Homogeneous and Photopatterned Films	54
3.5	Influence of Film Rigidity on Bacterial Behavior	58
3.6	Conclusion	61
	Acknowledgments	61
	References	62
4	Nanofilm Biomaterials: Dual Control of Mechanical and Bioactive Properties	65
	<i>Emmanuel Pauthe and Paul R. Van Tassel</i>	
4.1	Introduction	65
4.2	Surface Cross-Linking	67
4.3	NP Templating	69
4.4	Discussion	73
4.5	Conclusions	75
	Acknowledgments	75
	References	75
5	Bioactive and Spatially Organized LbL Films	79
	<i>Zhengwei Mao, Shan Yu, and Changyou Gao</i>	
5.1	Introduction	79
5.2	Role of Chemical Properties	80
5.2.1	Bulk Composition	80
5.2.1.1	Introducing Natural Polyelectrolytes as Building Blocks	80
5.2.1.2	Incorporating Hormones and Growth Factors	81
5.2.2	Surface Chemistry	83
5.2.2.1	Role of the Final Layer	83
5.2.2.2	Surface Modification with Cell Binding Molecules	83
5.3	Role of Physical Properties	85
5.3.1	Mechanical Property	85
5.3.1.1	Chemical Cross-linking	86
5.3.1.2	Incorporating Stiff Building Blocks	86
5.3.1.3	Control Environmental pH or Salt Concentration	87
5.3.2	Topography	89
5.4	Spatially Organized PEMs	89
5.4.1	Patterned PEMs	89
5.4.2	Gradient PEMs	91
5.5	Conclusions and Future Perspectives	92
	Acknowledgments	94
	References	94
6	Controlling Stem Cell Adhesion, Proliferation, and Differentiation with Layer-by-Layer Films	103
	<i>Stewart Wales, Guak-Kim Tan, and Justin J. Cooper-White</i>	
6.1	Introduction	103

6.1.1	Types of Stem Cells	103
6.1.2	Stem Cell Fate Choices	104
6.1.3	The Stem Cell “Niche”	104
6.1.3.1	Soluble Factors	105
6.1.3.2	Cell–Cell Interactions	105
6.1.3.3	Cell–ECM Interactions	106
6.1.4	Influencing Stem Cell Fate Choice	106
6.2	Mesenchymal Stem Cells and Layer-by-Layer Films	107
6.2.1	Human MSC Adhesion, Proliferation, and Differentiation	107
6.2.2	Murine MSC Adhesion, Proliferation, and Differentiation	114
6.3	Pluripotent Stem Cells and Layer-by-Layer Films	116
6.3.1	Murine ESC Adhesion, Proliferation, and Maintenance of Potency	117
6.3.2	Murine ESC Differentiation	120
6.3.3	Human ESC Adhesion, Proliferation, and Differentiation	122
6.4	Future Directions and Trends	123
	References	124

Part II: Delivery of Small Drugs, DNA and siRNA 131

7	Engineering Layer-by-Layer Thin Films for Multiscale and Multidrug Delivery Applications	133
	<i>Nisarg J. Shah, Bryan B. Hsu, Erik C. Dreaden, and Paula T. Hammond</i>	
7.1	Introduction	133
7.1.1	The Promise of LbL Delivery	133
7.1.1.1	High Drug Density and Scalability	133
7.1.1.2	Translatable to 2D and 3D Geometries	133
7.1.1.3	Facile Encapsulation of Active Biologics	134
7.1.1.4	Multiple Drug Combinations	134
7.1.1.5	Controlled Time-Dependent Release and Opportunity for Multisequence Release	134
7.1.2	Growth in the LbL Delivery Field	135
7.1.3	Brief Outline of Chapter	135
7.2	Engineering LbL Release Mechanisms – from Fast to Slow Release	136
7.2.1	Overview	136
7.2.2	Tuning Hydrolytic Release	137
7.2.3	Small Molecule Release	139
7.2.3.1	Direct Adsorption of Charged Molecules	139
7.2.3.2	Complexation with Charged Polymer	139
7.2.3.3	Pre-encapsulation in Carrier	141
7.2.4	H-Bond-Based Release of Molecules	141
7.2.5	Impact of Assembly Approach and Spray-LbL	142
7.2.6	Other Mechanisms of Release	143

7.2.7	Controlling Release Kinetics and Manipulating Sequential Release	144
7.3	LbL Biologic Release for Directing Cell Behavior	145
7.3.1	Overview	145
7.3.2	Controlled Growth Factor Delivery for Tissue Engineering	146
7.3.2.1	Release of Therapeutic Growth Factors from LbL Films	146
7.3.3	Growth Factor Delivery with Synergistic Impact	148
7.3.3.1	BMP-2 and VEGF	148
7.3.3.2	Implant Osseointegration: The Synergistic Effect of BMP-2 and Hydroxyapatite	149
7.3.4	Staggering Release of Drugs from LbL Films with “Barrier” Layers	151
7.3.5	Nucleic Acid Delivery as a Modulator of Cell Response	152
7.3.5.1	Challenges of DNA/siRNA Release for Localized Delivery	152
7.3.5.2	Multilayer Polymer “Tattoos” for DNA-Based Vaccination	153
7.3.5.3	Wound Healing Mediated by siRNA for Sustained Localized Knockdown	154
7.4	Moving LbL Release Technologies to the Nanoscale: LbL Nanoparticles	156
7.4.1	Overview – Nanoparticle Delivery Challenges	156
7.4.2	Tuning LbL Systems for Systemic Delivery – Stability, Blood Half-life	156
7.4.3	Adapting LbL Nanoparticles for Targeting	158
7.4.3.1	Tumor Microenvironment, Hypoxic Response	159
7.4.3.2	Molecular Targeting	160
7.4.4	Dual Drug Combinations	160
7.4.4.1	siRNA Chemotherapy Combination Nanoparticle Systems	161
7.4.4.2	Future Potential	162
7.5	Conclusions and Perspective on Future Directions	162
7.5.1	Translation of Technologies	163
	Acknowledgments	165
	References	165
8	Polyelectrolyte Multilayer Coatings for the Release and Transfer of Plasmid DNA	171
	<i>David M. Lynn</i>	
8.1	Introduction	171
8.2	Fabrication of Multilayers Using Plasmid DNA and Hydrolytically Degradable Polyamines	173
8.3	Toward Therapeutic Applications <i>In vivo</i> Contact-Mediated Approaches to Vascular Gene Delivery	178
8.3.1	Transfer of DNA to Arterial Tissue Using Film-Coated Intravascular Stents	178
8.3.2	Transfer of DNA to Arterial Tissue Using Film-Coated Balloon Catheters	180

8.3.3	Beyond Reporter Genes: Approaches to the Reduction of Intimal Hyperplasia in Injured Arteries	182
8.3.4	Other Potential Applications	184
8.4	Exerting Temporal Control over the Release of DNA	184
8.4.1	New Polymers and Principles: Degradable Polyamines and “Charge Shifting” Cationic Polymers	185
8.4.2	Multicomponent Multilayers for the Release of Multiple DNA Constructs	187
8.4.2.1	Approaches to Promoting the Rapid Release of DNA	188
8.5	Concluding Remarks	190
	Acknowledgments	190
	References	191
9	LbL-Based Gene Delivery: Challenges and Promises	195
	<i>Joelle Ogier</i>	
9.1	LbL-DNA Delivery	195
9.1.1	Pioneer Designs	196
9.1.2	DNA Spatial and Temporal Scheduled Delivery	199
9.1.3	Pending Challenges: From <i>In Vitro</i> Substrate-Mediated Gene Delivery to <i>In Vivo</i> Formulations	201
9.2	LbL-siRNA Delivery	202
9.3	Concluding Remarks	204
	References	205
10	Subcompartmentalized Surface-Adhering Polymer Thin Films Toward Drug Delivery Applications	207
	<i>Boon M. Teo, Martin E. Lyngé, Leticia Hosta-Rigau, and Brigitte Städler</i>	
10.1	Introduction	207
10.2	Cyclodextrin (CD)-Containing LbL Films	208
10.2.1	Assembly	209
10.2.2	Drug Delivery Applications	209
10.3	Block Copolymer Micelle (BCM)-Containing LbL Films	212
10.3.1	Assembly	213
10.3.1.1	Glassy BCMs within LbL Films	213
10.3.1.2	Temperature and pH Responsive BCMs within LbL Films	213
10.3.2	Drug Delivery Applications	215
10.4	Liposome-Containing LbL Films	215
10.4.1	Assembly	216
10.4.2	Cargo Release Capability from Liposomes within LbL Films	219
10.4.3	Drug Delivery Applications	219
10.5	LbL Films Containing Miscellaneous Drug Deposits	222
10.6	Conclusion/Outlook	224
	References	225

Part III: Nano- and Microcapsules as Drug Carriers 233

11	Multilayer Capsules for <i>In vivo</i> Biomedical Applications	235
	<i>Bruno G. De Geest and Stefaan De Koker</i>	
11.1	Introduction	235
11.2	A Rationale for Functionally Engineered Multilayer Capsules	236
11.2.1	General Considerations	236
11.2.2	Multilayer Capsules Responding to Physicochemical and Physiological Stimuli	238
11.3	<i>In vivo</i> Fate of Multilayer Capsules	241
11.3.1	Tissue Response	241
11.3.2	<i>In vivo</i> Uptake and Degradation	243
11.3.3	Blood Circulation	245
11.4	Vaccine Delivery via Multilayer Capsules	246
11.5	Tumor Targeting via Multilayer Capsules	252
11.6	Concluding Remarks	253
	References	254
12	Light-Addressable Microcapsules	257
	<i>Markus Ochs, Wolfgang J. Parak, Joanna Rejman, and Susana Carregal-Romero</i>	
12.1	Introduction	257
12.2	Light-Responsive Components	258
12.2.1	Light-Responsive Polyelectrolytes and Molecules	258
12.2.2	Light-Responsive Shells	259
12.2.3	Light-Responsive Nanoparticles	259
12.3	Capsule Synthesis and Loading	261
12.4	Gold-Modified Layer-by-Layer Capsules	264
12.5	Morphological Changes of Capsules and Nanoparticles	267
12.6	Bubble Formation	267
12.7	Cytosolic Release	269
12.8	Triggering Cytosolic Reactions	272
12.9	Conclusions and Perspectives	274
	Acknowledgments	275
	References	275
13	Nanoparticle Functionalized Surfaces	279
	<i>Mihaela Delcea, Helmuth Moehwald, and Andre G. Skirtach</i>	
13.1	Introduction	279
13.2	Nanoparticles on Polyelectrolyte Multilayer LbL Capsules	281
13.2.1	Adsorption of Nanoparticles onto Polyelectrolyte Multilayer Capsules	281
13.2.2	Light- and Magnetic-Field-Induced Permeability Control	282
13.2.3	Fluorescence Imaging Using Quantum Dots	284
13.2.4	Magnetic Nanoparticles: Activation and Targeting	284

13.2.5	Catalysis Using Nanoparticles	285
13.2.6	Enhancement of Mechanical Properties of Capsules	285
13.2.7	Anisotropic Capsules	286
13.3	Nanoparticles on Polyelectrolyte LbL Films	287
13.3.1	LbL Films and Adsorption of Nanoparticles onto Films	287
13.3.2	Laser Activation	287
13.3.3	Fluorescent Labeling of Films	289
13.3.4	Increasing the Stiffness of Films for Cell Adhesion and Control over Asymmetric Particle Fabrication	289
13.3.5	Additional Functionalities through Addition of Nanoparticles	290
13.4	Conclusions	290
	References	292
14	Layer-by-Layer Microcapsules Based on Functional Polysaccharides	295
	<i>Anna Szarpak-Jankowska, Jing Jing, and Rachel Auzély-Velty</i>	
14.1	Introduction	295
14.2	Fabrication of Polysaccharide Capsules by the LbL Technique	296
14.2.1	Natural Charged Polysaccharides Used in LbL Capsules	296
14.2.2	General Methods for the Assembly of Polysaccharides into LbL Capsules	297
14.2.3	Cross-Linking of the Polysaccharide Shells	298
14.2.4	Functional Multilayer Shells Based on Chemically Modified Polysaccharides	300
14.2.4.1	Multilayer Shells Made of Alkylated Hyaluronic Acid	300
14.2.4.2	Multilayer Shells Made of Hyaluronic Acid and Dextran Bearing Pendant Cyclodextrins Along the Chain	300
14.2.4.3	Multilayer Shells Made of Quaternized Chitosan	301
14.3	Biomedical Applications	302
14.4	Interactions with Living Cells	305
14.5	Conclusion	306
	References	307
15	Nanoengineered Polymer Capsules: Moving into the Biological Realm	309
	<i>Katelyn T. Gause, Yan Yan, and Frank Caruso</i>	
15.1	Introduction	309
15.2	Capsule Design and Assembly	310
15.2.1	Templates	310
15.2.2	Materials and Assembly Interactions	312
15.2.2.1	Electrostatic Assembly	312
15.2.2.2	Hydrogen Bonding-Facilitated Assembly	312
15.2.2.3	DNA Base Pairing	313
15.2.2.4	“Click” Assembly and Cross-linking	314
15.2.3	Cargo Encapsulation	315

15.2.3.1	Preloading	316
15.2.3.2	Postloading	317
15.2.3.3	Cargo within Capsule Shells	317
15.2.4	Biological Stimuli-Responsive Cargo Release	318
15.2.4.1	Enzymatically Responsive Cargo Release	318
15.2.4.2	pH-Responsive Cargo Release	319
15.2.4.3	Redox-Responsive Cargo Release	320
15.3	Capsules at the Biological Interface	321
15.3.1	Circulation and Biodistribution	322
15.3.2	Cellular Interactions	323
15.3.3	Intracellular Trafficking	324
15.4	Biological Applications	326
15.4.1	Anticancer Drug Delivery	326
15.4.1.1	Targeting	326
15.4.2	Vaccine Delivery	329
15.4.3	Biosensors and Bioreactors	331
15.5	Conclusion and Outlook	335
	References	336
16	Biocompatible and Biogenic Microcapsules	343
	<i>Jie Zhao, Jinbo Fei, and Junbai Li</i>	
16.1	Introduction	343
16.2	LbL Assembly of Biocompatible and Biogenic Microcapsules	344
16.2.1	Lipid-Based Microcapsules	344
16.2.2	Polysaccharide-Based Microcapsules	346
16.2.3	Protein-Based Microcapsules	348
16.3	Applications	349
16.3.1	Drug Carriers for Cancer Treatment	350
16.3.1.1	Methods for Drug Loading	350
16.3.1.2	Thermotherapy	352
16.3.1.3	Photodynamic Therapy	354
16.3.2	Blood Substitutes	356
16.4	Conclusions and Perspectives	358
	Acknowledgments	358
	References	358
17	Three-Dimensional Multilayered Devices for Biomedical Applications	363
	<i>Rui R. Costa and João F. Mano</i>	
17.1	Introduction	363
17.2	Freestanding Multilayer Films	364
17.2.1	Pure Freestanding Membranes	364
17.2.2	Hybrid LbL-Assisted Techniques	366
17.3	Tubular Structures	366
17.4	Spherical Coated Shapes	368

17.4.1	Drug Carriers	369
17.4.2	Biosensors	371
17.5	Complex LbL Devices with Compartmentalization and Hierarchical Components	372
17.5.1	Confined Chemical Reactions	373
17.5.2	Customized Multifunctional Reactors	374
17.6	Porous Structures	376
17.7	Conclusions	377
	Acknowledgments	378
	References	378

Part IV: Engineered Tissues and Coatings of Implants 385

18	Polyelectrolyte Multilayer Film – A Smart Polymer for Vascular Tissue Engineering	387
	<i>Patrick Menu and Halima Kerdjoudj</i>	
18.1	Layer by Layer Coating	388
18.2	Anti-Adhesive Properties of PEMs	388
18.3	Adhesion Properties of PEMs and Their Use in Vascular Tissue Engineering	389
18.4	Polyelectrolyte Multilayer Films and Stem Cell Behavior	390
18.5	PEM Coating of Vascular Prosthesis	391
18.6	Functional PEMs Mimicking Endothelial Cell Function	391
18.7	Conclusion	392
	References	392
19	Polyelectrolyte Multilayers as Robust Coating for Cardiovascular Biomaterials	399
	<i>Kefeng Ren and Jian Ji</i>	
19.1	Introduction	399
19.2	The Basement Membrane: The Bioinspired Cue for Cardiovascular Regeneration	400
19.3	PEMs as a Feasible Method for Immobilization: From Antithrombosis to the Synergistic Interaction	401
19.4	Controlled Delivery from PEMs: From Small Molecule Drugs and Bioactive Molecules to Genes	403
19.5	Effects of Mechanical Properties of PEMs on Cellular Events	406
19.6	PEM as a Coating for Cardiovascular Device: From <i>In vitro</i> to <i>In vivo</i>	407
19.7	Conclusion and Perspectives	412
	References	412

20	LbL Nanofilms Through Biological Recognition for 3D Tissue Engineering 419 <i>Michiya Matsusaki and Mitsuru Akashi</i>
20.1	Introduction 419
20.2	A Bottom-Up Approach for 3D Tissue Construction 421
20.2.1	Hierarchical Cell Manipulation Technique 422
20.2.1.1	Fabrication of Multilayered Structure by Nano-ECM Coating 423
20.2.1.2	Effect of Nanofilms on Cellular Function 426
20.2.1.3	Control of Cellular Function and Activity in 3D Environments 426
20.2.1.4	Permeability Assay of Multilayered Fibrous Tissues 431
20.2.2	Blood Vessel Wall Model 432
20.2.2.1	Construction of Blood Vessel Wall Model 433
20.2.2.2	Quantitative 3D Analysis of Nitric Oxide Using Blood Vessel Wall Model 433
20.2.3	Blood Capillary Model 436
20.2.3.1	Fabrication of Blood Capillary Model by Cell-Accumulation Technique 436
20.2.3.2	Application for the Evaluation of the Interaction with Tissues 438
20.2.4	Perfusable Blood Vessel Channel Model 439
20.2.4.1	Construction of Blood Vessel Channel Model in Hydrogel 441
20.2.4.2	<i>In vitro</i> Permeability Assay 442
20.2.5	Engineering 3D Tissue Chips by Inkjet Cell Printing 442
20.2.5.1	Cell and ECM Printing 445
20.2.5.2	Human Liver Tissue Chips and Liver Function Assay 445
20.3	Conclusions 447
	Acknowledgments 447
	References 447
21	Matrix-Bound Presentation of Bone Morphogenetic Protein 2 by Multilayer Films: Fundamental Studies and Applications to Orthopedics 453 <i>Flora Gilde, Raphael Guillot, Laure Fourel, Jorge Almodovar, Thomas Crouzier, Thomas Boudou, and Catherine Picart</i>
21.1	Introduction 453
21.2	BMP-2 Loading: Physico-Chemistry and Secondary Structure 455
21.2.1	Tunable Parameters for BMP-2 Loading 455
21.2.2	Secondary Structure of BMP-2 in Hydrated and Dry Films 458
21.2.2.1	Secondary Structure of BMP-2 in Solution 458
21.2.2.2	Structure of BMP-2 Trapped in Hydrated or Dry (PLL/HA) Films 459
21.3	Osteoinductive Properties of Matrix-Bound BMP-2 <i>In vitro</i> 461
21.4	Early Cytoskeletal Effects of BMP-2 463
21.5	Toward <i>In vivo</i> Applications for Bone Repair 467
21.5.1	Characterization of PEM Film Deposition on TCP/HAP Granules and on Porous Titanium 467

21.5.2	Sterilization by γ -Irradiation	469
21.5.3	Osteoinduction <i>In vivo</i>	471
21.6	Toward Spatial Control of Differentiation	475
21.7	Conclusions	477
	Acknowledgments	478
	List of Abbreviations	478
	References	479
22	Polyelectrolyte Multilayers for Applications in Hepatic Tissue Engineering	487
	<i>Margaret E. Cassin and Padmavathy Rajagopalan</i>	
22.1	Introduction	487
22.1.1	The Liver	489
22.1.2	Hepatic Tissue Engineering	491
22.1.3	PEMs and Hepatic Tissue Engineering	491
22.2	PEMs for 2D Hepatic Cell Cultures	492
22.2.1	Tuning Mechanical and Chemical Properties of PEMs	492
22.3	PEMs for 3D Hepatic Cell Cultures	495
22.3.1	PEMs that Mimic the Space of Disse	495
22.3.2	Porous Scaffolds for Hepatic Cell Cultures	496
22.3.3	3D PEM Stamping for Primary Hepatocyte Co-cultures	498
22.4	Conclusions	498
	Acknowledgments	498
	References	499
23	Polyelectrolyte Multilayer Film for the Regulation of Stem Cells in Orthopedic Field	507
	<i>Yan Hu and Kaiyong Cai</i>	
23.1	Introduction	507
23.2	Layer-by-Layer Assembly and Classification	508
23.3	Classic Polyelectrolyte Multilayer Films (Intermediate Layer)	509
23.3.1	Bioactive Multilayer Films	509
23.3.1.1	Compositions of Polyelectrolyte Multilayer Films	510
23.3.1.2	Stiffness of Polyelectrolyte Multilayer Films	511
23.3.1.3	Cell Specific Recognition of Polyelectrolyte Multilayer Films	511
23.3.2	Gene-Activating Multilayer Film	512
23.4	Hybrid Polyelectrolyte Multilayer Film	514
23.4.1	Growth Factors or Cytokines Embedding Hybrid Layer	515
23.4.2	Drug Embedding Hybrid Layer	516
23.4.3	Nanoparticles Embedding Hybrid Layer	518
23.5	“Protecting” Polyelectrolyte Multilayer Film (Cover Layer)	518
23.6	Conclusion and Perspective	521
	References	521

24	Axonal Regeneration and Myelination: Applicability of the Layer-by-Layer Technology 525
	<i>Chun Liu, Ryan Pyne, Seungik Baek, Jeffrey Sakamoto, Mark H. Tuszynski, and Christina Chan</i>
24.1	Current Challenges of Spinal Cord Injury: Inflammation, Axonal Regeneration, and Remyelination 525
24.1.1	Spinal Cord Injury 525
24.1.2	Potential of Tissue Engineering for Treating SCI 527
24.2	PEM Film – Cell Interactions and Adhesion 530
24.2.1	Polyelectrolyte Multilayers in Tissue Engineering 531
24.2.2	Components of the Multilayers 532
24.2.3	LbL as an Adhesive Coating for Neural Cell Attachment 533
24.2.4	Patterned Co-cultures Using LbL Technique 534
24.3	Controlled Drug Delivery for Nerve Regeneration 536
24.3.1	Drug Release from LbL Films 536
24.3.2	Local Drug Release for Neural Regeneration 537
24.4	Future Perspective 538
	Acknowledgments 539
	References 539
	Index 547