

Cell Therapy

Part I: Technologies, Ethics & Regulations

by

Prof. K. K. Jain
MD, FRACS, FFPM
Jain PharmaBiotech
Basel, Switzerland

July 2018

A Jain PharmaBiotech Report

A U T H O R ' S B I O G R A P H Y

Professor K. K. Jain is a neurologist/neurosurgeon by training and has been working in the biotechnology/biopharmaceuticals industry for several years. He received graduate training in both Europe and USA, has held academic positions in several countries, and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of UK. Currently, he is a consultant at Jain PharmaBiotech.

Prof. Jain's 473 publications include 28 books (5 as editor + 23 as author) and 50 special reports, which have covered important areas in biotechnology, gene therapy and biopharmaceuticals. He has also written a textbook of gene therapy which is the first book on this subject to be translated into the Chinese language. A book on gene therapy companies was published in 2000 by John Wiley & Sons and the 2017 version is included in a special report on gene therapy published by Jain PharmaBiotech. Other reports written by Prof. Jain have been published by PJB Publications, D & MD, Reuter's Business Insight, and Decision Resources Inc. Cell Therapy is one of the several in-house publications of Jain PharmaBiotech.

Prof. Jain's recent books include "Handbook of Nanomedicine" (1st ed by Springer 2008, Chinese ed by Peking University Press 2011, 2nd edition 2012, 3rd ed 2017 by Springer), "Textbook of Personalized Medicine" (1st ed by Springer 2009; Japanese edition 2012; 2nd ed Springer 2015), "Handbook of Biomarkers" (Springer 2010; Chinese edition, Chemical Industry Press 2016; 2nd edn Springer 2017), Handbook of Neuroprotection (Springer 2011), Applications of Biotechnology in Cardiovascular Therapeutics (Springer 2011), Applications of Biotechnology in Neurology (Springer 2013), and "Applications of Biotechnology in Oncology" (Springer 2014). He has edited "Applied Neurogenomics" (Springer 2015).

July 2018 (first edition published July 2001)
Copyright © 2018 by

Jain PharmaBiotech
Bläsiring 7
CH-4057 Basel
Switzerland

Tel & Fax: +4161-6924461
Email: info@pharmabiotech.ch
Web site: http://pharmabiotech.ch/

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, or otherwise without the prior written permission of the Publisher. This report may not be lent, resold or otherwise traded in any manner without the consent of the Publisher. While all reasonable steps have been taken to ensure the accuracy of the information presented, the Publisher cannot accept responsibility for inadvertent errors or omissions.

TABLE OF CONTENTS

0. Executive Summary	27
1. Introduction to Cell Therapy	31
Introduction	31
Historical landmarks of cell therapy	31
Interrelationship of cell therapy technologies	33
Cells and organ transplantation	34
Cells and protein/gene therapy	34
Cell therapy and regenerative medicine.....	35
Cell therapy and tissue engineering.....	36
Therapy based on cells involved in disease.....	37
Advantages of therapeutic use of cells	37
Synthetic cell therapy	37
Cell-based drug delivery	38
<i>Cells as vehicles for gene delivery</i>	<i>38</i>
<i>Red blood cells as vehicles for drug delivery.....</i>	<i>38</i>
<i>Advantages of cell-based drug delivery.....</i>	<i>40</i>
<i>Limitations of cell-based drug delivery.....</i>	<i>40</i>
2. Cell Therapy Technologies	41
Introduction	41
Cell types used for therapy	41
Sources of cells.....	41
Bone marrow.....	42
Blood component therapy	42
<i>Therapeutic apheresis.....</i>	<i>42</i>
<i>Leukoreduction</i>	<i>43</i>
<i>Platelet therapy</i>	<i>43</i>
<i>Red blood cell transfusion</i>	<i>43</i>
Cell lines.....	44
<i>Immortalized cells.....</i>	<i>44</i>
Xenografts	45
Basic technologies for cell therapy	45
Cell culture	45
<i>Automated cell culture devices</i>	<i>45</i>
<i>Cell culture for adoptive cell therapy</i>	<i>46</i>
<i>Observation of stem cell growth and viability.....</i>	<i>46</i>
<i>OpTmizer™ CTS™ T cell expansion tissue culture medium</i>	<i>46</i>
<i>Stem cell movement and behavior in culture.....</i>	<i>46</i>
<i>Companies involved in cell culture.....</i>	<i>47</i>
Cell sorting	48
<i>Flow cytometry.....</i>	<i>48</i>
<i>Applications of flow cytometry</i>	<i>49</i>
<i>A dielectrophoretic system for cell separation.....</i>	<i>50</i>
<i>Adult stem cell sorting by identification of surface markers</i>	<i>50</i>
<i>ALDESORTER system for isolation of stem cells.....</i>	<i>50</i>
<i>Dynabead technology for cell sorting</i>	<i>50</i>
<i>Elutra® Cell Separation System.....</i>	<i>51</i>
<i>Magnetophoretic array-based cell sorting for further studies.....</i>	<i>51</i>
<i>Molecular beacons for specific detection and isolation of stem cells</i>	<i>51</i>
<i>Multitarget magnetic activated cell sorter.....</i>	<i>52</i>
<i>Nanocytometry.....</i>	<i>52</i>
<i>Scepter™ cytometer.....</i>	<i>52</i>
<i>Companies supplying cell sorters</i>	<i>52</i>
Cell analysis.....	54
<i>Cell analyzers.....</i>	<i>54</i>
<i>In vivo cell imaging.....</i>	<i>54</i>
<i>Measuring cell density</i>	<i>55</i>
Single-cell gene expression analysis.....	55
<i>Fluorescent in situ RNA sequencing</i>	<i>56</i>
<i>Single-cell RNA sequencing of stem cells.....</i>	<i>56</i>
Preservation of cells	57
<i>Innovations in cryopreservation.....</i>	<i>57</i>
Packaging of cells	58
Selective expansion of T cells for immunotherapy	59
Cloning and cell therapy	59
Techniques for cell manipulation	60

Altering function of adult human cells	60
Cell-based drug discovery	60
Advantages and limitations of cell-based assays for drug discovery	61
<i>Advantages and limitations of cell-based toxicity screening</i>	<i>61</i>
<i>Quality control of cells for drug discovery</i>	<i>61</i>
Companies involved in cell-based drug discovery	62
Introduction of foreign materials into cells to develop therapeutics	64
Use of cell-penetrating peptides for intracellular transduction	64
Drug delivery systems for cell therapy	64
Intravenous delivery of stem cells	65
Intraarterial delivery of stem cells	65
Pharmacologically active microcarriers	65
Targeted delivery of engineered cells to specific tissues via circulation	66
Devices for delivery of cell therapy	66
Artificial cells	67
Applications of artificial cells	67
Cell encapsulation	67
Cell-in-a-Box®	68
Diffusion capsule for cells	68
Encapsulated cell biodelivery	69
Ferrofluid microcapsules for tracking with MRI	69
Implantation of microencapsulated genetically modified cells	69
Nitric oxide delivery by encapsulated cells	70
Retrievable cell encapsulation device	70
Therapeutic applications of encapsulated cells	70
Companies involved in encapsulated cell technology	72
Electroporation	72
Gene therapy	73
Cell-mediated gene therapy	73
<i>Fibroblasts</i>	<i>74</i>
<i>Chondrocyte</i>	<i>74</i>
<i>Skeletal muscle cells</i>	<i>75</i>
<i>Vascular smooth muscle cells</i>	<i>75</i>
<i>Keratinocytes</i>	<i>75</i>
<i>Hepatocytes</i>	<i>76</i>
<i>Lymphocytes</i>	<i>76</i>
Cell-based CRISPR delivery	76
In vivo tracking of cells	77
Molecular imaging for tracking cells	77
<i>MRI technologies for tracking cells</i>	<i>78</i>
<i>Superparamagnetic iron oxide nanoparticles as MRI contrast agents</i>	<i>78</i>
<i>Survival of labeled hMSCs in regenerative therapy grafts</i>	<i>79</i>
<i>Visualization of gene expression in vivo by MRI</i>	<i>79</i>
Optogenetic monitoring of cell therapies	80
Role of nanobiotechnology in development of cell therapy	80
Nano-biocomposites containing living cells	81
Cell transplantation for development of organs	81
Cells transplantation and tolerance	81
Strategies to improve tolerance of transplanted cells	82
<i>Encapsulation to prevent immune rejection</i>	<i>82</i>
<i>Expansion of allospecific regulatory T cells</i>	<i>82</i>
<i>Prevention of rejection of xenotransplants</i>	<i>82</i>
Removal and replacement of pathogenic cells of the body	83
Therapeutic leukocytapheresis	83
3. Stem Cells	85
Introduction	85
Biology of stem cells	85
Embryonic stem cells	86
Growth and differentiation of ESCs	86
Mechanisms of differentiation of ESCs	87
<i>Chemical regulation of stem cell differentiation</i>	<i>87</i>
<i>In vitro differentiation of hESCs</i>	<i>87</i>
<i>SIRT1 regulation during stem cell differentiation</i>	<i>88</i>
Regulation of stem cell self-renewal and differentiation	88
<i>hESCs for reprogramming human somatic nuclei</i>	<i>88</i>
<i>Stem cells differentiation in the pituitary gland</i>	<i>89</i>
Influence of microenvironment on ESCs	89
Role of genes in differentiation of ESCs	89
<i>Global transcription in pluripotent ESCs</i>	<i>89</i>
<i>Role of p53 tumor suppressor gene in stem cell differentiation</i>	<i>90</i>

<i>Role of Pax3 gene in stem cell differentiation</i>	90
<i>Signaling pathways and ESC genes</i>	90
Epigenetics of hESCs	91
<i>Chromatin as gene regulator for ESC development</i>	92
Mechanism of regulation of stem cells for regeneration of body tissues.....	92
<i>Role of microenvironments in the regulation of stem cells</i>	92
<i>Regulation and regeneration of intestinal stem cells</i>	93
Parthenogenesis and human stem cells.....	93
<i>Uniparental ESCs</i>	94
<i>Haploid ESCs</i>	94
Bone marrow stem cells.....	95
Hematopoietic stem cells	95
<i>Clonal events that regulate HSC development</i>	97
<i>Derivation of HSCs from ESCs</i>	97
<i>Role of HSCs in the immune system</i>	97
Mesenchymal stem cells	98
<i>Cryopreservation of MSCs</i>	99
Multipotent adult progenitor cells	100
Side population stem cells.....	100
Differentiation of adult stem cells.....	101
Growth and differentiation of HSCs	102
<i>HSCs and aging</i>	102
<i>Mathematical modeling of differentiation of HSCs</i>	102
<i>Role of prions in self renewal of HSCs</i>	103
<i>Signaling pathways in the growth and differentiation of HSCs</i>	103
Sources of stem cells	103
Sources of of human embryonic stem cells.....	103
Nuclear transfer to obtain hESCs.....	104
Direct derivation of hESCs from embryos without nuclear transfer	105
Alternative methods of obtaining hESCs.....	105
<i>Establishing hESC lines without destruction of embryo</i>	105
<i>Altered nuclear transfer</i>	106
Advantages and disadvantages of ESCs for transplantation	107
Use of ESC cultures as an alternative source of tissue for transplantation	107
Spermatogonial stem cells	108
Very small embryonic-like stem cells.....	109
Amniotic fluid as a source of stem cells.....	109
<i>Amniotic fluid stem cells for tissue repair and regeneration</i>	109
<i>Generation of iPS cells from AF cells</i>	110
Placenta as source of stem cells.....	110
<i>Amnion-derived multipotent progenitor cells</i>	110
<i>Placenta as a source of HSCs</i>	111
<i>Umbilical cord as a source of MSCs</i>	111
Umbilical cord blood	112
<i>Applications of UCB</i>	113
<i>Advantages of UCB</i>	113
<i>Limitations of the use of UCB and measures to address them</i>	114
<i>Licensing and patent disputes involving UCB</i>	115
<i>Infections following UCB transplants</i>	115
<i>Unanswered questions about UCB transplantation</i>	116
<i>Companies involved in UCB banking</i>	116
<i>UCB banking in the UK</i>	117
<i>US national UCB banking system</i>	118
<i>Future of UCB</i>	119
UCB as source of stem cells.....	119
<i>Cryopreservation of UCB stem cells</i>	120
<i>Epigenetic programming for expansion of UCB cells</i>	120
<i>UCB as source of MSCs</i>	120
Techniques of nuclear reprogramming for stem cells	121
Induced pluripotent stem cells derived from human somatic cells	121
Characteristics of iPSCs	122
DNA methylation patterns of iPS cells	122
Techniques for obtaining iPSCs	122
iPSCs derived from skin	122
iPSCs derived through somatic cell nuclear transfer (SCNT).....	123
<i>iPSCs derived from oocytes</i>	123
<i>iPSCs derived from adult stem cells using SCNT</i>	123
iPSCs derived from blood	123
Use of CRISPR for generation of iPSCs.....	124
Use of retroviral vectors for generation of iPSCs	124
Use of non-integrating viral vectors for generation of iPSCs.....	125

Generation of other cells from iPSCs.....	126
<i>Generation of HSCs from iPSCs</i>	126
<i>Generation of MSCs from iPSCs</i>	126
<i>Generation of RBCs from iPSCs</i>	126
Banks providing patient-specific iPSC lines.....	126
Center for iPS Cell Research Application.....	127
Companies providing iPSCs.....	127
Generation of clinically relevant iPSCs.....	128
<i>Equivalence of human iPSCs and ESCs</i>	129
<i>Genome editing and iPSCs</i>	129
<i>iPSCs and disease modeling</i>	129
<i>iPSCs for patient-specific regenerative medicine</i>	130
<i>Concluding remarks about clinical potential of iPSCs</i>	130
Induced conditional self-renewing progenitor cells.....	131
iXEN cells.....	131
Epiblast stem cells.....	132
Comparison of development of human and mouse ESCs.....	132
Conversion of hESCs to mouse ESC-like naïve states.....	132
Sources of adult human stem cells.....	133
Adipose tissue as a source of stem cells.....	133
<i>Encapsulation and hypothermic storage of adipose-derived stem cells</i>	134
<i>Intravenous infusion of adipose tissue derived MSCs</i>	134
<i>iPSCs derived from adult human adipose stem cells</i>	134
<i>Regulation of adipose stem cells differentiation</i>	135
<i>Transforming adult adipose stem cells into other cells</i>	135
Endometrium as a source of adult stem cells.....	135
Multipotent stem-like cells derived from vascular endothelial cells.....	136
Skin as a source of stem cells.....	136
<i>Controlling the maturation of embryonic skin stem cells</i>	136
<i>Epidermal neural crest stem cells</i>	136
<i>Follicle stem cells</i>	137
<i>Mesenchymal stem cells in skin</i>	137
<i>Regulation of stem cells in hair follicles</i>	138
<i>Skin-derived precursor cells</i>	138
Regulation of epidermal stem cells by circadian rhythms.....	138
Stem cells in teeth.....	138
Peripheral blood stem cells.....	139
Spleen as a source of adult stem cells.....	140
Search for master stem cells.....	140
Vascular cell platform to self-renew adult HSC.....	140
Adult stem cells vs embryonic stem cells.....	141
Biological differences between adult and embryonic stem cells.....	141
Neural crest stem cells from adult hair follicles.....	141
Transdifferentiation potential of adult stem cells.....	142
Attempts at stimulus-triggered acquisition of pluripotency.....	143
Limitations of adult stem cells.....	143
Pitfalls of pluripotency.....	144
Comparison of human stem cells according to derivation.....	144
VENT cells.....	144
ESC banking.....	145
Stem cell technologies.....	145
Analysis of stem cell growth and differentiation.....	145
Activation of bone marrow stem cells into therapeutic cells.....	145
Role of nitric oxide in stem cell mobilization and differentiation.....	146
Role of natriuretic peptide receptor-C in self-renewal of murine ESCs.....	146
Stem cell biomarkers.....	146
<i>Endoglin as a functional biomarker of HSCs</i>	147
<i>STEMPRO® EZChek™ for analysis of biomarkers of hESCs</i>	147
<i>SSEA-4 as biomarker of MSCs</i>	147
<i>p75NTR as a biomarker to isolate adipose tissue-derived stem cells</i>	147
<i>Neural stem cell biomarker</i>	148
<i>Protein expression profile as biomarker of stem cells</i>	148
<i>Real-time PCR for quantification of protein biomarkers</i>	148
Study of stem cell pathways.....	149
Stem cell genomics.....	149
<i>Gene expression in hESCs</i>	149
<i>Genomic alterations in cultured hESCs</i>	150
<i>Study of transcriptional regulation of stem cell genes</i>	150
<i>Casanova gene in zebrafish</i>	150
<i>Nanog gene</i>	151
Gene inactivation to study hESCs.....	152

<i>RNAi to study gene inactivation in hESCs</i>	152
<i>Study of ESC development by inducible RNAi</i>	153
<i>Targeting Induced Local Lesions in Genomes</i>	153
<i>Homologous recombination of ESCs</i>	153
Gene modification in genomes of hESCs and hiPSCs using zinc-finger nuclease.....	154
miRNA and stem cells.....	154
<i>Role of miRNAs in gene regulation during stem cell differentiation</i>	154
<i>Influence of miRNA on stem cell formation and maintenance</i>	155
<i>Restricted differentiation potential of miRNA-deficient PSCs</i>	155
<i>Transcriptional regulators of ESCs control miRNA gene expression</i>	156
Stem cells and cloning.....	156
<i>Cell nuclear replacement and cloning</i>	156
<i>Nuclear transfer and ESCs</i>	156
<i>Cloning from differentiated cells</i>	158
<i>Cloning mice from adult stem cells</i>	158
<i>Creating interspecies stem cells</i>	159
<i>Cloned cells for transplantation medicine</i>	159
<i>Claims of cloning of hESCs</i>	159
<i>hESCs derived by SCNT</i>	161
Cytogenetics of embryonic stem cells.....	161
Stem cell proteomics.....	162
<i>Comparative proteomic analysis of somatic cells, iPSCs and ESCs</i>	162
<i>hESC phosphoproteome</i>	162
<i>Proteomic studies of mesenchymal stem cells</i>	163
<i>Proteomic profiling of neural stem cells</i>	163
<i>Proteome Biology of Stem Cells Initiative</i>	164
Technologies for mobilization, expansion, and engraftment of stem cells.....	164
<i>Chemoattraction of neuronal stem cells through GABA receptor</i>	165
<i>Enhancement of HSC engraftment by calcium-sensing receptor</i>	165
<i>Ex vivo expansion of human HSCs in culture</i>	165
<i>Ex vivo expansion of MSCs</i>	166
<i>Ex vivo expansion of UCB cells for transplantation</i>	166
<i>Expansion of adult stem cells by activation of Oct4</i>	167
<i>Expansion of transduced HSCs in vivo</i>	167
<i>Expansion of stem cells in vivo by Notch receptor ligands</i>	167
<i>In vivo adipogenesis induced by adipose tissue-derived stem cells</i>	167
<i>Selective mobilization of progenitor cells from bone marrow</i>	168
<i>Selective Amplification</i>	168
<i>Synthetic substrates for ESC growth and expansion</i>	168
Technologies for inducing differentiation of stem cells.....	169
<i>Enhancement of stem cell differentiation by Homspera</i>	169
<i>Generation of RBCs from HSCs</i>	169
<i>Generation of multiple types of WBCs from hESCs and iPSCs</i>	169
<i>Growth factor-induced differentiation of MAPCs</i>	170
<i>Lineage selection to induce differentiation of hESCs</i>	170
<i>Mechanical strain to induce MSC differentiation</i>	170
<i>Neurotrophin-mediated survival and differentiation of hESCs</i>	171
<i>Synthetic biology and stem cells</i>	171
<i>Use of RNAi to expand the plasticity of autologous adult stem cells</i>	172
<i>Use of various molecules to induce differentiation of stem cells</i>	172
Limitations of the currently available stem cell lines in the US.....	172
Stem cell separation.....	173
Stem cell culture.....	173
<i>Culture of hMSCs</i>	174
<i>Elimination of contaminating material in stem cell culture</i>	174
<i>Long-term maintenance of MSC multipotency in culture</i>	175
<i>Nanofiber scaffolds for stem cell culture</i>	176
Conversion of stem cells to functioning adipocytes.....	176
Mass production of stem cells.....	177
<i>Mass production of ESCs</i>	177
<i>Mass production of MSCs</i>	177
Promoting survival of dissociated hESCs.....	178
Analysis and characterization of stem cells.....	178
Harvesting and identification of EPCs.....	179
Labeling of stem cells.....	179
Labeling, imaging and tracking of stem cells in vivo.....	179
<i>Perfluorocarbon nanoparticles to track therapeutic cells in vivo</i>	179
<i>PET imaging for tracking of stem cells</i>	180
<i>Project for imaging in stem cell therapy research</i>	180
<i>Quantum dots for labeling and imaging of stem cells</i>	180
<i>Radiolabeling of MSCs for in vivo tracking</i>	181

<i>Superparamagnetic iron oxide nanoparticles for tracking MSCs</i>	181
<i>Tracking of transplanted muscle stem cells</i>	181
Applications of stem cells	182
Commercial development and applications of adult stem cells	183
<i>Preparation of cells for therapeutic administration to patients</i>	183
<i>Retrodifferentiation of stem cells</i>	183
<i>MultiStem</i>	183
Self renewal and proliferation of HSCs	184
Optimizing the preparation and transfer of allogeneic HSCs.....	184
Aging of stem cells.....	185
<i>Aging and rejuvenation of HSCs</i>	185
<i>Aging and MSCs</i>	185
iPSC-based modeling of late-onset age-related diseases	186
Peripheral blood stem cell transplantation	186
Role of stem cells in regeneration	186
<i>Pluripotent stem-cell-derived gastric organoids</i>	187
<i>Promotion of regeneration by Wnt/beta-catenin signaling</i>	187
<i>Stem cell activation for regeneration by using glucocorticoids</i>	187
Stem cells and human reproduction	188
<i>Expansion of spermatogonial stem cells</i>	188
<i>Conversion of ESCs into spermatogonial stem cells</i>	188
<i>Conversion of stem cells to oocytes</i>	189
<i>ESCs for treatment of infertility in women</i>	189
<i>Cloning human embryos from oocytes matured in the laboratory</i>	190
<i>In utero stem cell transplantation</i>	190
Innovations in delivery of stem cells.....	191
<i>Polymeric capsules for stem cell delivery</i>	192
Immunological aspects of hESC transplantation	192
<i>Immunosuppression to prevent rejection of hESC transplants</i>	192
<i>Histocompatibility of hESCs</i>	192
<i>Strategies for promoting immune tolerance of hESCs</i>	193
Stem cells for organ vascularization	193
<i>Activation of EphB4 to enhance angiogenesis by EPCs</i>	194
Advantages and limitations of clinical applications of iPSCs	194
Advantages and limitations of clinical applications of MSCs.....	195
Biofusion by genetically engineering stem cells	195
Stem cell gene therapy.....	196
<i>Combination of gene therapy with nuclear transfer</i>	196
<i>Gene delivery to stem cells by artificial chromosome expression</i>	196
<i>Genetic manipulation of ESCs</i>	196
<i>Genetic engineering of human stem cells for enhancing angiogenesis</i>	197
<i>HSCs for gene therapy</i>	197
<i>iPSCs for targeted gene correction of α1-antitrypsin deficiency</i>	198
<i>Helper-dependent adenoviral vectors for gene transfer in ESCs</i>	198
<i>Lentiviral vectors for in vivo gene transfer to stem cells</i>	198
<i>Linker based sperm-mediated gene transfer technology</i>	199
<i>Mesenchymal stem cells for gene therapy</i>	199
<i>Microporation for transfection of MSCs</i>	199
<i>Regulation of gene expression for SC-based gene therapy</i>	200
<i>Stem cells and in utero gene therapy</i>	200
<i>Therapeutic applications for hematopoietic stem cell gene transfer</i>	200
<i>Targeted genome editing for human repopulating HSCs</i>	201
<i>The future of hematopoietic stem cell gene therapy</i>	201
Stem cell pharmaceuticals	201
Pharmaceutical manipulation of stem cells	201
<i>Expansion of HSCs in culture by inhibiting aldehyde dehydrogenase</i>	202
<i>Expansion of HSCs in vivo by use of prostaglandin E2</i>	203
<i>Manipulation of stem cells with growth factors</i>	203
<i>Mobilization of stem cells by cytokines/chemokines</i>	205
<i>Mobilization of adult human HSCs by use of inhibitors</i>	206
<i>Mobilization of stem cells by HYC750</i>	206
<i>Mobilization of stem cells by hyperbaric oxygen</i>	206
<i>Mobilization by adenoviral vectors expressing angiogenic factors</i>	207
<i>Stem cell mobilization by acetylcholine receptor agonists</i>	207
<i>Use of parathyroid hormone to increase HSC mobilization</i>	207
<i>Use of small molecule compounds for expansion of HSCs</i>	208
<i>Use of a small molecule for targeting systemically infused MSCs</i>	208
Role of stem cells in therapeutic effects of drugs.....	208
Stem cells for drug discovery	209
<i>Target identification</i>	209
<i>High-throughput screening</i>	209

<i>ESCs as source of models for drug discovery</i>	209
<i>hESC-derived hepatocytes for drug discovery</i>	210
<i>hESC-derived cardiomyocytes for drug discovery</i>	211
<i>iPSCs for drug discovery</i>	211
<i>Advantages and limitations of use of stem cells for drug discovery</i>	212
Stem cells for drug delivery	213
Toxicology and drug safety studies using ESCs versus other cells	213
Future challenges for stem cell technologies	215
Generation of patient-specific pluripotent stem cells	216
Hybrid embryos/cybrids for stem cell research	216
In vivo study of human hemopoietic stem cells	217
Inhibition of stem cell-derived teratoma formation by small molecules	217
Markers for characterizing hESC lines	217
MBD3-deficient ESC line	218
Research into plasticity of stem cells from adults	218
Reversion of human stem cells to ground state pluripotency	218
Stem cell biology and cancer	219
Stem cells and aging	220
Stem cells in space	221
Study of the molecular mechanism of cell differentiation	222
Switch of stem-cell function from activators to repressors	222
Stem cell research at academic centers	222
International Regulome Consortium	224
Companies involved in stem cell technologies	224
Concluding remarks about stem cells	229
Challenges and prospects of stem cell research	229
4. Clinical Applications of Cell Therapy	231
Introduction	231
Cell therapy for hematological disorders	231
Transplantation of autologous hematopoietic stem cells	231
Cytomegalovirus infection after allogeneic HSC transplantation	231
<i>Lymphoproliferative disorders after allogeneic HSC transplants</i>	232
HSCs derived from pluripotent stem cells	232
Hemophilias	232
<i>Ex vivo cell/gene therapy of hemophilia B</i>	233
<i>Cell/gene therapy of hemophilia A</i>	233
Hematopoietic stem cell therapy for thrombocytopenia	234
Stem cell transplant for sickle cell anemia	234
Treatment of chronic acquired anemias	235
<i>Implantation of genetically engineered HSCs to deliver rhEpo</i>	235
<i>Drugs acting on stem cells for treatment of anemia</i>	235
Stem cell therapy of hemoglobinopathies	236
<i>iPSC-based therapy for β-thalassemia</i>	236
Stem cells for treatment of immunoglobulin-light chain amyloidosis	236
Future of cell therapy of hematological disorders	237
Cell therapy for immunological disorders	237
Role of dendritic cells in the immune system	238
Modifying immune responses of DCs by vaccination with lipiodol-siRNA mixtures	238
Potential of MSCs as therapy for immune-mediated diseases	238
Stem cell therapy of chronic granulomatous disease	238
Stem cell therapy of X-linked severe combined immunodeficiency	239
Stem cell therapy of autoimmune disorders	239
<i>Wiskott-Aldrich Syndrome</i>	240
<i>Treatment of rheumatoid arthritis with stem cells</i>	240
<i>Treatment of Crohn's disease with stem cells</i>	240
<i>Stem cell transplants for scleroderma</i>	241
Role of T Cells in immunological disorders	242
<i>Autologous T cells from adult stem cells</i>	242
Cell therapy for graft vs host disease	243
<i>T cell infusion for suppressing GVHD</i>	244
<i>Genetically modified Tregs expressing CAR for prevention of GVHD</i>	244
<i>Concluding remarks on prevention and treatment of acute GVHD</i>	244
<i>MSCs for GVHD</i>	245
Cell therapy for viral infections	245
Anti-HIV ribozyme delivered in hematopoietic progenitor cells	245
Dendritic-cell targeted DNA vaccine for HIV	246
Exosomes and viral infections	246
Manipulation of T cells for treatment of viral infections	246
<i>T cell therapy for CMV</i>	246
<i>T cell therapy for HIV infection</i>	247

<i>T cell immunity by Overlapping Peptide-pulsed Autologous Cells</i>	247
Modification of iPSCs with a mutation to confer resistance to HIV	248
Cell therapy of lysosomal storage diseases	248
Niemann-Pick disease.....	248
Gaucher's disease	249
Fabry's disease	249
Cell therapy for endocrine disorders	250
Hypopituitarism	250
Adrenal insufficiency	250
Cell therapy for diabetes mellitus	251
Limitations of current treatment	252
<i>Limitations of insulin therapy for diabetes mellitus</i>	252
<i>Limitations of pancreatic transplantation</i>	252
Islet cell transplantation	252
<i>Autologous pancreatic islet cell transplantation in chronic pancreatitis</i>	253
<i>Clinical trials of pancreatic islet cell transplants for diabetes</i>	253
<i>Drawbacks of islet cell therapy</i>	254
<i>Use of an antioxidant peptide to improve islet cell transplantation</i>	254
<i>Cdk-6 and cyclin D1 enhance human beta cell replication and function</i>	254
<i>Devices for delivery of therapeutic cells in diabetes</i>	255
<i>Monitoring of islet cell transplants with MRI</i>	255
<i>Concluding remarks about allogeneic islet transplantation for diabetes</i>	255
Encapsulation of insulin producing cells	256
<i>Encapsulated porcine pancreatic islet cells for pancreas</i>	256
<i>Encapsulated insulinoma cells</i>	256
<i>Magnetocapsule enables imaging/tracking of islet cell transplants</i>	257
Islet precursor cells.....	257
Dedifferentiation of β cells to promote regeneration	258
Pharmacological approaches for β cell regeneration.....	258
Xenotransplantation of embryonic pancreatic tissue	259
Non-pancreatic tissues for generation of insulin-producing cells	259
Exploiting maternal microchimerism to treat diabetes in the child	259
Bio-artificial substitutes for pancreas.....	260
Role of stem cells in the treatment of diabetes	260
<i>Embryonic stem cells for diabetes</i>	260
<i>HSC transplantation to supplement immunosuppressant therapy</i>	262
<i>Insulin-producing cells derived from UCB stem cells</i>	262
<i>iPSc for diabetes</i>	262
<i>Pancreatic stem cells</i>	263
<i>Pluripotent stem cell-derived pancreatic β-like cells</i>	263
<i>Stem cell injection into portal vein of diabetic patients</i>	264
Conversion of progenitor cells into insulin-producing cells	264
<i>Human neural progenitor cells converted into insulin-producing cells</i>	264
<i>Isolation of islet progenitor cells</i>	264
<i>Pancreatic progenitor cells</i>	265
Cell-based immunotherapy for type 1 diabetes	265
<i>Dendritic cell-based therapy</i>	265
<i>T regulatory cell therapy for diabetes</i>	265
<i>Vaccine for diabetes</i>	266
Synthetic biomimetic β -cells for dynamic insulin secretion.....	266
Gene therapy in diabetes	266
<i>Viral vectors for gene therapy of diabetes</i>	267
<i>Genetically engineered dendritic cells</i>	267
<i>Genetically altered liver cells</i>	267
<i>Genetically modified stem cells</i>	268
Companies developing cell therapy for diabetes.....	268
Concluding remarks about cell and gene therapy of diabetes.....	269
Cell therapy of gastrointestinal disorders	270
Inflammatory bowel disease.....	270
Cell therapy for liver disorders	271
Types of cells used for hepatic disorders	271
<i>Culture and expansion of primary human hepatocytes</i>	271
<i>Hepatocyte progenitor cells</i>	272
<i>Hybrid periportal hepatocytes</i>	272
Methods of delivery of cells for hepatic disorders	272
Hepatic failure	273
Bioartificial liver.....	273
<i>Hepatocyte-based artificial liver</i>	273
<i>Extracorporeal Liver Assist Device</i>	274
<i>Limitations of bioartificial liver</i>	274
<i>Proliferating cell-based bioartificial liver</i>	274

Stem cells for hepatic disorders	275
<i>Deriving hepatocytes from commercially available hMSCs</i>	275
<i>Implantation of hepatic cells derived from hMSCs of adipose tissue</i>	276
<i>Heterologous adult liver progenitor cells</i>	276
<i>Liver stem cell culture</i>	276
<i>MSC derived molecules for reversing hepatic failure</i>	277
Cell-based gene therapy for liver disorders.....	277
<i>Transplantation of genetically modified fibroblasts</i>	277
<i>Transplantation of genetically modified hepatocytes</i>	278
<i>Genetically modified hematopoietic stem cells</i>	278
<i>iPSCs derived from somatic cells for liver regeneration</i>	278
<i>Hepatocyte-like cells derived from human parthenogenetic stem cells</i>	278
Clinical applications	279
Future prospects of cell-based therapy of hepatic disorders.....	280
Cell therapy of renal disorders.....	280
Bioartificial kidney.....	280
Cell-based repair for vascular access failure in renal disease	281
Mesangial cell therapy for glomerular disease	281
Stem cells for renal disease.....	281
<i>Role of stem cells in renal repair</i>	282
<i>Bone marrow stem cells for renal disease</i>	282
<i>Human amniotic fluid stem cells for renal regeneration</i>	283
<i>MSC therapy for renal disease</i>	283
<i>MSCs as aid to renal graft survival</i>	283
Transplantation of cell-based bioengineered kidney	284
Cell therapy for pulmonary disorders.....	284
Delivery of cell therapy for pulmonary disorders	284
<i>Intratracheal injection of cells for pulmonary hypoplasia</i>	284
Role of stem cells in pulmonary disorders	285
<i>Lung stem cells</i>	285
<i>Lung tissue regeneration from stem cells</i>	285
<i>Role of autologous MSCs in the treatment of severe emphysema</i>	286
<i>Role of stem cells in construction of the Cyberlung</i>	286
<i>Respiratory epithelial cells derived from UCB stem cells</i>	286
<i>Respiratory epithelial cells derived from hESCs</i>	286
<i>Lung tissue engineering with adipose stromal cells</i>	287
<i>Cell-based tissue-engineering of airway</i>	287
Pulmonary disorders that can be treatable with stem cells	288
<i>Acute lung injury and ARDS treated with MSCs</i>	289
<i>Bronchopulmonary dysplasia treated with MSCs</i>	289
<i>Chronic obstructive pulmonary disease treated with MSCs</i>	290
<i>Cystic fibrosis treatment with genetically engineered MSCs</i>	290
<i>Idiopathic pulmonary fibrosis</i>	290
<i>Lung regeneration by integrin $\alpha 6 \beta 4$-expressing alveolar epithelial cell</i>	291
<i>Pulmonary arterial hypertension treatment with EPCs</i>	291
Cell therapy for disorders of bones, joints and tendons	292
Cell therapy for repair of fractures and bone defects	292
<i>Bone regeneration by human very small embryonic-like (hVSEL) cells</i>	293
<i>Cell therapy for cervical vertebral interbody fusion</i>	293
<i>Cell-mediated gene therapy for bone regeneration</i>	293
<i>ESCs for bone repair</i>	293
<i>hiPSCs for engineering personalized bone grafts</i>	294
<i>Intrauterine use of MSCs for osteogenesis imperfecta</i>	294
<i>In vivo bone engineering as an alternative to cell transplantation</i>	294
<i>In vivo differentiation of pluripotent stem cells for bone regeneration</i>	295
<i>MSCs for repair of bone defects</i>	295
<i>MSCs for repair of bone fractures</i>	298
<i>Osteoecel</i>	299
<i>Stem cells for repairing skull defects</i>	299
<i>Stem cell-based bone tissue engineering</i>	299
<i>Spinal fusion using stem cell-based bone grafts</i>	300
<i>Wnt stimulation to enrich BMSCs for repair of bone fractures</i>	301
Cell therapy of tendon injuries	301
<i>Autologous tenocyte implantation in rotator cuff injury repair</i>	301
<i>Platelet injection for tennis elbow</i>	302
Cell-based techniques for cartilage repair and regeneration.....	302
<i>Cartilage generation from stem cells</i>	302
<i>Cartilage engineering from iPSCs</i>	304
<i>Genetically modified fibroblasts expressing TGF-β for cartilage repair</i>	304
<i>Juvenile cartilage implant for repair of damage to articular cartilage</i>	304
Cell therapy for repair of knee cartilage injuries.....	304

<i>Autologous chondrocyte therapy of the knee</i>	306
<i>Meniscus-derived stem cells</i>	306
<i>MSC-based constructs for knee joint replacement</i>	306
<i>Nanobiotechnology scaffolds for MSC-based cartilage reconstruction</i>	307
<i>Role of cells in the repair of anterior cruciate ligament injury</i>	307
Osteoporosis	308
<i>Stem cell gene therapy for osteoporosis</i>	308
Osteoarthritis of the joints	308
<i>Autologous cultured chondrocytes</i>	309
<i>Autologous intervertebral disc chondrocyte transplantation</i>	310
<i>Intraarticular MSCs for osteoarthritis</i>	310
<i>Mosaicplasty</i>	311
<i>Stem cell therapy of osteoarthritis of the knee</i>	311
Osteonecrosis.....	312
<i>Cell therapy for osteonecrosis</i>	312
<i>Cell therapy for radionecrosis</i>	312
<i>Repair of osteonecrosis by bone marrow derived MSCs</i>	312
Rheumatoid arthritis.....	312
Cell therapy for diseases of the eye	313
Cell therapy for corneal repair	313
Use of human cultured endothelial cells for bullous keratopathy.....	315
Lens regeneration from endogenous stem cells.....	315
Stem cell therapy for limbal stem cell deficiency	315
Role of stem cells in fibrosis following eye injury.....	316
Stem cell transplantation for radiation sickness	316
MSCs for treatment of radiation damage to the bone.....	316
MSCs for regeneration of ovaries following radiotherapy damage	317
Cell therapy for wound healing	317
Cells to form skin substitutes for healing ulcers	318
CellSpray for wound repair.....	318
Cell therapy for burns.....	319
Closure of incisions with laser guns and cells.....	320
Genetically engineered keratinocytes for wound repair	320
MSCs for wound healing.....	320
Role of amniotic fluid MSCs in repair of fetal wounds	320
Treatment of diabetic foot ulcers with stem cells.....	321
Role of cells in regenerative medicine	321
Stem cells for regeneration of skin and appendages	321
<i>Bifunctional ectodermal stem cells and nail regeneration</i>	321
<i>Stem cells for regeneration of skin in junctional epidermolysis bullosa</i>	321
<i>Follicular stem cells for skin and wound repair</i>	322
<i>Regeneration of aging skin by adipose-derived stem cells</i>	323
<i>Reprogramming autologous stem cells for regeneration of skin</i>	323
<i>Concluding remarks on regeneration of skin by stem cells</i>	323
Cell therapy for regeneration of muscle wasting.....	323
Role of stem cells in regeneration of esophageal epithelium	324
Stem cell-based regenerative therapy for xerostomia	324
Concluding remarks for use of cells in regenerative medicine.....	325
<i>Genomic studies for examining the role of stem cells in regeneration</i>	325
<i>Cell therapy for regenerating organs</i>	325
<i>Umbilical cord blood for regeneration</i>	326
Future prospects of stem cells for regenerative medicine	327
Role of cells in tissue engineering and reconstructive surgery	327
Scaffolds for tissue engineering	327
Improving vascularization of engineered tissues	327
<i>Reconstruction of vasculature</i>	328
Repair of aging skin by injecting autologous fibroblasts	328
Enhancing vascularization by combining cell and gene therapy	329
Nanobiotechnology applied to cells for tissue engineering	329
Choosing cells for tissue engineering	330
Stem cells for tissue repair.....	330
<i>ESCs vs adult SCs for tissue engineering</i>	330
<i>Use of adult MSCs for tissue engineering</i>	331
<i>Measuring MSC interactions with environment for tissue engineering</i>	332
Stem cells for tissue engineering of various organs	332
<i>Breast reconstruction by adipose tissue-derived stem cells</i>	332
<i>Engineering of healthy living teeth from stem cells</i>	332
<i>Intra-uterine repair of congenital defects using amniotic fluid MSCs</i>	333
<i>Skin regeneration by stem cells as an alternative to face transplant</i>	334
<i>Tissue engineering of bone by stem cells</i>	334
Cell-based tissue engineering in genitourinary system.....	335

Urinary incontinence.....	335
Tissue engineering of urinary bladder	336
Label retaining urothelial cells for bladder repair	337
MSCs for bladder repair	337
Tissue-engineering of urethra using autologous cells	337
Repair of the pelvic floor with stem cells from the uterus	338
Reconstruction of vagina from stem cells	338
Reconstruction of cartilage for repair of craniofacial defects.....	338
Intraoperative cell therapy	339
Cell therapy for rejuvenation	339
Reversal of muscle weakness and atrophy in aging	340
Reversal of cognitive impairment in aging	340
Treatment of frailty of aging with MSCs	340
Cell therapy for performance enhancement in sports	341
Application of stem cells in veterinary medicine	341
Use of stem cells to repair tendon injuries.....	341
Stem cells for spinal cord injury in dogs.....	342
5. Cell Therapy for Cardiovascular Disorders	343
Introduction to cardiovascular disorders	343
Limitations of current therapies for myocardial ischemic disease.....	343
Types of cell therapy for cardiovascular disorders.....	343
Cell-mediated immune modulation for chronic heart disease	345
Inducing the proliferation of cardiomyocytes	345
Pericardial origin of colony-forming units	346
Role of splenic myocytes in repair of the injured heart.....	346
Reprogramming of fibroblasts into functional cardiomyocytes	346
Stem cell-based therapies for cardiovascular diseases	347
Human cardiovascular progenitor cells.....	347
Human pluripotent stem cell-derived cardiomyocytes	348
Large cardiac-muscle patches based on hiPSC technology	348
Magnetic antibody-linked nanoparticles to deliver cells to the heart.....	348
Role of the SDF-1-CXCR4 axis in therapies for myocardial ischemia.....	349
Small molecules to enhance myocardial repair by stem cells.....	349
Stem cells and atherosclerosis.....	349
Cell therapy for atherosclerotic coronary artery disease.....	350
MyoCell™ (Bioheart).....	350
Cardiac stem cells	350
Cardiomyocytes derived from epicardium.....	351
Cardiac atrial appendage stem cells	352
Methods of delivery of cells to the heart.....	352
Cellular cardiomyoplasty	352
IGF-1 delivery by nanofibers to improve cell therapy for MI.....	353
Non-invasive delivery of cells to the heart by Morph@guide catheter	353
Cell therapy for cardiac revascularization	353
Transplantation of cardiac progenitor cells for revascularization of myocardium	353
Stem cells to prevent restenosis after coronary angioplasty.....	354
Role of cells in cardiac tissue repair.....	354
Modulation of cardiac macrophages for repair of infarct	354
Transplantation of myoblasts for myocardial infarction.....	355
Patching myocardial infarction with fibroblast culture	356
Cardiac repair with myoendothelial cells from skeletal muscle	356
Myocardial tissue engineering.....	356
Role of stem cells in repair of the heart	357
Role of stem cells in cardiac regeneration following injury	357
Cardiomyocytes derived from adult skin cells	358
Cardiomyocytes derived from ESCs	358
Cardiomyocyte differentiation from hiPSCs	360
Studies to identify subsets of progenitor cells suitable for cardiac repair	360
Technologies for preparation of stem cells for cardiovascular therapy	360
Pravastatin for expansion of endogenous progenitor and stem cells.....	360
Cytokine preconditioning of human fetal liver CD133+ SCs	361
Expansion of adult cardiac stem cells for transplantation.....	361
Role of MSCs in growth of CSCs	362
Role of ESCs in repair of the heart	362
ESC transplantation for tumor-free repair of the heart.....	363
Transplantation of stem cells for myocardial infarction.....	363
Autologous bone marrow-derived stem cell therapeutics	363
Autologous bone marrow-derived mesenchymal precursor stem cells	364
Intracoronary infusion of mobilized peripheral blood stem cells	364
Transplantation of cord blood stem cells	365

<i>Transplantation of hESCs</i>	365
<i>Transplantation of HSCs</i>	365
<i>Transplantation of autologous angiogenic cell precursors</i>	366
<i>Transplantation of adipose-derived stem cells</i>	366
<i>Transplantation of bone marrow-derived cells for myocardial infarct</i>	367
<i>Transplantation of human umbilical cord perivascular cells</i>	368
<i>Transplantation of endothelial cells</i>	368
<i>Transplantation of cardiomyocytes differentiated from hESCs</i>	369
Stem cell therapy for cardiac regeneration	369
<i>3D printed scaffold for regeneration of myocardial infarct with cells</i>	369
<i>Cryopreserved hESC-derived cardiomyocytes for cardiac regeneration</i>	370
<i>Exosomal miRNAs from hiPSC-derived cardiomyocytes</i>	370
<i>HSCs for regeneration of the chronic myocardial infarcts</i>	370
<i>Human MSCs for cardiac regeneration</i>	370
<i>In vivo tracking of MSCs transplanted in the heart</i>	371
<i>MSCs for hibernating myocardium</i>	372
<i>Simultaneous transplantation of MSCs and skeletal myoblasts</i>	372
Transplantation of genetically modified cells	373
Transplantation of genetically modified MSCs	373
Transplantation of cells secreting vascular endothelial growth factor	373
Transplantation of genetically modified bone marrow stem cells.....	373
Cell transplantation for congestive heart failure	373
AngioCell gene therapy for congestive heart failure	374
Injection of adult stem cells for CHF	375
Intracoronary infusion of cardiac stem cells.....	375
Myoblasts for treatment of congestive heart failure	375
Stem cell therapy for dilated cardiac myopathy.....	376
Role of cell therapy in cardiac arrhythmias	376
Biological pacemakers	377
<i>Stem cells as biological pacemakers</i>	377
<i>Stem cells for cardiac arrhythmias</i>	378
Prevention of myoblast-induced arrhythmias by genetic engineering	378
Ventricular tachycardia	378
ESCs for correction of congenital heart defects	379
Cardiac progenitors cells for treatment of heart disease	379
Autologous stem cells for chronic myocardial ischemia	380
Role of cells in cardiovascular tissue engineering	380
Cell-based in vitro regeneration of heart for transplantation	380
Construction of blood vessels with cells	381
<i>Engineered arteries for bypass grafts</i>	381
Engineering heart valves with UCB progenitor cells	382
Epicardial regeneration from hPSCs.....	382
Fetal cardiomyocytes seeding in tissue-engineered cardiac grafts.....	382
Targeted delivery of endothelial progenitor cells labeled with nanoparticles	383
Cell therapy for peripheral vascular disease	383
ALD-301	383
Cell/gene therapy for PVD	383
Cell therapy for CLI in diabetics	384
Colony stimulating factors for enhancing peripheral blood stem cells	384
Intramuscular autologous bone marrow cells.....	384
Ixmyelocel-T cell therapy for critical limb ischemia.....	385
Stem cell-coated vascular grafts for femoral-tibial arterial bypass	385
Clinical trials of cell therapy in cardiovascular disease	385
Mechanism of the benefit of cell therapy for heart disease	388
A critical evaluation of cell therapy for heart disease	388
Publications of clinical trials of cell therapy for CVD	389
Current status of cell therapy for cardiovascular disease	389
Future directions for cell therapy of CVD	390
Combination of cells with biomedical scaffolds	390
Prospects of adult stem cell therapy for repair of heart	390
Role of cells in regeneration of the heart.....	391
Regeneration of cardiomyocytes without use of cardiac stem cells.....	391
6. Cell Therapy for Cancer	393
Introduction	393
Cell therapy technologies for cancer	393
Cell-based delivery of anticancer therapy	394
Cellular immunotherapy for cancer	394
Treatments for cancer by ex vivo mobilization of immune cells	395
Granulocytes as anticancer agents	395
Neutrophil granulocytes in antibody-based immunotherapy of cancer	396

Cancer vaccines	396
Autologous tumor cell vaccines	396
<i>BIOVAXID</i>	396
<i>OncoVAX</i>	397
<i>Tumor cells treated with dinitrophenyl</i>	397
Vaccines that simultaneously target different cancer antigens	397
Gene modified cancer cells vaccines	398
<i>GVAX cancer vaccines</i>	398
<i>K562/GM-CSF</i>	398
Active immunotherapy based on antigen specific to the tumor	399
The use of dendritic cells for cancer vaccination	399
<i>Autologous dendritic cells loaded ex vivo with telomerase mRNA</i>	399
<i>Dendritic cell-targeted protein vaccines</i>	400
<i>Dendritic/tumor cell fusion</i>	400
<i>Electro-hyperthermia for improving DC immunotherapy</i>	400
<i>Genetically modified dendritic cells</i>	401
<i>In vivo manipulation of dendritic cells</i>	401
<i>Preclinical and clinical studies with DC vaccines</i>	401
<i>Vaccines based on dendritic cell-derived exosomes</i>	402
<i>Limitations of DC vaccines for cancer</i>	402
<i>Future developments to enhance clinical efficacy of DC vaccines</i>	403
Cell-based cancer immunotherapy	404
<i>Adoptive cell therapy</i>	404
<i>CD8+ T cells for use in tumor immunotherapy</i>	405
<i>Combination of antiangiogenic agents with ACT</i>	406
<i>Expansion of antigen-specific cytotoxic T lymphocytes</i>	407
<i>Genetically modified T cells for targeting tumors</i>	407
<i>Genetic engineering of tumor cells to activate T helper cells</i>	407
<i>Targeting T regulatory cells</i>	408
<i>T cells with immunological memory and stem cell-like properties</i>	408
<i>T cell imaging for predicting response to cancer vaccines</i>	408
<i>Tumor infiltrating lymphocytes</i>	409
Chimeric antigen receptor T cells	409
<i>Basics of CAR-T cell</i>	409
<i>Basis of anticancer effect of CAR-T cells</i>	410
<i>CAR-T cell manufacture</i>	410
<i>CAR-T cell therapy for leukemia</i>	411
<i>CAR-T cell therapy for multiple myeloma</i>	412
<i>CAR-T cell therapy for lymphoma</i>	412
<i>CAR-T cell therapy for solid tumors</i>	413
<i>Companies developing CAR-T cell therapy</i>	414
<i>CAR NK cells derived from human iPSCs</i>	414
<i>ProCAR-NK cancer immunotherapy</i>	414
<i>Remote control of CAR-T cells</i>	414
<i>Safety of CAR-T cell therapy</i>	414
Chemoimmunotherapy	416
Hybrid cell vaccination	416
Stem cell-based anticancer therapies	416
Stem cell transplantation in cancer	416
<i>Peripheral blood stem cell transplantation</i>	417
<i>Stem cell transplantation for hematological malignancies</i>	419
<i>Long-term results of HSC transplantation</i>	420
<i>Prediction of T cell reconstitution after HSC transplantation</i>	421
<i>HSC transplantation followed by GM-CSF-secreting cell vaccines</i>	421
<i>HSC transplantation for renal cell cancer</i>	422
<i>Umbilical cord blood transplant for hematological malignancies</i>	422
Complications of stem cell transplants in cancer	423
<i>Graft-versus-host disease (GVHD)</i>	423
<i>Delayed immune reconstitution leading to viral infections and relapse</i>	423
<i>Tumor cell contamination</i>	424
<i>Neurological complications</i>	424
<i>Hepatic veno-occlusive disease</i>	425
<i>Current status and safety of allogeneic HSC transplantation</i>	425
<i>Complications of PBSC transplantation in children</i>	426
Role of MSCs in cancer	426
<i>MSC-mediated delivery of anticancer therapeutics</i>	426
<i>Mesenchymal progenitor cells for delivery of oncolytic adenoviruses</i>	427
<i>MSCs for oncolytic HSV delivery for brain metastases of melanoma</i>	427
Nonmyeloablative allogeneic hematopoietic stem cell transplantation	427
hESC-derived NK cells for treatment of cancer	428
ESC vaccine for prevention of lung cancer	428

Genetic modification of stem cells for cancer therapy	429
<i>Genetic modification of hematopoietic stem cells</i>	429
<i>Use of hematopoietic stem cells to deliver suicide genes to tumors</i>	429
<i>Delivery of anticancer agents by genetically engineered MSCs</i>	429
<i>Genetically modified NSCs for treatment of neuroblastoma</i>	430
Innovations in cell-based therapy of cancer	431
Use of immortalized cells	431
Cancer therapy based on natural killer cells.....	431
Cytokine-induced killer cells	431
Mesothelin as a target for cancer immunotherapy	432
Nanomagnets for targeted cell-based cancer gene therapy.....	432
Implantation of genetically modified encapsulated cells for anticancer therapy	432
<i>Antiangiogenesis therapy by implantation of microencapsulated cells</i>	432
<i>Recombinant tumor cells secreting fusion protein</i>	433
<i>A device for filtering cancer and stem cells in the blood</i>	433
Cancer stem cells.....	433
<i>Cancer stem cell biomarkers</i>	434
<i>Integrative nuclear signaling and development of cancer in stem cells</i>	434
<i>Origin of cancer in normal stem cells</i>	434
<i>Role of intestinal stem cells in intestinal polyposis</i>	435
<i>Role of endothelial progenitor cells in tumor angiogenesis</i>	435
<i>Role of cancer stem cells in metastases</i>	435
<i>Role of cancer stem cells in chemotherapy</i>	436
<i>Therapeutic implications of cancer stem cells</i>	436
<i>Targeting breast cancer stem cells</i>	437
<i>Targeting cancer stem cells in leukemia</i>	438
<i>Targeting cancer stem cells in ovarian cancer</i>	438
<i>Targeting cancer stem cells to screen anticancer drugs</i>	438
Companies involved in cell-based cancer therapy	439
American Association for Cancer Research and ESCs	440
Future of cell-based immunotherapy for cancer.....	440

7. Cell Therapy for Neurological Disorders..... 443

Introduction	443
Use of stem cells for research in neurosciences.....	443
Cerebral organoids for modeling human brain development	443
Use of human stem cell-derived neurons in neuropharmacology	443
Regeneration of brain by in vitro/in vivo reprogramming of cells.....	444
Molecular mechanism of neurogenesis	445
Generation of neurons from astroglia	446
In vivo cell replacement therapy by locally induced neural progenitor cells.....	446
In vivo reprogramming to generate new neurons.....	446
Types of cells used for treatment of neurological disorders.....	447
Activated T lymphocytes	448
Differentiation of placenta-derived multipotent cells into neurons.....	448
Fibroblast-derived human striatal neurons	448
Mesenchymal stem cells induced to secrete neurotrophic factors.....	448
MUSE cells transplantation for neuronal regeneration	449
Neural stem cells	449
<i>Development of human CNS stem cells</i>	449
<i>Direct conversion of adult fibroblasts into neural progenitor cells</i>	450
<i>Distinction between NSCs and intermediate neural progenitors</i>	450
<i>Embryonic stem cell-derived neurogenesis</i>	450
<i>Epidermal neural crest stem cells for neurological disorders</i>	451
<i>Fusion of NSCs with endogenous neurons</i>	451
<i>Induction of NSCs from hESCs</i>	451
<i>Induction of NSCs from adult MSCs</i>	453
<i>Mechanism of migration of NSCs to sites of CNS injury</i>	453
<i>Monitoring of implanted NSCs labeled with nanoparticles</i>	453
<i>Neural progenitor cells</i>	453
<i>Neural stem cells in the subventricular zone of the brain</i>	456
<i>Oligodendrocyte progenitor cells</i>	456
<i>Promotion of neural stem cells expansion by betacellulin</i>	456
<i>Proteomics of neural stem cells</i>	456
<i>Regulation of neural stem cells in the brain</i>	457
<i>Role of CSF in regulation of neural progenitor cells</i>	458
<i>Sequencing the transcriptomes of neural stem cells</i>	458
<i>Study of neural differentiation of hESCs by NeuroStem Chip</i>	459
<i>Transformation of neural stem cells into other cell types</i>	459
Stem cell transplantation in the CNS	459
<i>Development of CNS cells from non-CNS stem cells</i>	459

Expansion of adult human neural progenitors	460
Hair-follicle stem cells for neural repair	461
Human NSCs for treatment of neurological disorders	461
NSCs and scaffolds for regeneration therapy of CNS disorders	462
Neurospheres	462
Stem cells from olfactory epithelium for transplantation in the CNS	462
Stem cells from human umbilical cord blood for CNS disorders	463
Choroid plexus cells for transplantation	463
Dental pulp cells for neuroprotection	463
Derivation of CNS cells from peripheral nervous system	464
Fetal tissue transplants	464
Immortalized cells for CNS disorders	465
Laboratory mice with human brain cells	465
Olfactory ensheathing cells for CNS repair	466
Ideal cells for transplantation into the nervous system	466
Cell therapy techniques for neurological applications	466
Carbon nanotubes to aid stem cell therapy of neurological disorders	466
Cell transplantation for regeneration of the nervous system	467
Cells used for gene therapy of neurological disorders	467
<i>Fibroblasts</i>	467
<i>Stem cells</i>	468
<i>Neuronal cells</i>	468
<i>Immortalized neural progenitor cells</i>	468
<i>Astrocytes</i>	468
<i>Cerebral endothelial cells</i>	469
<i>Human retinal pigmented epithelial cells</i>	469
Enhancement of growth of stem cells in the brain by drugs	469
<i>C3-induced differentiation and migration of NPC for repair of the brain</i>	470
Stem cell therapies of neurological disorders combined with HBO	470
hESCs for CNS repair	471
Motor neurons derived from stem cells	471
MSCs for CNS repair	472
Neuronal differentiation of stem cells	472
<i>Apigenin promotes differentiation of stem cells into neural lineage</i>	473
Stem cells preparations for CNS disorders	473
Tracking of stem cells in the CNS by nanoparticles and MRI	474
Use of neural stem cells to construct the blood brain barrier	474
Methods of delivery of cells to the CNS	475
<i>Cerebrospinal fluid-stem cell interactions for therapy of CNS disorders</i>	475
<i>CNS delivery of cells by catheters</i>	476
<i>Engineered stem cells for drug delivery to the brain</i>	476
<i>Encapsulated cells</i>	476
<i>Intrathecal delivery of stem cells</i>	476
<i>Intraparenchymal delivery of stem cells to the spinal cord</i>	477
<i>Intravascular administration</i>	477
<i>Neural stem cells as therapeutic delivery vehicles</i>	478
Neurological disorders amenable to cell therapy	478
Neuroprotection by cell therapy	479
<i>Cells secreting neuroprotective substances</i>	479
<i>Stem cells for neuroprotection</i>	479
Neuroprotection by intravenous administration of HSCs	479
<i>Human UCB-derived stem cells for the aging brain</i>	480
Neurodegenerative disorders	480
<i>MSCs for therapy of neurodegenerative disorders</i>	480
<i>Role of stem cells in neurodegenerative disorders</i>	481
<i>Role of NSCs in disorders associated with aging brain</i>	482
<i>NSCs for improving memory</i>	482
Parkinson's disease	483
<i>Cell therapies for PD</i>	483
<i>Delivery of cells for PD</i>	485
<i>Dopamine neurons for PD</i>	485
<i>Encapsulated cells for PD</i>	486
<i>Graft survival-enhancing drugs</i>	486
<i>Human retinal pigment epithelium cells for PD</i>	486
<i>Potential of regeneration of endogenous stem cells in PD</i>	487
<i>Pluripotent stem cell-derived neurons</i>	487
<i>Stem cell transplantation in animal models of PD</i>	488
<i>Stem cells for production of glial derived neurotrophic factor</i>	489
<i>Transplantation of embryonic medial ganglionic eminence cells</i>	490
<i>Trials of stem cell transplantation in PD patients</i>	490
<i>Tumorigenic potential of transplanted dopaminergic hESCs</i>	492

<i>Xenografting porcine fetal neurons</i>	492
<i>Personalized stem cell therapy for PD</i>	492
<i>Future perspectives of clinical trials of stem cell therapy for PD</i>	493
MSCs for multiple system atrophy	493
Cell therapy for Huntington's disease.....	494
<i>Fetal striatal cell transplantation</i>	494
<i>Transplantation of encapsulated porcine choroids plexus cells</i>	494
<i>iPSCs for HD</i>	495
<i>Mobilization of endogenous neural progenitor cells in HD</i>	495
Cell therapy for Alzheimer's disease	495
<i>Choroid plexus epithelial cells for AD</i>	495
<i>Implantation of genetically engineered cells producing NGF</i>	496
<i>Neural stem cell implantation for Alzheimer's disease</i>	496
<i>Use of autologous stem cells for dementia</i>	497
Cell therapy for amyotrophic lateral sclerosis.....	497
<i>Stem cell techniques for study of ALS</i>	498
<i>Rational for use of stem cells for ALS</i>	498
<i>Experimental studies with various types of stem cells for ALS</i>	498
<i>Clinical trials of stem cells for ALS</i>	500
<i>Transplantation of glial restricted precursors in ALS</i>	501
<i>Stem cell-based drug discovery for ALS</i>	501
Cell therapy for demyelinating disorders	502
<i>Autologous bone marrow stem cell therapy for multiple sclerosis</i>	502
<i>ESCs for remyelination</i>	502
<i>Fusokine method of personalized cell therapy of MS</i>	503
<i>Genetically engineered macrophages expressing Nav1.5</i>	503
<i>Hematopoietic stem cell transplantation for MS</i>	503
<i>MSCs for multiple sclerosis</i>	504
<i>Neural progenitor cells for neuroprotection in MS</i>	505
<i>NSC transplantation for repair of demyelination after</i>	505
<i>iNSCs for antiinflammatory effect in MS</i>	506
<i>Oligodendrocyte generation from human iPSCs</i>	506
<i>T cell-based personalized vaccine for MS</i>	506
<i>T cell-directed therapies for MS</i>	506
<i>Stem cells for chronic inflammatory demyelinating polyneuropathy</i>	506
<i>Stem cell transplantation for Pelizaeus-Merzbacher disease</i>	507
<i>X-linked adrenoleukodystrophy</i>	507
Cell therapy of stroke	507
<i>Adult stem cell therapy in stroke</i>	508
<i>Cell therapy of intracerebral hemorrhage</i>	509
<i>Implantation of genetically programmed ESCs</i>	509
<i>Intravenous infusion of MSCs</i>	510
<i>Intravenous infusion of human UCB stem cells</i>	510
<i>Intravenous MSCs to prevent rupture of experimental aneurysms</i>	511
<i>Intracerebral administration of human adipose tissue stromal cells</i>	511
<i>Neural stem cell therapy for stroke</i>	512
<i>Transplantation of encapsulated porcine choroids plexus</i>	513
<i>Transplantation of fetal porcine cells</i>	513
<i>Role of cell therapy in management of stroke according to stage</i>	513
<i>Clinical trials of cell therapy for stroke</i>	514
<i>Future of cell therapy for stroke</i>	515
Cell therapy of traumatic brain injury	516
<i>Cell/gene therapy for TBI</i>	517
<i>Clinical trials of autologous stem cell therapy for TBI</i>	517
<i>Limitations of stem cell therapy for acute TBI</i>	518
<i>Improving the microenvironments of transplanted cells in TBI</i>	518
<i>MSC-derived exosomes for treatment of TBI</i>	518
Cell therapy for spinal cord injury	519
<i>Autoimmune T cells against CNS myelin-associated peptide</i>	519
<i>Fetal neural grafts for SCI</i>	519
<i>Olfactory-ensheathing cells for SCI</i>	519
<i>Oligodendrocyte precursor cells for treatment of SCI</i>	520
<i>Schwann cell transplants for SCI</i>	520
<i>Transplantation of glial cells for SCI</i>	520
Stem cells for SCI	521
<i>Bone marrow stem cells for SCI</i>	521
<i>Embryonic stem cells for SCI</i>	521
<i>ESC-derived neural aggregates for treatment of SCI</i>	522
<i>Transplantation of induced pluripotent stem cells in SCI</i>	523
<i>Transplantation of MSCs for SCI</i>	523
<i>Transplantation of NSCs for SCI</i>	523

<i>Transplantation of human dental pulp stem cells</i>	524
<i>Transdifferentiation of BM stem cells into cholinergic neurons for SCI</i>	524
<i>Evaluation of experimental studies of stem cell transplantation in SCI</i>	525
Spinal stem cells for treatment of ischemic injury of spinal cord.....	525
Combined approaches for regeneration in SCI.....	525
<i>Combined cell/gene therapy for SCI</i>	526
Delivery of cells in SCI.....	526
<i>Intrathecal injection of cells labeled with magnetic nanoparticles</i>	527
<i>Intravenous injection of stem cells for spinal cord repair</i>	527
Clinical applications of stem cells for SCI.....	527
<i>Autologous bone marrow cell transplantation for SCI</i>	527
<i>Cell therapy of syringomyelia</i>	528
Cell therapy for neurogenetic disorders.....	528
<i>Hurler's syndrome treated with stem cells</i>	528
<i>Krabbe's disease treated with UCB stem cells</i>	529
<i>Krabbe's disease treated with combination of cell and gene therapy</i>	529
<i>Mitochondrial encephalomyopathies treated with stem cells</i>	530
<i>Sanfilippo syndrome type B treated with UCB stem cells</i>	530
Cell therapy for lysosomal storage disorders.....	531
<i>Cell therapy for Batten disease</i>	531
<i>Cell/gene therapy for Farber's disease</i>	531
<i>Genetically modified HSCs for metachromatic leukodystrophy</i>	532
<i>Neural stem cells for lysosomal storage disorders</i>	532
Cell therapy of epilepsy.....	532
<i>Cell therapy of posttraumatic epilepsy</i>	533
<i>Cell therapy for temporal lobe epilepsy</i>	533
<i>Cell therapy for pharmaco-resistant epilepsies</i>	533
Cell therapy for developmental neurological disorders.....	534
Cell therapy for cerebral palsy.....	534
Cell-based therapies for malignant CNS tumors.....	535
<i>Bone morphogenetic protein for inhibition of glioblastoma multiforme</i>	535
<i>Dendritic cell therapy for brain tumors</i>	535
<i>Encapsulated cells for brain tumors</i>	536
<i>Engineered human NSCs for treatment of spinal cord gliomas</i>	536
<i>Immunotherapy of GBM targeting cancer stem cells</i>	537
<i>Mesenchymal stem cells for the treatment of gliomas</i>	537
<i>Neural stem cells for treatment of malignant brain tumors</i>	538
<i>Role of cancer stem cells in resistance to radiotherapy</i>	539
<i>Stem cell-based therapy targeting EGFR in GBM</i>	540
<i>Targeting stem cells in brain tumors</i>	540
<i>Clinical trials of cell therapy of glioblastoma multiforme</i>	540
Cell therapy for chemobrain.....	540
Cell therapy for muscle disorders.....	541
<i>Duchenne muscular dystrophy</i>	541
<i>Combination of cell and pharmacotherapy for DMD</i>	542
<i>Myoblast transplant for DMD</i>	542
<i>Myoblast-based gene transfer</i>	542
<i>Myoblasts lacking the MyoD gene</i>	543
<i>Myoblast injection for treatment of other muscular dystrophies</i>	543
<i>Role of satellite cells in the treatment of DMD</i>	544
<i>Stem cells for DMD</i>	544
<i>Wnt7a treatment for DMD</i>	546
Cell therapy for autism.....	546
Management of chronic intractable pain by cell therapy.....	546
<i>Implantation of chromaffin cells</i>	547
<i>Role of stem cells in management of pain</i>	547
<i>Implantation of astrocytes secreting enkephalin</i>	548
<i>Cells for delivery of antinociceptive molecules</i>	548
<i>Implantation of genetically engineered cells</i>	548
<i>Cell therapy for low back pain</i>	548
Cell therapy for neuropathic itch.....	549
Cell therapy for neuroendocrine disorders.....	549
<i>Pituitary stem cells</i>	549
Cell therapy for regenerating optic pathways.....	550
Cell therapy for retinal degenerative disorders.....	550
<i>Delivery of CNTF by encapsulated cell intraocular implants</i>	551
<i>Genetically engineered retinal pigmented epithelial cell lines</i>	551
Stem cell-based therapies for retinal degenerative disorders.....	551
<i>Adipose-derived stem cells for retinal degeneration</i>	552
<i>Adipose-derived stem cells transplantation for diabetic retinopathy</i>	552
<i>ESCs for retinal degenerative disorders</i>	552

<i>hESC-derived RPE cells for AMD</i>	552
<i>Human retinal stem cells</i>	553
<i>iPSCs for AMD</i>	554
<i>Neuroprotective effect of neural progenitor cell transplantation</i>	555
<i>Stem-cell based therapy for retinitis pigmentosa</i>	555
<i>Stem cell transplantation in the retina</i>	555
<i>Combining stem cell and gene therapies for retinal disorders</i>	556
Clinical trials of cell therapy for retinal degenerative disorders	556
Stem cell therapy for hearing loss	557
Cell therapy for peripheral nerve lesions.....	558
<i>Cell transplants for peripheral nerve injuries</i>	558
<i>Role of adipose-derived stem cells in peripheral nerve regeneration</i>	558
<i>Treatment of diabetic neuropathy with endothelial progenitor cells</i>	558
Complications of cell therapy of neurological disorders	559
Tumor formation after CNS transplantation of stem cells.....	559
<i>Donor stem cell-derived brain tumor</i>	559
<i>Glioproliferative lesion of spinal cord as a complication of cell therapy</i>	559
<i>Uncontrolled differentiation of implanted ESCs</i>	559
Tumorigenicity of ESC-derived retinal progenitor cells	560
Clinical trials of cell therapy in neurological disorders	560
Future of cell therapy of CNS disorders	562

8. Ethical, Legal and Political Aspects of Cell therapy 563

Introduction	563
Political and ethical aspects of hESC research in the US	563
Ethical issues concerning fetal tissues.....	564
<i>Morality and hESC research</i>	564
Opponents of hESC research in the US	564
<i>Use of hESCs in NIH-supported research</i>	566
<i>Politics of hESC research in the US</i>	566
<i>Public opinion in the US about hESC research</i>	568
<i>Human stem cell cloning in the US</i>	570
<i>Stem cell guidelines of various US institutions</i>	570
Ethics of transplanting human NSCs into the brains of nonhuman primates	571
Stem cell research around the world	572
ESC lines available worldwide	572
ESC policies around the world	573
Countries with no defined policies on hESC research	574
Australia	574
Canada.....	575
China	575
Denmark	576
France.....	576
Germany	577
India	578
Ireland	579
Israel	579
Italy.....	580
Japan	580
Russia	581
The Netherlands	581
Saudi Arabia.....	581
Singapore	582
South Africa	582
South Korea.....	583
Spain	583
Sweden	583
Switzerland	584
United Kingdom	584
<i>UK StemCellBank</i>	585
European Union	585
<i>EU guidelines for stem cell research</i>	586
<i>European stem cell bank</i>	587
<i>EMBO's recommendations for stem cell research</i>	588
Public opinion in Europe about hESC research.....	588
United Nations, cloning and nuclear transfer.....	589
The Embryo Project for information on ESC research	590
Concluding remarks about ethics of ESC research	590
Ethical issues concerning umbilical cord blood	590
Legal issues associated with stem cells	591
Stem cell patents	591

Stem cell patents in the United States	591
Current status of Thomson patents at WARF.....	591
Stem cell patents in the European Union.....	592
Cell therapy tourism	593

9. Safety and Regulatory Aspects of Cell Therapy	595
Introduction	595
Safety issues of cell therapy	595
Immune-mediated reactions to transplanted stem cells	595
Human virus infections associated with stem cell transplantation	596
<i>Herpes simplex virus type 1</i>	596
<i>Cytomegalovirus</i>	596
Opportunistic infections among hematopoietic stem cell transplant recipients	596
Cord colitis syndrome	596
Carcinogenic potential of stem cells and its prevention	597
Regulatory challenges for the clinical use of cell products.....	597
Prediction of in vivo performance of cell-based therapies	598
FDA safety regulations for cell and tissue products	598
FDA Guidance on license applications for umbilical cord blood products.....	599
Regulation of cord blood banks in the US	599
Regulatory issues for biotechnology-derived drugs	599
Regulation of products for adoptive cell therapy of cancer	600
Regulation of cell selection devices for PBSCs at point of care	600
FDA rules for human cells and tissues	601
FDA regulation of fetal cellular or tissue products.....	602
<i>FDA and ESC lines</i>	602
FDA and clinical trials using hESCs	602
Cell and gene therapy INDs placed on hold by the FDA.....	603
Regulatory issues for genetically engineered cell transplants	604
FDA guidelines for human tissue transplantation	604
FDA considers cultured stem cells for therapy as drugs.....	604
FDA perspective on safety-efficacy and risk-benefit of stem cell therapy	604
FDA action against unapproved cell therapy in the US	607
Xenotransplantation	608
Clinical Protocol Review and Oversight.....	608
Informed consent and patient education	608
Xenotransplantation product sources	609
FDA guidelines for xenografts.....	609
US regulations for manufacture of cell therapy products	611
<i>GMP in USA</i>	612
Regulations relevant to cell therapy in the European Union.....	612
Regulations about use of stem cells in the EU	614
Guidelines for cell therapy in the UK.....	614
Quality requirements for ex vivo-expanded MSC products for clinical use.....	614
European regulations for manufacture of cell therapy products	615
<i>GMP in Europe</i>	615
Global regulation of stem cell approval.....	615
Transport of stem cells between countries	616
Temperature limitations during transport of stem cells	616
NIH and stem cells.....	616
hESC lines approved under the new NIH guidelines	616
Clinical trials in cell therapy.....	617
Assessment of clinical trial registration and publication	617
Misuse of listing on ClinicalTrials.gov to provide unapproved stem cell therapy	618

Tables

Table 1-1: Landmarks in the history of cell therapy.....	31
Table 1-2: Examples of cells involved in various diseases	37
Table 2-1: Types of human cells used in cell therapy.....	41
Table 2-2: A selection of companies providing cell culture media	47
Table 2-3: A sampling of companies supplying cell sorters	53
Table 2-4: Companies involved in cell-based drug discovery	62
Table 2-5: Methods of delivery of cells for therapeutic purposes	64
Table 2-6: Therapeutic applications of encapsulated cells.....	71
Table 2-7: Companies working on encapsulated cell technology.....	72
Table 2-8: Molecular imaging methods for tracking cells in vivo.....	77
Table 3-1: Various levels of potency relevant to stem cells	86
Table 3-2: Clinical trials of UCB	113
Table 3-3: Companies involved in cord blood banking as a source of stem cells	116
Table 3-4: Comparison of techniques for nuclear reprogramming of stem cells	121
Table 3-5: Banks of patient-specific iPSC lines.....	127

Table 3-6: Companies providing iPSCs	127
Table 3-7: Sources of adult human stem cells	133
Table 3-8: Comparison of human stem cells according to derivation.....	144
Table 3-9: Enhancing engraftment, mobilization and expansion of stem cells	164
Table 3-10: Applications of stem cells	182
Table 3-11: Advantages and limitations of methods for optimizing MSCs	195
Table 3-12: Pharmaceutical manipulation of stem cells.....	202
Table 3-13: Growth factors with positive effects on stem cells and applications	203
Table 3-14: Examples of drugs that induce granulocytopenia at stem cell level.....	214
Table 3-15: Academic institutes involved in stem cell research	222
Table 3-16: Companies involved in stem cell technologies	224
Table 4-1: Therapeutic applications of regulatory T cells (Tregs).....	242
Table 4-2: Various tissue/cell therapy approaches to the treatment of type 1 diabetes	251
Table 4-3: Companies involved in cell therapy for insulin-dependent diabetes	268
Table 4-4: Major pulmonary disorders potentially treatable by stem cell manipulation	288
Table 4-5: Cell-based repair of knee cartilage damage	305
Table 4-6: Intraoperative cell therapy	339
Table 5-1: Classification of various types of cell therapy for cardiovascular disorders	344
Table 5-2: Clinical trials of cell therapy in cardiovascular disease	385
Table 6-1: Cell therapy technologies used for cancer	393
Table 6-2: Companies involved in developing cell-based therapies for cancer	439
Table 7-1: Studies in rats or mice of in vivo reprogramming of cells for brain repair.....	447
Table 7-2: NSCs-based approaches for neurological disorders.	461
Table 7-3: Experimental use of immortalized cells for CNS disorders	465
Table 7-4: Combination of stem cells and HBO in models of neurological disorders	471
Table 7-5: Therapeutic applications of MSCs for neurological disorders	472
Table 7-6: Methods for delivering cell therapies in CNS disorders.....	475
Table 7-7: Neurological disorders amenable to cell therapy	478
Table 7-8: Types of cell used for investigative treatment of Parkinson's disease	483
Table 7-9: Status of cell therapies for Parkinson's disease	484
Table 7-10: Role of cell therapy in management of stroke according to stage	513
Table 7-11: Clinical trials of cell therapy for stroke: completed, ongoing and pending	514
Table 7-12: Clinical trials of cell therapy for retinal degenerative disorders	556
Table 7-13: Clinical trials with cell therapy in neurological disorders (excluding stroke)	560
Table 8-1: Listed numbers of ESC lines around the world.....	573
Table 8-2: Stem cell policies around the world	573
Table 8-3: European public attitudes about research involving human stem cells	589
Table 9-1: Possible adverse reactions and safety issues of cell therapy.....	595

Figures

Figure 1-1: Interrelationships of cell therapy to other technologies	34
Figure 1-2: Interrelationships of gene, cell and protein therapies.....	35
Figure 1-3: Engineering of RBCs for drug delivery	39
Figure 3-1: A simplified biological scheme of embryonic stem Cells	86
Figure 3-2: Steps of iPSC cell production	122
Figure 3-3: hESC-derived by somatic cell nuclear transfer	161
Figure 3-4: Approaches for optimizing preparation of HSCs for transplantation	184
Figure 3-5: Flow chart of development of stem cells with potential bottlenecks.....	229
Figure 4-1: Reprogramming ESCs/iPSCs cells to β -cells for type 1 diabetes	263
Figure 4-2: Fluorescently labeled polarized Upcyte® hepatocytes	272
Figure 5-1: Ex vivo vs in vivo approaches to regeneration of the heart	344
Figure 5-2: hESC-derived cardiomyocytes from laboratory to bedside	359
Figure 5-3: Steps in growing a new heart in vitro for transplantation.....	381
Figure 6-1: A scheme of generation and administration of tumor antigen-pulsed dendritic cells	403
Figure 6-2: Chimeric antigen receptor (CAR)-T cells attacking tumor cells.....	410
Figure 6-3: Stem cell transplantation techniques	418
Figure 7-1: Cell-based methods for repair of the brain.....	444
Figure 7-2: Reprogramming methods for in vivo generation of neurons.	445
Figure 7-3: Stem cells that can give rise to neurons.....	455
Figure 7-4: Sources of dopaminergic neurons for transplantation in Parkinson's disease	484
Figure 7-5: Scheme of iPSCs for personalized cell therapy of Parkinson disease.....	493
Figure 7-6: Potential mechanisms of stem cell efficacy in ALS	498
Figure 7-7: Approaches to stem cell therapy in stroke	509
Figure 8-1: Global stem cell research publications 2013-2017	572