

Stem Cell-Based Therapeutic Delivery: Challenges & Opportunities

This cutting edge & insightful report can be used to interpret & assess the potential of stem cell-based medicines. It provides opinions & market projections to:

- assess the commercial potential of stem cell-based therapies in all of the key therapeutic areas: autoimmune diseases, cardiovascular, CNS & hematological malignancies;
- identify key pharma & delivery specialists advancing the next generation of regenerative medicines;
- gain an in-depth understanding of the technological manufacturing & delivery issues which face companies developing stem cell-based therapies;
- evaluate the options available for delivering stem cell-based therapies now & in the future;
- discover which companies are tackling the technological hurdles & are in a prime position to exploit new opportunities;
- analyzes how the market will evolve over the next decade highlighting key trends, opportunities & challenges.



Providing Independent, tailor-made, pharmaceutical thematic research

PharmaVision.co.uk

KEY FINDINGS:

- Stem cells have grabbed the attention of scientists across the globe and the pace of research has been astonishing. It is just 10 years since the first human embryonic stem cells (hESCs) were isolated and cultured; new therapies based on this research are now reaching the clinical phase of testing.
- Many challenges have faced those aiming to develop therapies derived from stem cells including: ethical debates and funding, immune rejection, cancerous potential and issues surrounding the manufacture of stable, pure cell therapeutics.
- It is evidence of the growing maturity of the field that many potential products have overcome these hurdles and have entered clinical testing.
- Our research has revealed a total of 122 stem cell-derived therapeutic projects being undertaken in companies across the globe. The majority of these projects are in the earliest stages (28%) or in preclinical studies (43%). Of the projects that have

reached clinical trials, only a handful have passed initial Phase 1/2 testing, with a total of eight (7%) being investigated in Phase 3 studies.

- The market for stem cell therapeutics is forecast to grow from 2011, as the first products enter the marketplace, and is expected to generate global sales in excess of US\$1.2 billion by 2015.
- Autologous products, derived from a patient's own tissue, will be the first to reach the market, but 'off-the-shelf' allogeneic products may offer greater commercial potential. The first allogeneic product to achieve approval is likely to be Osiris Therapeutics' Prochymal for graft versus host disease.
- Delivery of stem cell-based therapeutics can be challenging. Osiris' Prochymal is unique among those reviewed, as it is delivered intravenously, offering obvious commercial advantages. Other therapies are being delivered directly to the site of injury, involving state-of-the-art catheters and imaging systems. The delivery of stem cells for CNS disorders remains a challenging area.

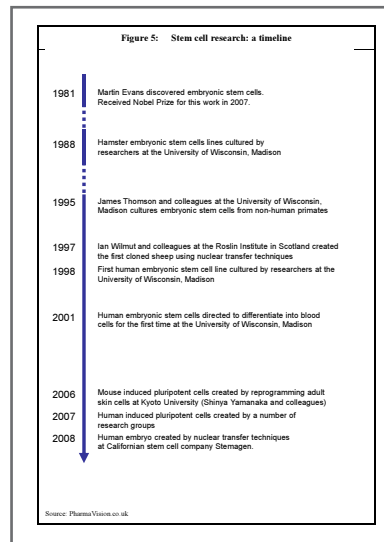
Introduction

“Stem cell-derived therapeutics are on the brink of a new era, with a handful of therapies expected on the market within the next 2 or 3 years. Big pharma and biotech companies such as Pfizer and Genzyme have recently invested large sums in this exciting and fast-moving area, further demonstrating its growing maturity. The results of numerous Phase 1/2 clinical trials that are underway now will provide a clearer picture of the potential of stem cell-derived therapies for the future.”

Dr Sara Sleigh

The pace of stem cell research is astonishing. It is less than 30 years since the discovery of the embryonic stem cell, and less than a decade since scientists determined the right conditions under which human embryonic stem cells (hESCs) could be directed to differentiate into a variety of cell types. Within the last few years, companies have built up sufficient data to support applications to start human clinical trials based on hESCs that have differentiated into oligodendrocytes for the treatment of spinal cord injury.

Embryonic stem cells are just part of the stem cell story. Adult stem cells, and those from other sources such as umbilical cord blood, have also been the subject of intense research over the past few years. While there has been a precedent for the use of bone marrow stem cells in the treatment of hematological malignancies, the development of new therapies based on cultured, expanded populations of specific cell



types opens up a vista of new possibilities.

Regenerative medicine has a wide definition covering therapies that aim to repair, replace, restore and regenerate damaged or diseased cells, tissues and organs. Innovative therapies derived from stem cells fall within this definition and will, in the coming years, provide options for the treatment of a variety of diseases including: autoimmune diseases such as diabetes, Crohn's disease and osteoarthritis, CNS disorders and neurodegenerative diseases, heart diseases, as well as eye diseases.

Stem cell therapies are already offered at various locations across the globe, including China and Thailand, despite a lack of robust, randomized clinical trials demonstrating their safety and

SAMPLE PAGES

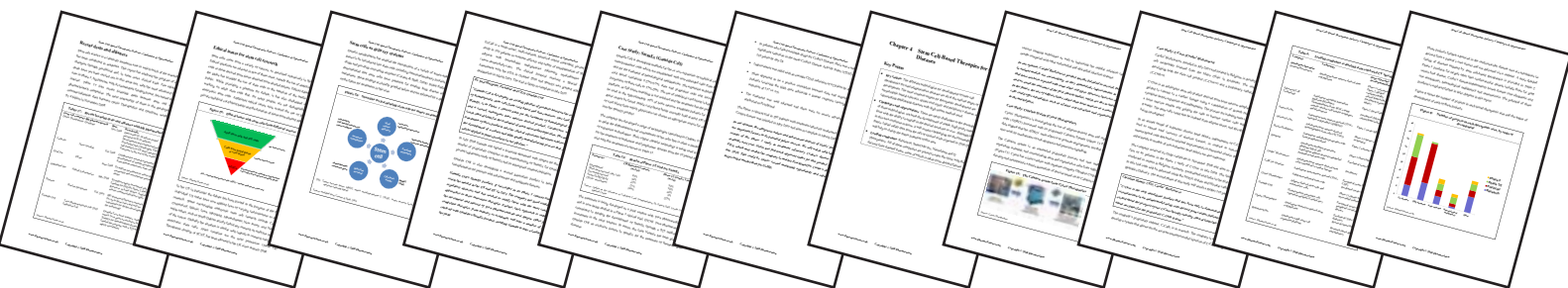
Table 1: Pros and cons of different stem cell types	
<p>Pros</p> <ul style="list-style-type: none"> Embryonic Ability to differentiate into any cell type. Wide range of potential therapeutic targets Capable of self-replication and hence scalable manufacturing processes 	<p>Cons</p> <ul style="list-style-type: none"> Ethical issues associated with their use in some places Immunogenicity not clear, although cells developed using SCNT from a patient's own DNA may not suffer from immune rejection Potential to form teratomas Robust manufacturing quality, cell line stability at scale and cost effectiveness issues
<p>Adult – autologous (skeletal muscle, adipose tissue, bone marrow, neural stem cells, peripheral blood)</p> <ul style="list-style-type: none"> No issues with immune rejection 	<ul style="list-style-type: none"> Time and cost to develop robust manufacturing processes high Logistical and costs implications of individualised therapy Some methods of stem cell harvesting are too invasive, particularly in very sick patients such as those chronic heart failure Not suitable for treatment of acute conditions, such as trauma or acute myocardial infarction, in which delay to treatment cannot be tolerated
<p>Adult – allogeneic (from bone marrow, adipose tissue or fetal tissue)</p> <ul style="list-style-type: none"> Dependent on cell type and source Off-the-shelf product for use in many patients Easier to develop robust, high quality manufacturing processes 	<ul style="list-style-type: none"> Ethical issues associated with the use of fetal tissue in some places
<p>Cord blood or placental derived stem cells</p> <ul style="list-style-type: none"> Fewer issues with immune rejection 	<ul style="list-style-type: none"> Ethical issues around public versus privately funded cord blood banks Quality of cord blood banking storage and preservation protocols
<p>SCNT: somatic cell nuclear transfer</p> <p>Induced pluripotent cells are not included due to early stage of research</p> <p>Source: PharmaVision.co.uk</p>	

The immunogenicity of different stem cell populations has been the source of some debate within the stem cell community in recent years. There is some evidence that ESCs are immunoprivileged, due to their involvement in fetal development and the need for the cells, containing maternal and paternal DNA, to avoid rejection. However, in recent months Joseph Wu and colleagues at Stanford University have published

efficacy. The fact that stem cell therapies are available in these locations and that patients' travel across the globe to receive them illustrates the high unmet medical need associated with some of the targets being investigated. Clinical evidence from high quality clinical trials is now imperative in order to protect these vulnerable patient populations.

The challenges facing companies developing stem cell-derived therapies are high and range from ethical discussions surrounding the use of hESCs to difficulties associated with manufacture of cell-based products at scale and proving that products lack the potential to cause an immune response or cancer in a recipient. Nevertheless a growing pool of companies is investing heavily to bring this rapidly moving science to the clinic.

SAMPLE PAGES FROM THE REPORT



EXPERTS FROM LEADING ORGANIZATIONS CONSULTED:

Christian Homsy, Chief Executive Officer, Cardio3 BioSciences

John Sinden, Founder and Chief Scientific Officer, ReNeuron

Kristin Comella, Associate VP Quality and R&D, Bioheart Inc

Lee Buckler, Principal, Cell Therapy Group

Michael Schuster, Vice President of Operations Director of Business Development and co-founder of Angioblast

Randal Mills, President and CEO, Osiris Therapeutics, Inc.

Tom Baker, Investor Relations, Cytori Therapeutics

William Prather, Senior VP Corporate Development, Pluristem Therapeutics

Yael Margolin, President & Chief Executive Officer, Gamida Cell Ltd

KEY QUESTIONS THIS REPORT ANSWERS:

- Which companies & academic institutes are actively involved in stem cell therapy research?
- What are the key areas of therapeutic focus for stem cell therapeutics in the near & long-term?
- What are the key obstacles companies & delivery technologists need to overcome to commercialize stem cell-derived therapies?
- How will the delivery technology drive the development of innovative stem cell-derived therapies in the future?
- Which stem cell technologies & agents are likely to win in the near-term & long-term, & why?
- Where are the market opportunities now & in the future?
- When are stem cell-derived medicines likely to reach the market?
- What do we predict will be the value of the stem-cell derived therapeutics by 2015 & 2020?

COMPANIES MENTIONED:

Astrom Biosciences, Advanced Cell technology, Aldagen, Amorce Inc, Angioblast, Arteriocyte Inc, AstraZeneca, Athersys, Baxter Healthcare, Beike Biotechnology, BioE, Bioheart, BrainStorm Cell Therapeutics, California Stem Cell Inc, Cardio3 BioSciences, CDI, Celegos, Celgene Cellular Therapeutics, Cell Cure Neurosciences, Cellartis, CellCyte Genetics, Cellerant Therapeutics, Cellerix, Cytori Therapeutics, EndGenitor Technologies Inc, Gamida Cell, Genzyme, Geron Corporation, GlaxoSmithKline, MaxCyte, MedCell, Neuralstem Inc, NeuroGeneration, Neuronyx, Northern Therapeutics, Novartis, Novo Nordisk, Novocell, Opexa Therapeutics, Osiris Therapeutics, Pfizer, Plureon, Pluristem Therapeutics Inc, Q Therapeutics Inc, Regenotech Inc, Reliance Life Sciences, ReNeuron, RhinoCyte, Roche, Saneron CCEL Therapeutics Inc, StemCells Inc, Stemedica, Stemnion, Teva Pharmaceuticals, Theradigm, TheraVita, Vesta Therapeutics, ViaCord

About the author:



Dr Sara Sleigh is a freelance writer and editor with experience in writing for and about the pharma industry. Sara graduated from the University of York in 1997 with a DPhil in protein structure and biochemistry. Her doctorate characterized protein-ligand interactions using x-ray crystallography and calorimetry.

Having completed her studies, Sara developed her skills as a writer and editor in the education department at the Royal Society of Chemistry. In 1999, Sara took up a post at Pfizer in which she wrote clear, concise documents to support drug regulatory submissions. These

documents included Clinical Expert Reports, summaries of drug safety and efficacy, and clinical study reports. Sara also worked extensively with clinical research teams to prepare presentations and responses to queries from regulatory authorities. She wrote about a variety of drugs in a range of therapeutic areas including anti-fungals and psychotherapeutics.

Sara has been developing her business as a freelance writer since 2003. She writes in a variety of styles and for different audiences and has prepared conference reports, journal publications and regulatory submissions documents for a variety of pharma companies. In 2005, Sara joined forces with PharmaVision to provide independent analysis of pharmaceutical technologies. She specializes in technologies for drug and biomarker discovery, drug delivery and personalized medicine.

purchase online NOW at www.pharmavision.co.uk

FUTURE TOPICS:

“Stem Cell-Based Therapeutic Delivery: Challenges & Opportunities” is the first in a new series of innovative technology-specific delivery reports. Each report provides in-depth scientific, technical and commercial analysis, opinion and market projections on delivery platforms and assesses the challenges and opportunities which face innovators in four rapidly advancing fields of research: stem cell-based therapies, biopharmaceuticals, RNAi-diagnostics & therapeutics, and diagnostics & imaging.

Forthcoming titles include:

- **January 2009 Delivering New Biopharmaceutical Therapies: Challenges & Opportunities**
Author: Paul Evers
- **February 2009 RNAi Diagnostics & Therapeutic Delivery: Challenges & Opportunities**
Author: Dr Cheryl L Barton
- **April 2009 Diagnostics & Imaging: Challenges & Opportunities**
Author: Dr Cheryl Barton

Previous Drug Delivery Technology report series include:

- **December 2007 Drug Delivery Technology: Revolutionizing CNS Treatment** Author: Ruth Ohlsen
- **November 2007 Drug Delivery Technology: Developing a New Generation of Vaccines** Author: Dr Sara Sleight
- **September 2007 Drug Delivery Technology: Revolutionizing Diabetes Treatment** Author: Paul Evers
- **July 2007 Drug Delivery Technology: Revolutionizing Cardiovascular Therapies** Author: Dr Cheryl L Barton
- **May 2007 Drug Delivery Technology: Revolutionizing Cancer Therapies** Author: Dr Cheryl L Barton

For more details see: <http://www.pharmavision.co.uk/papers14-drugdelivery.php>

PURCHASE THIS REPORT NOW

Stem Cell-Based Therapeutics Delivery: Challenges & Opportunities

PUBLICATION DATE: December 15th, 2008

NUMBER OF PAGES: 180+

FORMAT: PDF (download direct from web or order CD-ROM)

PRICE: £945 / \$1,400 (approx) / €1,080 (approx)

How to order:

1) Purchase securely online at: www.pharmavision.co.uk

OR

2) Place your order by telephone. Call PharmaVision on +44 (0) 1243 785 496

CONTACT

Justin Anwyl, Purchasing
T: +44 (0) 1243 785 496
E: info@pharmavision.co.uk

www.pharmavision.co.uk

Registered in England Number 4598078
VAT Registration Number 801 1969 47

Nurses Cottage
Post Office Lane
North Mundham
Chichester
West Sussex
PO20 1JY
United Kingdom

Providing independent, tailor-made, pharmaceutical thematic research

PharmaVision.co.uk

purchase online NOW at www.pharmavision.co.uk

Table of Contents

Key Findings	10
Stem Cells & Cell-Based Delivery.....	10
The Market for Stem Cell-Based Therapies.....	10
Stem Cell-Based Therapies for Cardiovascular Disease.....	11
Stem Cell-Based Therapies for CNS Disorders.....	11
Stem Cell Therapies for Diabetes.....	12
Stem Cell Therapies for Cancer.....	13
Stem Cell-Based Therapeutics: Challenges & Opportunities.....	13
Future of Stem Cell-Based Therapeutics & Market Trends.....	14
Chapter 1 Stem Cells & Cell-Based Delivery	16
Key Points.....	16
Introduction.....	17
An introduction to stem cell science.....	19
Embryonic stem cells.....	19
Adult stem cells.....	20
Creating pluripotent cells from adult tissue.....	21
Nuclear transfer/therapeutic cloning.....	22
Combining embryonic stem cell therapy with gene therapy.....	24
Stem cell therapy - a discovery timeline.....	25
Major scientific challenges for the development of stem cell therapies.....	27
Report structure.....	30
Chapter 2 Stem Cell-Based Therapies: Pipeline Analysis	33
Key Points.....	33
Key therapy areas covered by stem cell-based therapies.....	34
Product pipelines.....	34
Stem cells for drug discovery.....	39
Stem cell culture, expansion and manufacturing.....	40
Stem cell companies analysed in this report.....	40
Chapter 3 Stem Cell-Based Therapies for Cardiovascular Disease	43
Key Points.....	43
Introduction.....	44
Autologous cell platforms.....	49
Case Study: MyoCell (Bioheart Inc).....	50
Case Study: Myoblast (Advanced Cell Technology).....	54
Case study: CardioCure (Gamida Cell Ltd).....	56
Case Study: C-Cure (Cardio3 BioSciences).....	57
Case Study: Celution System (Cytori Therapeutics).....	59
Allogeneic cell platforms.....	61
Mesenchymal stem cell therapies.....	62
Case Study: Prochymal (Osiris Therapeutics).....	62
Case study: Revascor? (Angioblast Systems Inc).....	65
Case study: PLX-PAD (Pluristem Therapeutics Inc).....	67
Human embryonic stem cell therapies.....	69
Case Study: ACT Cellerate (Advanced Cell Technology).....	69
Cell delivery technologies.....	72
Our opinion on stem cell-derived therapies for CV diseases.....	75
Where the technology is now, its evolution, achievements and pitfalls.....	75
Competition.....	75
Potential future applications.....	76
Activity in the market.....	76
Major players.....	77
Winners.....	77
Chapter 4 Stem Cell-Based Therapies for CNS Diseases	80
Points.....	80
Introduction.....	81
Autologous cell platforms.....	85
Case Study: NurOwn (BrainStorm Cell Therapeutics Inc).....	86
Case study: NeuroGeneration.....	87
Allogeneic cell platforms.....	88
Stem cells from donated tissue.....	89
Case Study: HuCNS-SC® (StemCells Inc).....	89
Case Study: ReNeuron.....	91
Case Study: Neuralstem.....	94
Case study: Q-cells (Q Therapeutics Inc).....	95
Case study: StemedicaMCT (Stemedica USA and Stemedica International).....	96
Stem cells from umbilical cord blood.....	97
Case study: Beike Biotechnology.....	97
Human embryonic stem cells.....	98
Case Study: GRNOPC1 (Geron).....	98
Case study: hESCs from California Stem Cell Inc.....	101
Cell delivery technologies.....	102
Our opinion on stem cell-based therapies for CNS diseases.....	104
Where the technology is now, its evolution, achievements and pitfalls.....	104
Competition.....	104
Potential future applications.....	104
Activity in the market.....	105

Contents Cont'd

Chapter 5	Stem Cell-Based Therapies for Autoimmune, Inflammatory & Other conditions.....	107
Key Points.....		107
Introduction.....		108
Crohn's disease.....		112
Case study: Prochymal for Crohn's disease (Osiris).....		112
Case Study: Ontaril (Cellerix).....		113
Diabetes.....		115
Autologous stem cell transplants for diabetes.....		116
Allogeneic stem cell transplants for diabetes.....		117
Osteoarthritis.....		121
Lung diseases.....		122
Chronic obstructive pulmonary disease.....		122
Pulmonary arterial hypertension.....		122
Our opinion on stem cell-based therapies for autoimmune and other diseases.....		124
Where the technology is now, its evolution, achievements and pitfalls.....		124
Competition.....		124
Potential future applications.....		124
Major players and winners.....		125
Chapter 6	Stem Cell-Based Therapies for Graft versus Host Disease, Hematological Malignancies and Cancer.....	127
Key Points.....		127
Introduction.....		128
Cancer stem cells.....		128
Stem cells as a delivery vehicle.....		129
Graft versus host disease.....		132
Expanded umbilical cord blood transplants for malignant diseases.....		135
Case Study: StemEx (Gamida Cell).....		137
Stem cells as delivery systems.....		139
Lung cancer.....		140
Metastatic cancer and intracranial tumors.....		140
Hematological malignancy.....		142
Multi-lineage progenitor cells (BioE).....		142
Conclusion.....		143
Our opinion on stem cell-derived therapies for GvHD, hematological malignancies and cancer.....		144
Where the technology is now, its evolution, achievements and pitfalls.....		144
Competition.....		144
Potential future applications.....		145
Activity in the market, major players and winners.....		145
Chapter 7	Challenges & Opportunities for Stem Cell-Based Therapies.....	147
Key Points.....		147
Introduction.....		148
Ethical issues for stem cell research.....		149
Funding stem cell research.....		150
Intellectual property.....		155
Manufacturing stem cell-based products.....		156
Regulation.....		157
Reimbursement.....		159
Delivering stem cell-based therapies and tissue engineering.....		159
Challenges.....		159
Opportunities.....		160
Chapter 8	Market size, Evolution & Prospects.....	162
Key Points.....		162
Key stem cell therapy companies.....		163
Recent deals and alliances.....		168
The global stem cell market 2008-2014.....		170
Analysis parameters.....		170
Market forecast 2008-2014.....		175
Global stem cell-based therapy market in 2020.....		176
Drivers and market trends.....		176
Summary & Conclusions.....		178
Acknowledgements.....		180
Bibliography & Endnotes.....		181

List of Figures

Figure 1:	Source of embryonic stem cells: the blastocyst.....	19
Figure 2:	Differentiation of embryonic stem cells.....	20
Figure 3:	Somatic cell nuclear transfer.....	23
Figure 4:	Combining gene therapy and cell therapy for sickle cell anaemia in a mouse model.....	25
Figure 5:	Stem cell research: a timeline.....	26
Figure 6:	Stem cell therapeutics: defining therapeutic areas.....	34
Figure 7:	Number of projects in the different stages of pharmaceutical development.....	35
Figure 8:	Number of projects in each therapeutic area, by stage of development.....	36
Figure 9:	Proportions of autologous and allogeneic technology platforms.....	38
Figure 10:	Stem cell sources (embryonic, adult or cord blood/placenta).....	39
Figure 11:	MyoCell: Heart failure treatment process.....	51
Figure 12:	Advanced Cell Technologies Myoblast Phase 1 programme; Results.....	55
Figure 13:	The Celution system from Cytori Therapeutics.....	59
Figure 14:	Preclinical data demonstrating the effects of Prochymal therapy on the heart.....	63
Figure 15:	PLX cells growing in Pluristem's PluriX™ bioreactor.....	67
Figure 16:	ACTCellerate Technology.....	71
Figure 17:	Schematic of cell-based therapy administration to the myocardium.....	73
Figure 18:	Cells affected by different CNS diseases/disorders.....	82
Figure 19:	NeuroGeneration's Parkinson's disease therapy.....	87
Figure 20:	StemCells Inc technology platform.....	89
Figure 21:	ReNeuron's process for generating therapeutic cells.....	92
Figure 22:	Stemedica's established cell lines.....	97
Figure 23:	Results of animal studies with Geron's oligodendroglial progenitor cells derived from human ESCs.....	100
Figure 24:	Stem cell sources under investigation to treat type 1 diabetes.....	116
Figure 25:	Stem cells applications in cancer and other malignant diseases.....	128
Figure 26:	Strategies for potentiating stem cells for tumor treatment.....	139
Figure 28:	Challenges and opportunities for stem cell science.....	148
Figure 29:	Ethical issues with stem cells from different sources.....	149
Figure 30:	Federal funding of embryonic stem cell research in the US: a timeline.....	152
Figure 31:	US patent ownership in the stem cell field.....	155
Figure 32:	Stem cell-based therapeutics: market drivers.....	177

List of Tables

Table 1:	Pros and cons of different stem cell types.....	29
Table 2:	Diseases targeted by stem cell-based therapeutics.....	37
Table 3:	Stem cell therapy companies discussed in this report.....	41
Table 4:	Leading companies evaluating stem cell-based CV therapies.....	46
Table 5:	Leading academic institutions researching the use of stem cells to treat CV diseases.....	48
Table 6:	Leading companies evaluating stem cell-based therapies for CNS diseases.....	83
Table 7:	Leading institutes evaluating stem cell-based therapies for CNS diseases.....	85
Table 8:	Geron's stem cell-based product pipeline.....	99
Table 9:	Leading companies evaluating stem cell therapies for autoimmune and other diseases.....	109
Table 10:	Leading academic institutes evaluating stem cell therapies for autoimmune and other diseases.....	111
Table 11:	Leading companies evaluating stem cell therapies for GvHD and hematological malignancies.....	130
Table 12:	Academic institutions with an interest in GvHD, hematological malignancies and cancer.....	131
Table 13:	Other clinical trials of mesenchymal stem cells for the prevention or treatment of GVHD.....	133
Table 14:	Results of Phase 1/2 trial for StemEx.....	137
Table 15:	Global positions on research on embryonic stem cells derived from IVF procedures.....	150
Table 16:	Current funds available from individual US states for embryonic and adult stem cell research.....	153
Table 17:	Summary of leading stem cell-based therapeutics companies.....	163
Table 18:	Recent licensing deals and alliances with big pharma/biotech.....	168
Table 19:	Stem cell-based therapies included in the market forecast.....	173
Table 20:	Forecast of pipeline stem cell therapy products 2008-2014 (US\$m).....	175
Table 21:	Forecast of pipeline stem cell therapy products 2015-2020 (US\$m).....	176