

Contents

Foreword *xvii*

1	Skin Structure and Biology	1
	<i>Wei-Meng Woo</i>	
1.1	Introduction	1
1.2	Skin Structure	2
1.2.1	Overview of Skin Tissue Organization	2
1.2.1.1	Thick Skin and Thin Skin	2
1.2.2	Epidermis	3
1.2.2.1	Stratum Basale	5
1.2.2.2	Stratum Spinosum	5
1.2.2.3	Stratum Granulosum	6
1.2.2.4	Stratum Lucidum	6
1.2.2.5	Stratum Corneum	6
1.2.3	Dermis	6
1.2.4	Hypodermis	7
1.2.5	Skin Appendages	8
1.3	Skin Biology	9
1.3.1	Homeostasis: Epidermal Self-renewal	9
1.3.2	Formation of a Water Barrier	10
1.3.3	Getting Across the Water Barrier	11
	References	12
2	Wound Healing and Its Imaging	15
	<i>Jiah Shin Chin, Leigh Madden, Sing Yian Chew, Anthony R.J. Phillips and David L. Becker</i>	
2.1	Hemostasis and Essential Inflammation	15
2.2	Re-epithelialization	18
2.3	Granulation Tissue Formation	19
2.4	Scar Tissue Formation	20
2.5	Imaging of Wound Healing	21
2.6	Macroscopic Digital Imaging for Wound Size	22
2.7	Hyperspectral and Multispectral Imaging	22
2.8	Near-Infrared Spectroscopy	23
2.9	Raman Imaging	23

2.10	Confocal Microscopy	24
2.11	Multiphoton Imaging and Second Harmonics	24
	References	27
3	Common Skin Diseases: Chronic Inflammatory and Autoimmune Disorders	35
	<i>Navin Kumar Verma, Maurice Adrianus Monique van Steensel, Praseetha Prasannan, Zhi Sheng Poh, Alan D. Irvine and Hazel H. Oon</i>	
3.1	Introduction	35
3.2	Psoriasis	36
3.2.1	Definition and Prevalence	36
3.2.2	Clinical Features, Pathogenesis, and Pathophysiology	37
3.2.3	Diagnosis	39
3.2.4	Therapy	40
3.3	Atopic Dermatitis (AD)	40
3.3.1	Definition and Prevalence	40
3.3.2	Clinical Features, Pathogenesis, and Pathophysiology	41
3.3.3	Diagnosis	42
3.3.4	Therapy	43
3.4	Scleroderma	43
3.4.1	Definition and Prevalence	43
3.4.2	Clinical Features, Pathogenesis, and Pathophysiology	44
3.4.3	Diagnosis	44
3.4.4	Therapy	45
3.5	Dermatomyositis (DM)	45
3.5.1	Definition and Prevalence	45
3.5.2	Clinical Features, Pathogenesis, and Pathophysiology	46
3.5.3	Diagnosis	46
3.5.4	Therapy	47
3.6	Cutaneous Lupus Erythematosus (CLE)	47
3.6.1	Definition and Prevalence	47
3.6.2	Clinical Features, Pathogenesis, and Pathophysiology	47
3.6.3	Diagnosis	48
3.6.4	Treatment	49
3.7	Generalized Vitiligo (GV)	49
3.7.1	Definition and Prevalence	49
3.7.2	Clinical Features, Pathogenesis, and Pathophysiology	49
3.7.3	Diagnosis	50
3.7.4	Treatment	51
3.8	Concluding Remarks	51
	Acknowledgments	51
	References	52
4	Common Skin Diseases: Autoimmune Blistering Disorders	61
	<i>Navin Kumar Verma, Shermaine Wan Yu Low, Hazel H. Oon, Dermot Kelleher and Maurice Adrianus Monique van Steensel</i>	
4.1	Introduction	61
4.2	Pemphigus	62

4.2.1	Definition and Prevalence	62
4.2.2	Clinical Features, Pathogenesis, and Pathophysiology	62
4.2.2.1	Pemphigus Vulgaris (PV)	63
4.2.2.2	Pemphigus Foliaceus (PF)	64
4.2.2.3	Paraneoplastic Pemphigus (PNP)	64
4.2.2.4	IgA Pemphigus	66
4.2.2.5	Pemphigus Erythematosus (PE)	66
4.2.2.6	Drug-Induced Pemphigus	66
4.2.3	Diagnosis	67
4.2.4	Treatment	67
4.3	Pemphigoid	68
4.3.1	Definition and Prevalence	68
4.3.2	Clinical Features, Pathogenesis, and Pathophysiology	68
4.3.2.1	Bullous Pemphigoid (BP)	68
4.3.2.2	Mucous Membrane Pemphigoid (MMP)	69
4.3.2.3	Pemphigoid Gestationis (PG)	69
4.3.3	Diagnosis	70
4.3.4	Treatment	70
4.4	Dermatitis Herpetiformis (DH)	70
4.4.1	Definition and Prevalence	70
4.4.2	Clinical Features, Pathogenesis, and Pathophysiology	71
4.4.3	Diagnosis	71
4.4.4	Treatment	71
4.5	Epidermolysis Bullosa Acquisita (EBA)	72
4.5.1	Definition and Prevalence	72
4.5.2	Clinical Features, Pathogenesis, and Pathophysiology	72
4.5.3	Diagnosis	73
4.5.4	Treatment	73
4.6	Concluding Remarks and Future Directions	73
	Acknowledgments	74
	References	74
5	Common Skin Diseases: Skin Cancer	83
	<i>Tuyen T.L. Nguyen, Eric Tarapore and Scott X. Atwood</i>	
5.1	Introduction	83
5.2	Basal Cell Carcinoma	83
5.2.1	Risk Factors	84
5.2.2	Classification	85
5.2.3	Cell of Origin	85
5.2.4	Signaling Pathways	86
5.2.5	Common Treatments	87
5.3	Squamous Cell Carcinoma	88
5.3.1	Risk Factors	89
5.3.2	Classification	89
5.3.3	Cell of Origin	90
5.3.4	Signaling Pathways	90
5.3.5	Common Treatments	91
5.4	Melanoma	92

5.4.1	Risk Factors	92
5.4.2	Classification	93
5.4.3	Cell of Origin	94
5.4.4	Signaling Pathways	94
5.4.5	Common Treatments	94
5.5	Concluding Remarks	95
	References	96
6	Preclinical Models for Drug Screening and Target Validation	105
	<i>Ivo J.H.M. de Vos, Julia Verbist and Maurice A.M. van Steensel</i>	
6.1	Introduction	105
6.2	<i>Ex Vivo</i> Models of Human Skin	105
6.2.1	Introduction	105
6.2.2	<i>Ex Vivo</i> Models of Skin Barrier Function and Dermal Absorption	107
6.2.3	<i>Ex Vivo</i> Models of Cutaneous Wound Healing	107
6.2.4	<i>Ex Vivo</i> Hair Follicle Culture	108
6.3	<i>In Vitro</i> Models of Human Skin	108
6.3.1	Introduction	108
6.3.2	Two-Dimensional Cell Culture Models	109
6.3.3	Three-Dimensional Reconstructed Human Skin Models	109
6.3.3.1	Reconstituted Human Epidermis Models	110
6.3.3.2	Reconstituted Human Dermis Models	111
6.3.3.3	Reconstituted Skin Equivalent Models	111
6.3.3.4	Organoids	112
6.4	<i>In Vivo</i> Animal Models	112
6.4.1	<i>Caenorhabditis elegans</i>	112
6.4.1.1	Introduction	112
6.4.1.2	Anatomy and Physiology of the Roundworm Epidermis	112
6.4.1.3	The Use of <i>Caenorhabditis elegans</i> to Study Cutaneous Wound Healing	113
6.4.2	<i>Drosophila melanogaster</i>	113
6.4.2.1	Introduction	113
6.4.2.2	Anatomy and Physiology of the Fruit Fly Epidermis	114
6.4.2.3	Studying Cutaneous Wound Healing Using Fruit Flies	114
6.4.2.4	Insights in Cutaneous Innate Immunity from <i>Drosophila melanogaster</i>	115
6.4.2.5	Fruit Fly Models of Bullous Dermatoses	115
6.4.2.6	Fruit Fly Models of Skin Cancer	115
6.4.3	<i>Danio rerio</i>	116
6.4.3.1	Introduction	116
6.4.3.2	Anatomy and Physiology of Zebrafish Skin	116
6.4.3.3	Zebrafish Models to Study Pigmentation and Melanoma	117
6.4.3.4	Studying Cutaneous Wound Healing Using <i>Danio rerio</i>	117
6.4.3.5	Zebrafish as Platform for Drug Development	117
6.4.3.6	Zebrafish Models of Genodermatoses	118
6.4.4	<i>Mus musculus</i>	118

6.4.4.1	Introduction	118
6.4.4.2	Anatomy and Physiology of Murine Skin	119
6.4.4.3	Murine Models for Studying Cutaneous Wound Healing	120
6.4.4.4	Murine Models of Psoriasis	120
6.4.4.5	Mouse Models of Autoimmune Bullous Dermatoses	120
6.4.4.6	Studying Melanoma Using Mouse Models	121
6.4.4.7	Mouse and Rat Models of Alopecia Areata	121
6.4.4.8	Insights in Acne Pathogenesis and Comedolysis from Mouse Models	122
6.4.5	<i>Cavia porcellus</i>	122
6.4.5.1	Introduction	122
6.4.5.2	Anatomy and Physiology of Guinea Pig Skin	123
6.4.5.3	Studying Dermatophytoses Using Guinea Pigs	123
6.4.5.4	Guinea Pig Models of Epidermal Permeability Topical Irritant Testing	123
6.4.5.5	Studying Burn Wounds Using Guinea Pigs	123
6.4.5.6	Guinea Pig Models for Pigmentation Studies	124
6.4.6	<i>Oryctolagus cuniculus</i>	124
6.4.6.1	Introduction	124
6.4.6.2	Anatomy and Physiology of Leporine Skin	124
6.4.6.3	Rabbit Models of Acne Venenata and Contact Dermatitis	125
6.4.6.4	Rabbit Models of Cutaneous Wound Healing and Scarring	125
6.4.6.5	Rabbit Models for Genodermatoses	126
6.4.7	<i>Canis lupus familiaris</i>	126
6.4.7.1	Introduction	126
6.4.7.2	Anatomy and Physiology of Dog Skin	126
6.4.7.3	Dog Models of Atopic Dermatitis	126
6.4.7.4	Dog Models of Autoimmune Disorders	127
6.4.7.5	Studying Follicular Hyperkeratosis and Keratolysis in Dogs	127
6.4.7.6	Dog Models of Mucosal Melanoma	127
6.4.7.7	Bullous Dermatoses in Dogs	128
6.4.8	<i>Sus scrofa domestica</i>	128
6.4.8.1	Introduction	128
6.4.8.2	Anatomy and Physiology of Pig Skin	128
6.4.8.3	Porcine Models of Cutaneous Wound Healing	129
6.4.8.4	Pig Models of Cutaneous Permeability	129
	References	129
7	Skin Tissue Engineering with Nanostructured Materials	147
	<i>Zahra Davoudi and Qun Wang</i>	
7.1	Introduction	147
7.2	Nanostructured Materials for Skin Tissue Engineering	148
7.2.1	Natural Biomaterials for Skin Tissue Engineering	148
7.2.1.1	Collagen, CS, and Blend of Two	148
7.2.1.2	Fibronectin and Hyaluronic Acid (HA)	149

7.2.2	Synthetic Polymers for Skin Tissue Engineering	152
7.2.2.1	PLA, PGA, and Polyurethane Homopolymers	152
7.2.2.2	PLGA Copolymers and Blenders	153
7.2.3	Blend of Natural and Synthetic Materials	153
7.3	Fabrication Techniques	154
7.3.1	Self-Assembly and Phase Separation	154
7.3.2	Electrospinning	156
7.4	Clinical Application of Tissue Engineered Skin	157
7.4.1	Skin Grafts	157
7.4.2	Stem Cell Application in Skin Tissue Engineering	159
7.5	Summary	162
	References	163

8 Topical and Transdermal Delivery with Chemical Enhancers and Nanoparticles 169

Chandrashekhhar Voshavar, Praveen Kumar Vemula and Srujan Marepally

8.1	Introduction	169
8.2	Anatomy of Skin/Skin Structure	170
8.3	Skin Permeation Routes	171
8.4	Chemical Enhancers (CEs) or Skin Penetration Enhancers	172
8.4.1	Characteristics of an Ideal Chemical Enhancer	173
8.4.2	Classification of Chemical Enhancers	173
8.4.2.1	Water	173
8.4.2.2	Alcohols, Fatty Alcohols, and Glycols	175
8.4.2.3	Amides/Azones and Derivatives	175
8.4.2.4	Esters	176
8.4.2.5	Sulfoxides and Similar Chemicals	177
8.4.2.6	Ureas	177
8.4.2.7	Fatty Acids	178
8.4.2.8	Essential Oils (EOs), Terpenes, and Terpenoids	179
8.4.2.9	Surfactants	180
8.4.2.10	Pyrrolidones and Derivatives	181
8.4.2.11	Phospholipids	182
8.4.2.12	Cyclodextrins	182
8.5	Transdermal Delivery Using Nanoparticles	182
8.5.1	Lipid Based Nanoparticles	184
8.5.2	Polymer Based Nanoparticles	185
8.5.2.1	Nanoparticles Based on Biodegradable Synthetic Polymers	186
8.5.2.2	Nanoparticles Based on Biodegradable Synthetic Polymers	187
8.5.2.3	Cationic Hybrid Polymeric Nanoparticles for Nucleic Acid Delivery	188
8.5.2.4	Mechanism of Polymeric Nanoparticles Skin Permeation	189
8.6	Peptides for Skin Permeation	189
8.7	Peptide–Nucleic Acid Nanoconjugates	190
8.8	Spherical Nucleic Acids	191
8.9	Conclusion	191
	References	192

9	Needle-Free Jet Injectors for Dermal and Transdermal Delivery of Actives	201
	<i>Michele Schlich, Rosita Primavera, Francesco Lai, Chiara Sinico and Paolo Decuzzi</i>	
9.1	Introduction	201
9.2	Components and Functioning Principle	203
9.3	Modulating the Depth of Active Delivery	203
9.4	Clinical and Preclinical Use of Needle-Free Jet Injectors for Systemic Drug Delivery	206
9.4.1	Vaccines	206
9.4.2	Insulin	208
9.4.3	Growth Hormone	210
9.4.4	Triptans	211
9.4.5	Others	211
9.5	Clinical and Preclinical Use of Needle-Free Jet Injectors for Local Drug Delivery	212
9.5.1	Local Anesthetics	212
9.5.2	Others	213
9.6	Future Perspectives: Jet Injection for Nano-/Microparticles	215
	References	216
10	Microneedles for Transdermal Drug Delivery	223
	<i>Eman M. Migdadi and Ryan F. Donnelly</i>	
10.1	Introduction	223
10.2	Microneedles	223
10.2.1	MN Delivery Strategies	225
10.2.1.1	Solid MNs	225
10.2.1.2	Coated MNs	226
10.2.1.3	Hollow MNs	227
10.2.1.4	Dissolving MNs	228
10.2.1.5	Hydrogel-Forming MNs	230
10.2.2	MN Fabrication Methods	232
10.2.3	MNs and Vaccine Delivery	235
10.2.4	MNs for Patient Drug Monitoring	237
10.2.5	MN Skin Insertion and Recovery Process	239
10.2.6	Pain Perception and Skin Adverse Reactions of MN Application	242
10.2.7	MN Products	243
10.2.8	Combination of MNs with Other Techniques	245
10.2.9	MN-Assisted Microparticle and Nanoparticle Permeation	245
10.3	Microneedles in Management of Skin Disorders	247
10.4	Future Considerations for MN Technology	249
10.5	Conclusion	250
	References	251
11	Ultrasound-Enhanced Transdermal Drug Delivery	271
	<i>James Jing Kwan and Sunali Bhatnagar</i>	
11.1	Introduction	271
11.2	Principles in Ultrasound	271

11.2.1	Acoustic Waves	271
11.2.2	Ultrasound Transducers and Instrumentation	272
11.2.3	Propagation of Ultrasound	274
11.2.4	Ultrasound Phenomena	274
11.2.4.1	Mechanical Effects	274
11.2.4.2	Thermal Effects	275
11.2.4.3	Acoustic Cavitation	275
11.2.5	Mechanisms of Action	276
11.3	State of the Art in Ultrasound-Enhanced Transdermal Drug Delivery	277
11.3.1	Modes of Delivery	277
11.3.1.1	Ultrasound Pretreatment	277
11.3.1.2	Co-application of Ultrasound and Drug	278
11.3.2	Drug Dosage Medium	279
11.3.3	Ultrasound-Assisted Drug Delivery: Drug Formulations and Safety Concerns	280
11.3.3.1	Drug Formulations	280
11.3.3.2	Safety Concerns	282
11.3.4	Applications of Ultrasound-Enhanced Transdermal Delivery	283
11.3.4.1	Immunization Using Ultrasound	283
11.4	Conclusions	284
	References	284
12	Iontophoresis Enhanced Transdermal Drug Delivery	291
	<i>Xiayu Ning, Razina Z. Seeni and Chenjie Xu</i>	
12.1	Introduction	291
12.1.1	Hyperhidrosis	292
12.1.2	Delivery of Anesthetics for Pain Management	292
12.1.3	Diagnosis of Cystic Fibrosis	292
12.1.4	Glucose Monitoring	293
12.1.5	Growing Interest	293
12.2	Enhancing Transdermal Drug Delivery Using Iontophoresis Alone	294
12.2.1	Iontophoretic Transdermal Delivery of Small Molecules	297
12.2.2	Iontophoretic Transdermal Delivery of Macromolecules	297
12.3	Enhancing Transdermal Drug Delivery Using Combination of Iontophoresis and Other Approaches	300
12.3.1	Iontophoresis with Chemical Enhancers	300
12.3.2	Iontophoresis with Microneedles	302
12.3.3	Iontophoresis and Nanoparticles	303
12.4	Summary and Outlook	304
	References	304
13	Ultrasound Imaging in Dermatology	309
	<i>Jihun Kim, Sangyeon Youn and Jae Youn Hwang</i>	
13.1	Introduction	309
13.2	The Physics of Ultrasound	309
13.3	Ultrasonic Transducers	313

13.3.1	Piezoelectric Materials	314
13.3.1.1	PZT Ceramics	316
13.3.1.2	Piezoelectric Single Crystals	316
13.3.1.3	Relaxor-Based Single Crystals	316
13.3.2	Matching Layer	317
13.3.3	Backing Layer	317
13.3.4	Single-Element Ultrasound Transducers	318
13.3.5	Array Ultrasound Transducers	318
13.4	Ultrasound Imaging Systems for Skin Diagnosis	320
13.4.1	Ultrasound Imaging with Single-Element Ultrasound Transducers	321
13.4.1.1	Scanning Methods for Ultrasound Imaging Based on Single-Element Ultrasound Transducers	322
13.4.1.2	High-Frequency Ultrasound Imaging of the Skin Using Advanced Techniques	323
13.4.2	Ultrasound Imaging with Array Ultrasound Transducers	326
13.5	Applications of Ultrasound Imaging in Dermatology	330
13.5.1	Ultrasound Imaging of Skin Cancer	330
13.5.2	Ultrasound Imaging of Inflammatory and Infectious Skin Diseases	332
13.5.3	Ultrasound Imaging for Other Skin Applications	334
13.6	Conclusions	334
	Acknowledgments	335
	References	335
14	Quantitative Magnetic Resonance Imaging of the Skin: <i>In Vitro</i> and <i>In Vivo</i> Applications	341
	<i>Bernard Querleux, Geneviève Guillot, Jean-Christophe Ginéfri, Marie Poirier-Quinot and Luc Darrasse</i>	
14.1	Introduction	341
14.2	Clinical Magnetic Resonance Imaging of the Skin	342
14.2.1	Hardware Challenges for Skin Imaging	342
14.2.1.1	Introduction: Challenges for High-Resolution MR Imaging	342
14.2.1.2	Optimized RF Coil Design for Skin Imaging	345
14.2.2	State of the Art of Clinical MR Applications of Healthy and Diseased Skin	348
14.2.3	MR Imaging of the Skin on the Face	349
14.2.4	Water States in Skin by Quantitative MR Imaging	350
14.3	Quantitative MR Imaging of the Skin <i>In Vitro</i>	351
14.3.1	Opportunities with Preclinical MR Systems	351
14.3.2	State of the Art of <i>In Vitro</i> MR Applications	352
14.3.3	Quantification of Water States in Reconstructed Skin	354
14.3.3.1	Introduction	354
14.3.3.2	Basics of MT	354
14.3.3.3	MR Protocol on Reconstructed Skin Samples	355
14.3.3.4	Water States in Reconstructed Skin Samples	356
14.4	Conclusion and Perspectives	359
	References	360

15	High-Resolution Optical Coherence Tomography (OCT) for Skin Imaging	371
	<i>Xiaojun Yu, Xianghong Wang, Lulu Wang, Razina Z. Seeni and Linbo Liu</i>	
15.1	Introduction	371
15.2	HR-OCT Systems for Skin Imaging	373
15.2.1	TD-OCT Systems	373
15.2.1.1	Conventional TD-OCT	373
15.2.1.2	High-Definition (HD)-OCT	374
15.2.2	FD-OCT Systems	375
15.2.2.1	Full-Field (FF)-OCT	375
15.2.2.2	Micro-OCT (μ OCT)	376
15.2.3	PS-OCT	381
15.3	Skin Imaging with HR-OCT	382
15.3.1	Normal Skin Imaging Applications	382
15.3.2	Skin Imaging in Clinical Practice	387
15.3.3	Skin Imaging for Laboratory Research	388
15.3.3.1	Characterization of <i>In Situ</i> Microneedle Real-Time Swelling in Skin	388
15.3.3.2	OCT-Based Forensic Subsurface Fingerprint Detection	392
15.4	Discussions	398
15.5	Conclusion	400
	Acknowledgments	400
	References	400
16	Photoacoustic Imaging of Skin	411
	<i>Emelina Viennau, Tri Vu and Junjie Yao</i>	
16.1	Introduction	411
16.2	Photoacoustic Imaging Technology	412
16.3	Applications to Skin Imaging	414
16.3.1	Skin Cancers	414
16.3.1.1	Melanoma Detection and Diagnosis	414
16.3.1.2	Circulating Tumor Cell Detection	416
16.3.1.3	Detection of Non-Melanoma Skin Cancers	417
16.3.2	Tumor Environment Analysis	418
16.3.2.1	Angiogenesis	418
16.3.2.2	Oxygen Saturation	420
16.3.2.3	Blood Flow and Metabolic Rate of Oxygen (MRO_2)	421
16.3.3	Detection of Noncancerous Skin Diseases	422
16.3.3.1	Port Wine Stain	422
16.3.3.2	Psoriasis	422
16.3.3.3	Other Pigmented Lesions	422
16.3.4	Burn Injury Assessment and Monitoring of Healing	423
16.3.5	Monitoring Glucose Levels	425
16.3.6	Other Molecular Applications in Skin Imaging	426
16.4	Outlook	428
	References	429

17	Laser Speckle Techniques for Flow Monitoring in Skin	443
	<i>Renzhe Bi, Malini Olivo and Kijoon Lee</i>	
17.1	Introduction	443
17.2	Laser Speckle Contrast Imaging	444
17.2.1	Working Principle of Laser Speckle Contrast Imaging	444
17.2.2	Applications of LSCI	446
17.3	Diffuse Speckle Contrast Analysis	448
17.3.1	Theory of Diffuse Speckle Contrast Analysis	449
17.3.2	Deep Tissue Blood Flow and Cold-Induced Vasodilation	451
17.4	Diffuse Speckle Tomography	456
17.4.1	Depth Sensitivity of Flow Measurement	456
17.4.2	Tomographic Flow Imaging	458
17.5	The Future of Diffuse Speckle Analysis and Imaging	459
	References	460
	Index	465