Table of Contents

Preface — V

2.9

2.10

Contributing authors — VII		
	1	Mesenchymal stem cells in the context of stem cell biology ——1
	1.1	Introduction – Definitions —— 1
	1.2	Embryonic and adult tissue stem cells — 2
	1.3	Adult tissue stem cells and progenitors — 3
	1.4	Adult stem cells and tissue homeostasis —— 5
	1.5	Adult stem cell niches — 5
	1.6	Commitment and differentiation — 7
	1.7	The case for bone marrow MSCs — 8
	1.8	Clinical prospects —— 10
	1.9	Concluding remark —— 11
		References —— 11
	2	Are mesenchymal stem cells immune privileged? —— 17
	2.1	Introduction – Definition of mesenchymal stem cells (MSCs) —— 17
	2.2	The immunosuppressive effect of MSCs on immune cells —— 18
	2.3	The potential clinical benefits of MSCs as immunosuppressants —— 20
	2.4	The mechanisms of immunosuppression by MSCs —— 21
	2.5	The mechanisms of immunosuppression by human MSCs —— 21
	2.6	Immunosuppression by murine MSCs and the species difference underlying
		the mechanisms of immunosuppression by MSCs —— 25
	2.7	Immunosuppression mediated by fibroblasts —— 28
	2.8	The mechanisms of the immunosuppressive effect of MSCs are shared with

3 Mesenchymal stem cell therapies for autoimmune diseases — 37 Introduction — 37 3.1 3.2 Autoimmune disease --- 39 3.3 Mesenchymal stem cells (MSCs) — 41 3.3.1 Animal models — 42 3.4 Results of MSCs clinical trials — 44 Safety of MSCs --- 45 3.5 3.6 Conclusion — 45

other nonstromal cells --- 28

References — 31

References — 46

Conclusion and discussion — 29

How long can MSCs survive in vivo? — 28

4	Mesenchymal stem cells in osteoarthritis and rheumatic disease — 51
4.1	Introduction – Rheumatic diseases —— 51
4.2	Rheumatoid arthritis (RA) —— 51
4.3	Osteoarthritis (OA) — 53
4.4	MSCs in healthy and rheumatic joint tissues ——55
4.5	Application of MSCs in rheumatic diseases —— 56
4.6	MSCs application in animals —— 60
4.7	Clinical studies in humans — 66
4.8	Risks and benefits of MSCs treatments in rheumatic diseases — 68
	References — 70
5	Mesenchymal stem cells in enthesis formation and repair —— 83
5.1	Introduction —— 83
5.2	Structure of the tendon-to-bone junction —— 84
5.3	Enthesis resident T cells are involved in enthesopathies provoking
	inflammation and bone remodeling —— 85
5.4	Biomaterials and growth factor-dependent regeneration of tendon-to-bone junctions — 87
5.5	Biomechanical stimulation for enthesis repair — 88
5.6	Mesenchymal stem cells (MSCs) —— 88
5.7	Stem cell-dependent approaches for repair of osteotendinous
	junctions — 89
5.8	Stem cell-dependent delivery of growth factors ——91
5.9	Stem cell-dependent delivery of tenogenic transcription factors —— 93
5.10	Stem cell-dependent delivery of matrix metalloproteinases — 94
5.11	Trophic activities of MSCs in enthesis repair —— 94
5.12	Outlook —— 95
	Acknowledgment — 96
	References — 96
6	Mesenchymal stem cells for clinical/therapeutic interventions of graft-
	versus-host disease —— 101
6.1	Clinical graft-versus-host disease —— 101
6.2	Chronic graft-versus-host disease —— 102
6.3	Rationale to use mesenchymal stromal cells for treatment of GvHD —— 103
6.4	Experience of MSCs in clinical acute graft-versus-host disease —— 105
6.5	Treatment of acute GvHD with stromal cells from alternate sources, adipose tissue-derived, umbilical cord blood-derived or fetal membrane-derived stromal cells —— 110
6.6	Mesenchymal stromal cells for treatment of chronic graft-versus-host disease —— 111

6.7	Clinical trials of prophylaxis with mesenchymal stromal cells for graft-versus-host disease ——113
6.8	Discussion on clinical use of mesenchymal stem cells —— 115
6.9	How should we best utilize MSC treatment of GvHD? —— 116 References —— 119
7	Mesenchymal stem cells for graft-versus-host disease in experimental animal models —— 125
7.1	Introduction – Experimental models of graft-versus-host disease (GvHD) —— 125
7.2	Immunobiology of experimental GvHD —— 127
7.3	Mesenchymal stromal cells in mice —— 128
7.4	Mesenchymal stromal cells and mouse models of graft-versus-host disease —— 130
	References —— 136
8	Mesenchymal stem cells and organ transplantation: initial clinical results —— 143
8.1	Introduction —— 143
8.2	Rationale for the use of MSCs in organ transplantation —— 144
8.2.1	Shortage of donor organs for transplantation —— 144
8.2.2	Ischemia-reperfusion injury —— 145
8.2.3	Chronic immunosuppression —— 145
8.3	Considerations regarding the choice of the clinical protocols —— 146
8.3.1	Definition, identity and product release criteria for human MSCs preparations —— 147
8.3.2	Source of human MSCs — 147
8.3.3	Potential interactions between MSCs and concomitant therapy —— 149
8.3.4	Safety of MSCs-based treatments —— 150
8.4	Clinical MSCs and solid organ transplantation trials —— 151
8.4.1	Autologous MSCs in the induction phase with standard immunosuppression —— 151
8.4.2	Autologous MSCs in the induction phase with avoidance of biologics at induction and reduced maintenance immunosuppression —— 154
8.4.3	Allogeneic MSCs in the induction phase —— 155
8.4.4	Autologous MSCs for the treatment of biopsy-proven subclinical rejection
	progressive renal interstitial fibrosis and tubular atrophy —— 156
8.5	Future perspectives — 158
	Acknowledgments: ——158
	References —— 159

9	Stem cell therapy in patients with ischemic heart disease — 163
9.1	Introduction —— 163
9.2	Cell type and source for clinical therapy —— 165
9.3	Mechanisms behind regeneration of damaged myocardium —— 166
9.4	Preclinical experience with stem cells for IHD —— 169
9.5	Cell-based therapy in patients with IHD —— 169
9.6	MSCs in patients with IHD —— 171
9.7	Ongoing clinical trials using MSCs — 174
9.8	Cell delivery and engraftment —— 174
9.9	Perspectives — 178
9.10	Conclusion —— 179
	References —— 179
10	Mesenchymal stem cells as a strategy for the treatment of multiple sclerosis and other diseases of the central nervous system —— 185
10.1	Introduction —— 185
10.2	MSCs transplantation for neurological diseases: why, which, and
	how — 186
10.3	Vascular diseases: ischemic stroke —— 187
10.3.1	Preclinical studies —— 187
10.3.2	Clinical studies — 189
10.4	Trauma spinal cord injury —— 190
10.4.1	Preclinical studies —— 191
10.4.2	Clinical studies — 192
10.5	Extrapyramidal diseases —— 192
10.5.1	Parkinson's disease (PD) —— 192
10.5.2	Preclinical studies — 193
10.5.3	Clinical studies — 194
10.5.4	Huntington's disease (HD) —— 194
10.5.5	Preclinical studies — 195
10.6	Multiple system atrophy (MSA) —— 196
10.6.1	Preclinical studies — 196
10.6.2	Clinical studies — 197
10.7	CNS demyelinating diseases: multiple sclerosis —— 197
10.7.1	Preclinical studies —— 198
10.7.2	Clinical studies —— 199
10.8	Motor neuron diseases: amyotrophic lateral sclerosis (ALS) — 200
10.8.1	Preclinical studies — 200
10.8.2	Clinical studies — 201
10.9	Dementia: Alzheimer's disease (AD) —— 202
10.9.1	Preclinical studies — 202

10.9.2	Clinical studies — 203
10.10	Concluding remarks — 203
	References —— 204
11	Mesenchymal stem cells for the treatment of inflammatory bowel
	disease —— 211
11.1	Introduction —— 211
11.2	Immunology and intestinal barrier function —— 212
11.3	Cell-based treatments for IBD —— 215
11.3.1	Hematopoietic cell transplantation —— 215
11.4	T regulatory cells (Tregs) —— 216
11.5	Mesenchymal stem cells (MSCs) —— 217
11.5.1	Immunologic basis for MSCs and IBD —— 217
11.6	MSC homing and engraftment —— 219
11.7	MSC clinical trials —— 222
11.8	Summary and future directions — 224
	References —— 226
12	Mesenchymal stem cells in chronic lung diseases: COPD and lung
	fibrosis — 233
12.1	Introduction — 233
12.2	Idiopathic pulmonary fibrosis — 235
12.3	MSCs and animal models of fibrotic lung disorders — 238
12.4	Chronic obstructive pulmonary disease (COPD) — 246
12.5	Conclusions and future directions — 252
	Acknowledgments —— 253
	References —— 253
13	Mesenchymal stem cells as therapeutics for liver repair and
	regeneration — 263
13.1	Introduction — 263
13.2	Cell therapy for liver disease — 264
13.3	The ideal cell for liver regeneration —— 265
13.4	Mesenchymal stem cells (MSCs) as cellular therapeutics — 266
13.5	MSCs for treating liver disease — 269
13.5.1	In vitro models to study MSCs hepatic differentiation —— 269
13.5.2	In vivo models to study MSCs as cellular therapies for liver disease/injury —— 270
12 6	• •
13.6	The fetal sheep model — 273 Clinical trials using MSCs for liver regeneration 270
13.7	Clinical trials using MSCs for liver regeneration — 279
13.8	Summary/Conclusions: — 280
	References —— 281

14	Mesenchymal stem cells attenuate renal fibrosis —— 293
14.1	Introduction – Kidney function —— 293
14.2	Kidney dysfunction and chronic kidney disease (CDK) — 295
14.2.1	Molecular and cellular interaction in renal fibrosis — 296
14.3	Mesenchymal stem cells (MSCs): Definition and basic features — 298
14.3.1	Therapeutic potential of MSCs and their mechanisms of action in the repair/regeneration of tissue injury —— 298
14.4	MSCs and kidney diseases — 301
14.4.1	MSCs have a prominent antifibrotic effect in distinct models of experimenta chronic kidney diseases —— 301
14.4.2	Mechanisms related to MSCs prevent renal fibrosis — 303
14.5	Final considerations — 304
	References — 305
15	Immunomodulation by mesenchymal stem cells – a potential therapeutic strategy for type 1 diabetes —— 309
15.1	Introduction — 309
15.2	Mechanisms of immunomodulation —— 310
15.3	MSC therapy for type 1 diabetes (T1D) — 311
15.3.1	Why does MSC therapy hold value in T1D? — 311
15.3.2	Preclinical studies to prevent and reverse T1D — 312
15.3.3	MSC implications in islet cell transplantation —— 313
15.3.4	MSCs and clinical trials for T1D — 314
15.4	Safety of MSC therapy — 315
-51,	References: — 315
16	Fibrogenic potential of human multipotent mesenchymal stem cells in inflammatory environments —— 319
16.1	Introduction —— 319
16.2	Fibrogenic potential in ex vivo expanded MSCs — 320
16.3	Evidence of MSCs infiltration into tumor stroma —— 321
16.4	Controversies regarding therapeutic benefits of bone marrow-derived MSCs in liver fibrosis —— 322
16.5	Limited contribution of MSCs to liver regeneration in acute liver injury —— 324
16.6	Conclusion — 326 References — 326

17	Mesenchymal stem cells and the tumor microenvironment —— 331
17.1	Introduction —— 331
17.2	The tumor microenvironment and its role in cancer initiation and progression —— 333
17.3	How do we define MSCs in cancer? —— 334
17.4	What are the roles of MSCs in cancer progression? —— 335
17.4.1	Effect of MSCs on tumor cell proliferation — 337
17.4.2	MSCs promote survival — 337
17.4.3	MSCs are proangiogenic —— 338
17.4.4	MSCs have an immunosuppressive function —— 338
17.4.5	MSCs promote epithelial to mesenchymal transition —— 339
17.5	How do tumor cells communicate with MSCs? — 341
17.6	Are MSCs recruited by tumor cells? —— 343
17.7	Can we target MSCs in human cancer? — 345
17.8	Conclusion — 346
	References —— 346
18	Mesenchymal stem cells as a carrier for
	tumor-targeting therapeutics —— 353
18.1	Introduction —— 353
18.2	Enhanced angiogenesis as a target for tumor therapy —— 354
18.3	Why current therapies are not effective enough —— 355
18.3.1	Shortcomings of current anti-angiogenic pharmaceuticals — 356
18.4	Why mesenchymal stem cells would be useful for tumor targeting —— 358
18.4.1	The tumor-homing properties of MSCs —— 358
18.4.2	MSCs as a diagnostic tool —— 361
18.4.3	Antitumor effects of unmanipulated MSCs — 361
18.4.4	Vesicular communication of MSCs: How MSCs can be used as a drug- delivery vehicle —— 362
18.5	MSCs as a gene product-delivering vehicle — 364
18.5.1	Genetically modified MSCs for therapeutic delivery — 364
18.5.2	Potential for MSCs-delivered anti-angiogenic therapies — 365
18.5.3	MSCs-mediated tumor-homing of oncolytic adenovirus enhances
	tumor therapy — 366
18.5.4	Delivery of TRAIL by genetically modified MSCs to induce apoptosis —— 367
18.5.5	Tumor-specific promoter-driving thymidine kinase (TK) expression for prodrug conversion —— 367
18.6	Methods of therapeutic MSCs administration — 369
18.7	The advantage of MSCs being immunoprivileged — 370
18.8	Sources of acquiring MSCs for tumor therapy — 371

18.9	Remaining challenges for the use of MSCs to deliver therapeutics — 372
18.9.1	The immunoprivileged nature of MSCs — 372
18.9.2	Varying responses to MSCs depending on cancer type, injection site,
	etc. — 372
18.9.3	Changes in MSCs induced by cancer cells within the tumor
	microenvironment — 373
18.10	Summary and prospective —— 375
	Acknowledgments — 375
	References — 376
10	Contains his law annuals to story calls the constant and inflammation 201
19	Systems biology approach to stem cells, tissues and inflammation — 381
19.1	Introduction — 381
19.2	Biological aspects — 382
19.2.1	9 ,
19.2.2	Influence of cell number and phenotype —— 383
19.3	Technological aspects — 383
19.3.1	Technology and type of molecules —— 383
19.3.2	When "pictures start moving" — 384
19.4	Mathematical aspects — 385
19.4.1	Comparative statistics and interpretation —— 385
19.4.2	Interpretation based on pre-existing knowledge —— 386
19.4.3	Network models — 386
19.5	Systems biology of differentiation — 388
19.6	Important tasks — 389
19.7	Conclusion — 390
	References — 391

Index — 395