

Contents

<i>List of Contributors</i>	xiii
<i>Foreword</i>	xxi
<i>Preface</i>	xxiii
1. A General Review of the Current Knowledge of Stem Cell Therapy for Lung Disorders	1
<i>Daniel J. Weiss</i>	
1. Introduction and Terminology	2
2. Endogenous Lung Stem and Progenitor Cells	7
3. Endogenous Lung Progenitor Cells as Lung Cancer Stem Cells	11
4. Structural Engraftment of Circulating or Exogenously Administered Stem or Progenitor Cells	12
5. Immunomodulation of Lung Inflammatory and Immune Pathways	18
6. Lung Tissue Bioengineering	21
7. Clinical Trials in Lung Cell Therapy	24
8. Conclusions	26
References	26
2. Development of the Lung: Clues for Regeneration and Repair	53
<i>Sheila G. Haworth and Alison A. Hislop</i>	
1. Introduction	54
2. Normal Development of the Airways and the Regulation of Development	54

3. Regulation of Alveolar Development	60
4. Development of the Human Pulmonary Vasculature	61
5. Regulation of Pulmonary Vascular Development	64
6. Remodelling to Adapt to Extra-Uterine Life	67
7. Interaction between Airways and Arteries during Development	70
8. Can the Adult Lung Begin to Grow Again?	72
9. Lung Repair and Regeneration	73
10. Will it be Possible to Regenerate or Grow a New Lung?	76
11. Conclusion and the Way Forward	78
References	78
3. Epithelial-Mesenchymal Interactions During Lung Development and Their Potential Relevance to Lung Repair	91
<i>Alexandra Firsova, Tomoko Hyakumura, Timothy J. Cole and Richard Mollard</i>	
1. Formation of the Lung Epithelium and Mesenchyme	92
2. Respiratory Endodermal Specification and Primary Epithelial Bud Outgrowth	93
3. Left and Right Bud Outgrowth and Left–Right Patterning	95
4. Endodermal Specification and Left–Right Symmetry	97
5. Secondary Branching and Branching Morphogenesis	98
6. Fgf Signalling Within the Epithelium and Mesenchyme During Lung Branching Morphogenesis	100
7. Epithelial Shh Signalling Regulates Mesenchymal Patterning and the Fgf10 Signal	104
8. Epithelial Dicer Signalling Regulates Mesenchymal Fgf10 Expression	106
9. Epithelial Sprouty Modifies the Mesenchymal Fgf10 Signal	106
10. Interaction of the Epithelial Bmp and Mesenchymal Fgf Signals	107
11. Wnt Signalling	109
12. Conclusion and the Way Forward	112
References	112

4. Epithelial Progenitor Cells of the Mammalian Lung	125
<i>Roxana M. Teisanu, Joshua C. Snyder and Barry R. Stripp</i>	
1. Introduction	126
2. Progenitor Cells and Lineage Specification in the Developing Lung	128
3. Adult Stem Cells and Tissue Maintenance by a Stem Cell Hierarchy	129
4. Approaches to Characterise and Hierarchically Organise Progenitor Cells	130
5. Progenitor Cells of Tracheobronchial Airways	133
6. Progenitor Cells of Bronchiolar Airways	137
7. Progenitor Cells of the Alveolar Compartment	142
8. Conclusions and Future Directions	144
Acknowledgements	144
References	144
5. Safety of Exogenous Stem Cells	155
<i>Elizabeth K. Sage, Michael R. Loebinger and Sam M. Janes</i>	
1. Introduction	156
2. Exogenous Stem Cells	156
3. Potential Malignant Transformation	158
4. Clinical Trials	161
5. Conclusion	163
Acknowledgements	164
References	164
6. Lung Stem Cell Bioprocessing: Fundamentals of Producing Lung Cells	169
<i>Siti Norhayati Ismail, Julia M. Polak and Anastasios Mantalaris</i>	
1. The Clinical Need	170
2. Lung Architecture	170
3. Cell Expansion and Sources	173
4. Stem Cell Bioprocessing for Lung Cellular Therapies	178

5. Integrated 3D Bioprocessing for Lung Cell Production	185
6. Conclusions and Future Prospects	187
Acknowledgements	187
References	188
7. Lung Repair and Regeneration — Animal Models	199
<i>Hiroshi Kubo</i>	
1. Lung Regeneration	200
2. Repair Process after Acute Lung Injury	214
3. Conclusion and the Way Forward	219
References	219
8. Fibrocytes (Reactive or Reparative)	237
<i>Alberto Bellini and Sabrina Mattoli</i>	
1. Introduction	238
2. Mechanisms of Fibrocyte Development and Differentiation	238
3. Functional Consequences of Fibrocyte Accumulation	243
4. Involvement of Fibrocytes in Lung Diseases	245
5. Conclusions and Implications for Therapy	250
References	252
9. Three-Dimensional Pulmonary Constructs	261
<i>Christine M. Finck, Blair Roszell and Peter I. Lelkes</i>	
1. Introduction	262
2. Culture of Distal Lung Cells <i>In Vitro</i>	263
3. Two-Dimensional Models	263
4. Three-Dimensional Growth	265
5. Growth Factor Supplementation and Culture Media Composition	269
6. Importance of Endothelial–Epithelial Interactions in Heterogeneous Co-Culture	275
7. Conclusions and Future Challenges	279
References	280

10. Stem Cells as Vehicles for Gene Therapy in Lung Repair	287
<i>Shirley H. J. Mei and Duncan J. Stewart</i>	
1. Introduction	288
2. Types of Stem/Progenitor Cells Used as Vehicles for Gene Therapy for Lung Diseases	290
3. Pulmonary Diseases Targeted by Stem/Progenitor Cells-Based Gene Therapy	293
4. Conclusion and the Way Forward	301
References	302
11. Repair of the Lung Epithelium in Cystic Fibrosis	313
<i>Viranuj Sueblinvong and Daniel J. Weiss</i>	
1. Introduction and Pathophysiology of Cystic Fibrosis	314
2. Gene Therapy Approaches for Cystic Fibrosis	315
3. Endogenous Lung Progenitor Cells in Cystic Fibrosis	316
4. Cell-Based Therapies for CF Lung Disease	321
5. Conclusion and the Way Forward	326
References	326
12. Pulmonary Hypertension and Stem Cell Therapy	337
<i>Manoj M. Lalu, Rohit Moudgil and Duncan J. Stewart</i>	
1. Introduction	338
2. Pulmonary Arterial Hypertension — A Brief Overview	338
3. Pulmonary Arterial Hypertension — Evolution of Treatments	342
4. Pulmonary Arterial Hypertension — Endothelial Progenitor Cell Therapy	345
5. Preclinical Studies of Cellular Therapy for PAH	349
6. Clinical Applications of Cell Therapy for PAH	351
7. Conclusions and Future Directions	355
References	355

13. Molecular Induction of Alveolar Regeneration	367
<i>Matthew Hind and Siân Stinchcombe</i>	
1. Introduction	368
2. Lung Development	368
3. Retinoic Acid (RA) has a Master Role in Patterning the Developing Lung	369
4. RA has a Role in Alveolar Development	370
5. The Adult Lung Structure Maintenance Programme	372
6. RA in the Adult Structure Maintenance Programme	373
7. Evidence of Molecular Plasticity: Endogenous Programmed Alveolar Regression and Regeneration	374
8. Calorie Restriction	375
9. Oestrogen	376
10. Experimental Evidence of Alveolar Regeneration	378
11. Cell Biology of Regeneration	383
12. Bone Marrow-Derived Stem Cell Engraftment	384
13. Intrinsic Alveolar Cell Response	387
14. Alveolar Regeneration by Adrenomedullin	389
15. Conclusion and the Way Forward	391
References	391
14. Assessment of Cell Engraftment	405
<i>Robert Zweigerdt and William Rust</i>	
1. Introduction	406
2. Visual Detection of Engrafted Cells — Mechanisms Underlying Misleading Results	407
3. <i>In Vivo</i> Monitoring of Cell Engraftment and Assessment of Functional Improvement	413
4. Conclusion and the Way Forward	417
References	417
15. <i>In Vivo</i> Imaging for Cell Therapy	421
<i>Richard Newton and Guang-Zhong Yang</i>	
1. Introduction	422
2. Imaging for Cell Repair	422

3.	Biophotonics <i>in Vivo</i>	429
4.	Photogenic Small Animal Models and Cell Delivery	438
5.	Conclusion and the Way Forward	440
	References	442
16.	Haematopoietic Transplantation and Pulmonary Chimerism	453
	<i>Benjamin T. Suratt</i>	
1.	Introduction	454
2.	A Brief Review of HSCT Concepts and Techniques	454
3.	Techniques for the Detection of Pulmonary Chimerism Following HSCT	456
4.	Evidence for Pulmonary Chimerism Following HSCT	462
5.	Possible Origins of Pulmonary Chimerism	465
6.	Conclusions and Future Perspectives	467
	References	468
17.	Stem Cells and Lung Cancer	473
	<i>Arielle C. Lebrenne, Shahriar Islam and Malcolm R. Alison</i>	
1.	Stem Cells and the Origins of Lung Tumours	474
2.	Histogenesis and Molecular Pathogenesis of Lung Tumours	477
3.	Cancer Stem Cells	483
4.	Conclusion and the Way Forward	490
	References	491
	<i>Index</i>	501