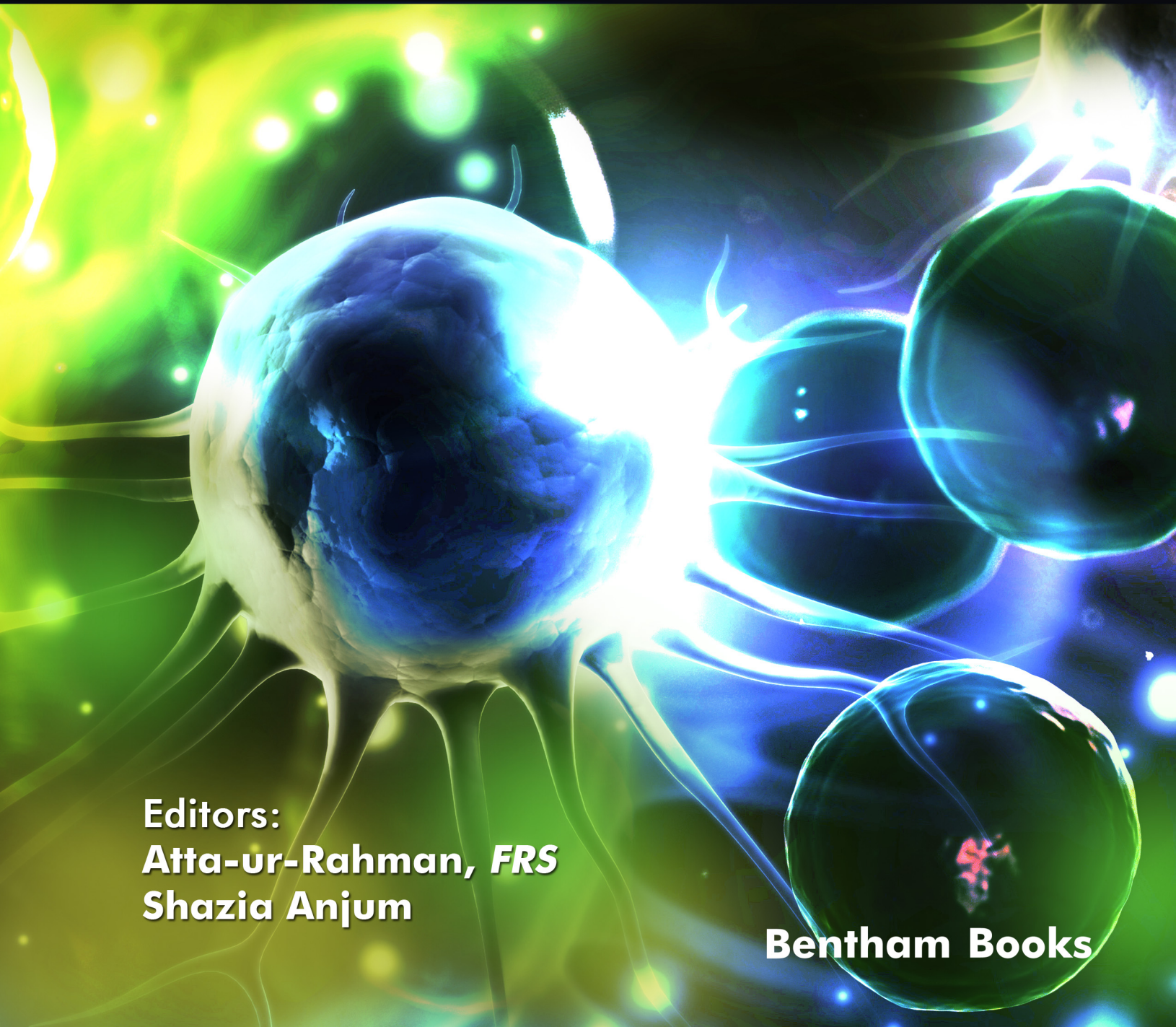


# Frontiers in Stem Cell and Regenerative Medicine Research

Editors:  
**Atta-ur-Rahman, *FRS***  
**Shazia Anjum**

**Bentham Books**



**Frontiers in Stem Cell and  
Regenerative Medicine Research**  
*(Volume 9)*

**Edited by**

**Atta-ur-Rahman.*HTU***

*Kings College, University of Cambridge, Cambridge, UK*

**&**

**Shazia Anjum**

*Department of Chemistry, Cholistan Institute of Desert Studies,  
The Islamia University of Bahawalpur, Bahawalpur, Pakistan*

# **Ht qpvlet ulp'Uvgo 'Egnlcpf 'Tgi gpgt cv&g'O gf lekg'Tgugct ej**

*Volume # 9*

Editors: Prof. Atta-ur-Rahman, *FRS* and Dr. Shazia Anjum

ISSN (Online): 2352-7633

ISSN (Print): 2467-9593

ISBN (Online): 978-1-68108-762-7

ISBN (Print): 978-1-68108-763-4

©2020, Bentham eBooks imprint.

Published by Bentham Science Publishers Pte. Ltd. Singapore. All Rights Reserved.

## **BENTHAM SCIENCE PUBLISHERS LTD.**

### **End User License Agreement (for non-institutional, personal use)**

This is an agreement between you and Bentham Science Publishers Ltd. Please read this License Agreement carefully before using the book/echapter/ejournal (“**Work**”). Your use of the Work constitutes your agreement to the terms and conditions set forth in this License Agreement. If you do not agree to these terms and conditions then you should not use the Work.

Bentham Science Publishers agrees to grant you a non-exclusive, non-transferable limited license to use the Work subject to and in accordance with the following terms and conditions. This License Agreement is for non-library, personal use only. For a library / institutional / multi user license in respect of the Work, please contact: [permission@benthamscience.net](mailto:permission@benthamscience.net).

### **Usage Rules:**

1. All rights reserved: The Work is the subject of copyright and Bentham Science Publishers either owns the Work (and the copyright in it) or is licensed to distribute the Work. You shall not copy, reproduce, modify, remove, delete, augment, add to, publish, transmit, sell, resell, create derivative works from, or in any way exploit the Work or make the Work available for others to do any of the same, in any form or by any means, in whole or in part, in each case without the prior written permission of Bentham Science Publishers, unless stated otherwise in this License Agreement.
2. You may download a copy of the Work on one occasion to one personal computer (including tablet, laptop, desktop, or other such devices). You may make one back-up copy of the Work to avoid losing it.
3. The unauthorised use or distribution of copyrighted or other proprietary content is illegal and could subject you to liability for substantial money damages. You will be liable for any damage resulting from your misuse of the Work or any violation of this License Agreement, including any infringement by you of copyrights or proprietary rights.

### ***Disclaimer:***

Bentham Science Publishers does not guarantee that the information in the Work is error-free, or warrant that it will meet your requirements or that access to the Work will be uninterrupted or error-free. The Work is provided "as is" without warranty of any kind, either express or implied or statutory, including, without limitation, implied warranties of merchantability and fitness for a particular purpose. The entire risk as to the results and performance of the Work is assumed by you. No responsibility is assumed by Bentham Science Publishers, its staff, editors and/or authors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products instruction, advertisements or ideas contained in the Work.

### ***Limitation of Liability:***

In no event will Bentham Science Publishers, its staff, editors and/or authors, be liable for any damages, including, without limitation, special, incidental and/or consequential damages and/or damages for lost data and/or profits arising out of (whether directly or indirectly) the use or inability to use the Work. The entire liability of Bentham Science Publishers shall be limited to the amount actually paid by you for the Work.

### **General:**

1. Any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims) will be governed by and construed in accordance with the laws of Singapore. Each party agrees that the courts of the state of Singapore shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims).
2. Your rights under this License Agreement will automatically terminate without notice and without the

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

**Bentham Science Publishers Pte. Ltd.**

80 Robinson Road #02-00

Singapore 068898

Singapore

Email: [subscriptions@benthamscience.net](mailto:subscriptions@benthamscience.net)



## CONTENTS

PREFACE .....	i
LIST OF CONTRIBUTORS .....	ii
<b>CHAPTER 1 INSIGHTS INTO EXOGENOUS, ENDOGENOUS AND COMBINATION THERAPIES OF NEURAL STEM CELLS IN SPINAL CORD INJURY</b> .....	1
<i>Hunaid Hasan and Ping Wu</i>	
<b>INTRODUCTION</b> .....	2
<b>SPINAL CORD INJURY</b> .....	2
Epidemiology .....	2
Pathophysiology .....	3
<i>Primary Phase</i> .....	3
<i>Secondary Phase</i> .....	3
<b>CLINICAL MANAGEMENT</b> .....	6
Surgical .....	6
Medical .....	6
<i>Supportive</i> .....	6
<i>Pharmacotherapy</i> .....	7
<i>Exercise Rehabilitation</i> .....	7
<b>STEM CELL BASED TREATMENT FOR SCI</b> .....	7
Exogenous Transplantation Methods for SCI .....	8
<i>Stem Cells</i> .....	8
<i>Bone Marrow Stem Cells</i> .....	8
Mesenchymal Stem Cells .....	8
<i>Embryonic Stem Cells</i> .....	9
<i>Umbilical Cord Stem Cells</i> .....	10
<i>Adipose Derived Stem Cells</i> .....	10
<i>Neural Stem Cells</i> .....	10
<i>Other Cell Types for Transplantation</i> .....	12
<i>Schwann Cells Grafts</i> .....	12
<i>Olfactory Ensheathing Cells</i> .....	12
Endogenous Stem Cells for SCI .....	14
<i>Advantages of Endogenous versus Exogenous Stem cells</i> .....	14
<i>Areas of Neurogenesis in Spinal Cord</i> .....	14
<i>Histology of the Central Spinal Cord</i> .....	15
<i>Forms of Stem Cells in the Spinal Cord</i> .....	15
<i>Environmental Support for Stem Cells</i> .....	16
<i>Implications of Spinal Cord Injury and its Effects on Regeneration</i> .....	17
<i>Glial Scar Debate</i> .....	18
<i>Hub Gene Network Analysis</i> .....	19
<i>Purinergic Receptors</i> .....	19
Genetic Fate Mapping .....	21
<i>Types of Labelling Techniques</i> .....	21
<i>Cell Structure Markers</i> .....	21
<i>Tamoxifen-Dependent Cre System</i> .....	22
<i>Ependymal Cells, Oligodendrocytes, Astrocytes</i> .....	23
<i>Oligodendrocytes</i> .....	23
<i>Astrocytes</i> .....	24
<b>STEM CELL TRANSPLANTATION</b> .....	24
Methods for Transplantation .....	24

Mechanism, Benefits and Adverse Effects .....	24
Clinical Trials .....	25
Clinical Results and Outcomes .....	25
<i>Benefit in the Acute Setting</i> .....	25
<i>Motor Evoked Potentials</i> .....	34
<i>Effects on Muscle Tone</i> .....	34
<i>Effects on Sphincteric Tone</i> .....	34
<i>Summary of Findings</i> .....	35
<b>FACTORS INFLUENCING THE EFFICACY OF STEM CELL TRANSPLANTATION</b> ...	35
Combination Therapies .....	35
Cytokines .....	37
Neurovascular Niche .....	39
Growth Factors .....	39
<i>Vascular Endothelial Growth Factor</i> .....	39
<i>Ephrins</i> .....	40
<i>Fibroblast Growth Factor-2</i> .....	40
<i>Adrenomedullin</i> .....	40
<i>Endothelial Growth Factor</i> .....	41
<i>Angiopoietin</i> .....	42
Transcription Factors .....	42
Electrical Stimulation .....	42
<b>CONCLUSION</b> .....	43
<b>CONSENT FOR PUBLICATION</b> .....	44
<b>CONFLICT OF INTEREST</b> .....	44
<b>ACKNOWLEDGEMENTS</b> .....	44
<b>REFERENCES</b> .....	44

<b>CHAPTER 2 TOWARD INDUCED PLURIPOTENT STEM CELLS FOR CLINICAL USE:</b>	
<b>SOURCES, METHODS AND SELECTION</b> .....	76
<i>Maria P De Miguel, Adrian Moratilla, Alba Cabrera-Fisac and P Gonzalez-Molina</i>	
<b>INTRODUCTION TO INDUCED PLURIPOTENT STEM CELLS</b> .....	76
<b>SOURCES</b> .....	77
In the Beginning: Mouse Embryonic Fibroblasts .....	77
Human Fetal and Neonatal Cells .....	78
<i>Human Neonatal Fibroblasts</i> .....	78
<i>Fetal Stem Cells</i> .....	78
<i>Human Umbilical Cord Endothelial Cells</i> .....	78
Adult Human Cells .....	79
How to Choose the Cell Source .....	80
<b>METHODS</b> .....	81
Viral Methods .....	82
<i>Integrative</i> .....	82
<i>Non-Integrative Viruses</i> .....	83
<i>Transgene Excision</i> .....	83
Nonviral Methods .....	84
<i>Nucleic Acids</i> .....	85
<i>Nucleic Acid-Free</i> .....	85
Various Gene Combinations .....	86
<i>Additional Factors/Epigenetic Modulators</i> .....	87
Epigenetic Modulators .....	87
Culture Conditions .....	88
<i>Various Substrates: MEFs Versus Vitronectin, Matrigel and Others</i> .....	89

<i>Various Media and Supplements</i> .....	89
How to Choose the Reprogramming Method .....	90
<b>SELECTION</b> .....	92
Completely <i>Versus</i> Partially Reprogrammed Cells .....	92
Differentiation into Several Cell Types .....	94
How to Remove Pluripotent Cells In a Differentiated Culture .....	95
How to Prevent Mutations and How to Select for Unmutated Cells .....	96
Clinical Uses: Regenerative Medicine, Disease Modeling, Drug Testing .....	97
Quality Control .....	101
<b>CONCLUSIONS AND FUTURE PERSPECTIVES</b> .....	102
<b>CONSENT FOR PUBLICATION</b> .....	103
<b>CONFLICT OF INTEREST</b> .....	103
<b>ACKNOWLEDGEMENTS</b> .....	103
<b>REFERENCES</b> .....	103
<b>CHAPTER 3 REPROGRAMMING OF ADIPOSE-DERIVED STEM CELLS TO NEURONAL-LINEAGE CELLS IS REGULATED BY BOTH CELL SIGNALLING AND REDOX STATUS</b> .....	114
<i>Sajan George, Anine Crous and Heidi Abrahamse</i>	
<b>INTRODUCTION</b> .....	114
<b>NERVOUS SYSTEM</b> .....	115
Development and Distinction of Neuronal-Lineage Cells .....	115
Anatomy of Central and Peripheral Nervous Systems .....	115
Diseases and Disorders of the Nervous System .....	116
<b>STEM CELLS</b> .....	117
Advantages of Using Mesenchymal Stem Cells (MSCs) .....	117
ASCs for Replacement Therapy .....	118
ASCs for Neuroglial Trans-differentiation .....	119
<b>CELL SIGNALLING</b> .....	120
Cell Signalling for Neuronal Differentiation .....	120
Differentiation of Neurotransmitter Release Neurons .....	122
Epigenetic Changes in Neuronal Differentiation .....	123
<b>CELL MARKERS</b> .....	124
Temporal Changes During Differentiation of Neurons .....	124
Markers on Neurotransmitter Release Neurons .....	126
Changes in Surface Markers of Differentiating Glia .....	127
<b>REDOX STATUS</b> .....	127
<b>PHOTOBIMODULATION</b> .....	129
<b>PRESPECTIVES</b> .....	131
<b>CONCLUSION</b> .....	134
<b>CONSENT FOR PUBLICATION</b> .....	134
<b>CONFLICT OF INTEREST</b> .....	134
<b>ACKNOWLEDGEMENTS</b> .....	134
<b>REFERENCES</b> .....	135
<b>CHAPTER 4 ADVANCES IN SKIN REGENERATION AND RECONSTRUCTION</b> .....	143
<i>Ana-Maria Rosca, Raluca Tutuianu and Irina Titorencu</i>	
<b>INTRODUCTION</b> .....	143
<b>SKIN BIOLOGY</b> .....	144
<b>THE WOUND HEALING PROCESS</b> .....	150
<b>MICRO-RNAS AND WOUND HEALING</b> .....	155
MiR-21 .....	156



MiR-31 .....	156
MiR-203 .....	157
MiR-210 .....	157
MiR-377 .....	158
MiRNAs Delivery Approaches for Skin Therapy .....	158
<b>CELLULAR THERAPY FOR SKIN REGENERATION .....</b>	<b>160</b>
Resident Skin Stem Cells .....	160
Epidermal Basal Layer Stem Cells .....	161
Stem Cells Residing in the Hair Follicle Bulge .....	162
Keratinocytes .....	162
Fibroblasts .....	163
Mesenchymal Stem Cells .....	164
Hematopoietic Stem Cells .....	165
Induced Pluripotent Stem Cells .....	165
<b>SKIN SUBSTITUTES .....</b>	<b>167</b>
<b>CONCLUDING REMARKS .....</b>	<b>173</b>
<b>CONSENT FOR PUBLICATION .....</b>	<b>174</b>
<b>CONFLICT OF INTEREST .....</b>	<b>174</b>
<b>ACKNOWLEDGEMENTS .....</b>	<b>174</b>
<b>REFERENCES .....</b>	<b>174</b>
<b>CHAPTER 5 MIRNA MEDIATED STEM CELL THERAPY FOR CARDIAC ARRHYTHMIA .....</b>	<b>188</b>
<i>Priyadarshan Kathirvelu, Bhuvaneshwari Sampath and Kavitha Sankaranarayanan</i>	
<b>INTRODUCTION .....</b>	<b>188</b>
<b>CARDIAC CHANNELOPATHIES AND ARRHYTHMIA .....</b>	<b>190</b>
<b>STEM CELL THERAPY FOR CARDIAC ARRHYTHMIAS .....</b>	<b>191</b>
<b>MIRNA-BIOGENESIS AND FUNCTION .....</b>	<b>194</b>
<b>MICRORNA REGULATION OF CARDIAC ION CHANNEL GENES .....</b>	<b>195</b>
<b>THERAPEUTIC POTENTIAL OF MIRNA IN CARDIAC ARRHYTHMIAS .....</b>	<b>196</b>
<b>COMPUTATIONAL PREDICTION OF MIRNA TARGETS OF ION CHANNELS .....</b>	<b>198</b>
<b>MIRNA MEDIATED STEM CELL THERAPY- DELIVERY TOOLS FOR MIRNAS .....</b>	<b>205</b>
<b>CONCLUSION .....</b>	<b>208</b>
<b>CONSENT FOR PUBLICATION .....</b>	<b>209</b>
<b>CONFLICT OF INTEREST .....</b>	<b>209</b>
<b>ACKNOWLEDGEMENTS .....</b>	<b>209</b>
<b>REFERENCES .....</b>	<b>209</b>
<b>CHAPTER 6 MALARIA TREATMENT AND STEM CELLS .....</b>	<b>220</b>
<i>Norma Rivera, Marcela Rojas-Lemus, Nancy G. Flores-Jiménez and Teresa I. Fortoul</i>	
<b>INTRODUCTION .....</b>	<b>220</b>
The Use of Stem Cell Therapy in Malaria .....	224
The Effect of Malaria Infection on Neurogenesis .....	225
<b>CONCLUDING REMARKS .....</b>	<b>228</b>
<b>CONSENT FOR PUBLICATION .....</b>	<b>228</b>
<b>CONFLICT OF INTEREST .....</b>	<b>228</b>
<b>ACKNOWLEDGEMENTS .....</b>	<b>229</b>
<b>REFERENCES .....</b>	<b>229</b>
<b>SUBJECT INDEX .....</b>	<b>233</b>

## PREFACE

The ninth volume of ‘Frontiers in Stem Cell and Regenerative Medicine Research’ presents important recent developments in this fast growing field.

Hasan and Wu review the current literature on the utility of exogenous and endogenous neural stem cells in spinal cord injury. Miguel *et al.* focus on the various sources of somatic cells for human induced pluripotent stem cells (iPSC) generation, their characterization, and the progress on directed differentiation toward several cell types.

Cell signaling and redox reactions are involved in the regulation of neural-lineage cells for reprogramming of adipose-derived stem cells. Abrahamse *et al.* discuss the role of reactive oxygen species (ROS) and ROS mediated cellular signaling for differentiation of stem cells.

The human skin represents the largest and most accessible part of the body that is exposed to infections, physical wounds, diseases *etc.* Titorencu *et al.* describe commercially available skin substitutes that are in demand and also described the use of stem cells for skin regeneration. Recently, the role of microRNA in cardiac conduction diseases, arrhythmogenesis and their therapeutic potential has caught the attention of researchers. Sankaranarayanan *et al.* have reviewed the role of miRNAs in cardiac rhythmic disorders and their potential in diagnosis and treatment. Finally, Rivera *et al.* discuss the use of stem cell therapy in the treatment of malaria.

We owe our special thanks to all the contributors for their valuable contribution in bringing together the ninth volume of this book series. We also thank the editorial staff of Bentham Science Publishers for their help and support.

**Atta-ur-Rahman, FRS**  
Kings College,  
University of Cambridge,  
Cambridge,  
UK

**Shazia Anjum**  
Department of Chemistry,  
The Islamia University of Bahawalpur,  
Pakistan

## List of Contributors

<b>Hunaid Hasan</b>	Department of Neurology – Clinical Neurophysiology, NYU Langone Medical Center 301 E. 17 <sup>th</sup> Street, Suite 1534, New York, 10003, USA
<b>Ping Wu</b>	Department of Neuroscience and Cell Biology, University of Texas Medical Branch 4.212B Research Building 17 Galveston, Texas, 77555, USA
<b>Maria P De Miguel</b>	Cell Engineering Laboratory, La Paz University Hospital Health Research Institute, IdiPAZ, Madrid, Spain
<b>Adrian Moratilla</b>	Cell Engineering Laboratory, La Paz University Hospital Health Research Institute, IdiPAZ, Madrid, Spain
<b>Alba Cabrera-Fisac</b>	Cell Engineering Laboratory, La Paz University Hospital Health Research Institute, IdiPAZ, Madrid, Spain
<b>P Gonzalez-Molina</b>	Cell Engineering Laboratory, La Paz University Hospital Health Research Institute, IdiPAZ, Madrid, Spain
<b>Sajan George</b>	Laser Research Centre, Faculty of Health Science, University of Johannesburg P.O. Box 17011, Doornfontein, South Africa
<b>Anine Crous</b>	Laser Research Centre, Faculty of Health Science, University of Johannesburg P.O. Box 17011, Doornfontein, South Africa
<b>Heidi Abrahamse</b>	Laser Research Centre, Faculty of Health Science, University of Johannesburg P.O. Box 17011, Doornfontein, South Africa
<b>Ana-Maria Rosca</b>	Institute of Cellular Biology and Pathology, “Nicolae Simionescu”, Bucharest, Romania
<b>Raluca Tutuianu</b>	Institute of Cellular Biology and Pathology, “Nicolae Simionescu”, Bucharest, Romania
<b>Irina Titorencu</b>	Institute of Cellular Biology and Pathology, “Nicolae Simionescu”, Bucharest, Romania
<b>Priyadarshan Kathirvelu</b>	Ion Channel Biology Laboratory, AU-KBC Research Center, Madras Institute of Technology campus of Anna University, Chennai, India
<b>Bhuvaneshwari Sampath</b>	Ion Channel Biology Laboratory, AU-KBC Research Center, Madras Institute of Technology campus of Anna University, Chennai, India
<b>Kavitha Sankaranarayanan</b>	Ion Channel Biology Laboratory, AU-KBC Research Center, Madras Institute of Technology campus of Anna University, Chennai, India
<b>Norma Rivera</b>	Departamento de Microbiología y Parasitología, Facultad de Medicina, UNAM, CDMX 04510, Mexico
<b>Marcela Rojas-Lemus</b>	Departamento de Biología Celular y Tisular, Facultad de Medicina, UNAM, CDMX 04510, Mexico
<b>Nancy G. Flores-Jiménez</b>	Departamento de Microbiología y Parasitología, Facultad de Medicina, UNAM, CDMX 04510, Mexico
<b>Teresa I. Fortoul</b>	Departamento de Biología Celular y Tisular, Facultad de Medicina, UNAM, CDMX 04510, Mexico

**CHAPTER 1****Insights into Exogenous, Endogenous and Combination Therapies of Neural Stem Cells in Spinal Cord Injury****Hunaid Hasan<sup>1,\*</sup> and Ping Wu<sup>2</sup>**<sup>1</sup> Department of Neurology – Clinical Neurophysiology NYU Langone Medical Center 301 E. 17<sup>th</sup> Street, Suite 1534 New York, 10003, USA<sup>2</sup> Department of Neuroscience and Cell Biology University of Texas Medical Branch 4.212B Research Building 17 Galveston, Texas, 77555, USA

**Abstract:** Advancements in the understanding of spinal cord injury (SCI) and repair have taken great leaps in the past decade. Although understanding has evolved significantly there continues to be major limitations in the clinical interventions available for patients with spinal cord injuries. Exogenous stem cells (ExNSC) have progressed to human clinical studies, but have limitations due to ethical issues, technique and long term outcomes. However, the use of ExSCs through a stimulatory effect on growth factors, cytokine production and neurotrophic factors post injury may be beneficial. Bone marrow derived stem cells, mesenchymal stem cells, embryonic stem cells, umbilical cord stem cells, adipose derived stem cells, NSCs, Schwann cells grafts and olfactory ensheathing cells have been various types of exogenous cell types and techniques used in SCIs. The role of endogenous stem cells (eNSCs) in SCI has been promising, but still requires better lineage analyses to fully understand the responses of NSCs after SCI. It has been demonstrated that there exists a bidirectional interaction within the neuro vascular system forming the neuro vascular niche. Purinergic receptor activation was found to alter the intrinsic properties of the ependymal stem/progenitor cells enhancing regulation of proliferation, differentiation and lineage specification after a SCI. Therapies have been described using nervous tissue in combination with various synthetic bridges to overcome the structural barriers of regeneration through bypassing the injured area. More recently, newer techniques such as electrical stimulation have been described to stimulate mature neuronal differentiation. Various groups have emphasized that the glial scar is counter productive. Anderson *et al.* have shown the beneficial effects of a chronic glial scar in neural tissue preservation after SCI. Moreover, they have demonstrated higher levels of chondroitin sulfate proteoglycans in injured spinal cords independent of the glial scar. In sum, we have reviewed the previous and current literature on NSC and SCI to address the neurobiological utility of NSCs in spinal cord injury.

---

\* **Corresponding author Hunaid Hasan:** Department of Neurology – Clinical Neurophysiology NYU Langone Medical Center 301 E. 17<sup>th</sup> Street, Suite 1534 New York, 10003, USA; Tel: +17348588947; E-mails: hunaidhasan10@gmail.com, hunaidhasan@hotmail.com

Atta-ur-Rahman and Shazia Anjum (Eds.)  
All rights reserved-© 2020 Bentham Science Publishers

**Keywords:** Clinical Neurology, Cytokine, Electrical Stimulation, Electroacupuncture, Endogenous Neural Stem Cell, Exogenous Neural Stem Cell, Genetic Fate Mapping, Glial Scar, Growth Factor, Induced Pluripotent Stem Cell, Neural Stem Cell, Neurovascular Niche, Oligodendrocyte Ensheathing Cells, Progenitor, Purinergic Receptors, Schwann Cell Transplantation, Spinal Cord Injury, Stem Cell, Transplantation, Treatment, Transcription Factor.

## **INTRODUCTION**

Advancements in the understanding of spinal cord injury (SCI) and repair have taken great leaps in the past decade. The greatest challenge in SCI research has been the translation of what is known at the basic science level, and applying it to the clinical setting. Although, the understanding of the molecular basis of SCI has become more cogent, the therapeutic options continue to be limited. Although neural stem cells (NSCs) have been studied for over a decade, they continue to be at a translational research stage. Initially, exogenous stem cells (ExSCs) were an exciting breakthrough. However due to various reasons discussed below their clinical application as independent interventions has started to diminish. Recently, endogenous stem cells (eNSCs) have become more of an interest in SCI. Nature's endogenous process of healing spinal cord injuries was once thought to be counterproductive. However, as discussed below there has been evidence to suggest on the contrary. In sum, the function of eNSCs has been encouraging, and could help intervene in altering this natural process of healing. Further, its translation into clinical practice could improve the quality of life for numerous patients affected by SCIs.

## **SPINAL CORD INJURY**

### **Epidemiology**

Epidemiologically, SCI has been and continues to be a huge burden to society. Some reports find the incidence to be as low as 8 and as high as 246 cases per million depending on political, geographical, sociological and economic differences [1 - 4]. The mean age has increased from 28.3 years in the 1970s to 37.1 years surveyed in 2005-2008. Most concerning has been the epidemiological age group affected. As the majority affected have been in their peak productive years of their lives [5]. Also, more than 50% of SCIs affect the cervical region of the spinal cord, which is more likely to cause total body paralysis [6 - 8].

Mechanism of SCIs were either traumatic or nontraumatic [3]. Traumatic causes in young adults (age 15-29 years) were motor vehicle accidents (50%), violence (12%) and sport-related injuries (10%) [7, 9, 10]. Traumatic causes in the elderly (age >65 years) were mainly accidental falls [8 - 12]. Non-traumatic causes in

both age groups were congenital and inflammatory spinal cord disorders, tumor compression, vascular ischemia vertebral spondylosis [13].

## **Pathophysiology**

### ***Primary Phase***

SCI has been categorized into primary and secondary phases [14, 15]. The primary phase occurs due to compression and contusive injury resulting in shearing, laceration and stretching of the spinal cord. This exerts forces causing disruption of axonal function [16, 17]. It was suggested that at this stage full transection of the spinal cord was rare. There was sparing of demyelinated axons found at the subpial rim [17 - 21]. Animal models suggest that a minimum of 10% preservation of original axons could lead to significant neurological recovery [22, 23].

### ***Secondary Phase***

The pathophysiology of the secondary phase injury was directly proportional to the injuries occurring in the primary injury phase [17]. This phase was marked by a negative environment for neuronal regeneration [17]. The pathophysiology was marked by various processes such as ischemia, excitotoxicity, vascular dysfunction, oxidative stress and inflammation resulting in cell death [18, 24, 25]. Secondary phase injury was deleterious to surviving surrounding neurons, which further impaired functional recovery [14, 26]. The secondary phase had sub-phases which were: immediate (<2 hours), acute (2 hours – 2 days), subacute (3 days to 2 weeks), intermediate (2-3 weeks – 6 months) and chronic (>6 months) [17, 18, 27, 28].

Immediate phase consisted of upregulation of tumor necrosis factor (TNF)-alpha, interleukin (IL)-beta and elevation of extracellular glutamate [29 - 32]. This resulted in necrosis of neurons secondary to ischemia, lipid peroxidation, hemorrhage, reactive oxygen species (ROS) production, edema and cell membrane disruption. This led to early loss in function and neurogenic shock [16, 17, 23, 33, 34].

A patient with SCI has shown to be initially clinically intervened in the acute phase. This phase was further divided into early acute and subacute stages [17]. Genes that change after injury have been classified as either “early” or “late” genes. They were responsible for activating cascades at various stages [35]. After an SCI event there was an upregulation of pro-apoptotic, cell cycle and oxidative stress mediating genes. Moreover, there was downregulation of antiapoptotic genes, genes involved in neural excitation, neurotransmission, electrochemical

## Toward Induced Pluripotent Stem Cells for Clinical Use: Sources, Methods and Selection

**Maria P De Miguel\***, Adrian Moratilla, Alba Cabrera-Fisac and P Gonzalez-Molina

*Cell Engineering Laboratory, La Paz University Hospital Health Research Institute, IdiPAZ, Madrid, Spain*

**Abstract:** Since their development by Yamanaka in 2007, much progress has been made in the last decade toward the use of human induced pluripotent stem cells (iPSCs) in clinical practice. In this review, we will focus on the various sources of somatic cells for human iPSC generation, the methods used for generating human iPSCs, their characterization, and the progress on directed differentiation toward several cell types. We will also describe current efforts to prevent culture-driven mutations and the selection of nontumorigenic cells for clinical use. A comprehensive comparison of such methods will aid in the establishment of standardized techniques and highlight areas in which further research is still needed.

**Keywords:** cMyc, Cell Reprogramming, Cell Therapy, Clinical Grade iPSC, Differentiation, Disease Modelling, Epigenetics, Episomal Vectors, Embryonic Stem Cells, Genetic Stability, Induced Pluripotent Stem Cells, Klf4, Matrigel, Oct4, PBMCs, Pluripotency, Quality Control, Retrovirus, Sox2, SSEA, Transfection, Transplantation.

### INTRODUCTION TO INDUCED PLURIPOTENT STEM CELLS

Cell reprogramming has historically been achieved by various methods, such as somatic cell nuclear transfer [1, 2], cell fusion with pluripotent cells [3], incubation with pluripotent cell extracts [4], and derivation of pluripotent embryonic germ cells (EGCs) from primordial germ cells by addition of a specific cocktail of growth factors [5, 6].

More recently, studies on the genes involved in stemness led to the groundbreaking work of Yamanaka and Thomson, showing that forced expression of just

---

\* **Corresponding author Maria P De Miguel:** Cell Engineering Laboratory, La Paz University Hospital Health Research Institute, IdiPAZ, Madrid, Spain; Tel: 34-912071458; Fax: 34-917277050; E-mail: mariapdemiguel@gmail.com

four transcription factors can reprogram mouse and human fibroblasts into a full pluripotent state, the so-called induced pluripotent stem cells (iPSCs) [7 - 9].

Because the use of human embryonic stem cells in the clinic is controversial due to the ethics involved, to be able to reprogram adult somatic cells into pluripotent stem cells, thus avoiding any ethical or moral deterrent, was remarkable; so much so that Yamanaka received the Nobel Prize in Medicine only 6 years after the initial discovery.

## **SOURCES**

The selection of the cell source for reprogramming is a very important aspect to take into account, given not every cell type is equally efficiently reprogrammed or equally accessible. Here, we will take a look at the beginnings of iPSC derivation and the various cell types that have since been successfully used to create iPSCs. We will also evaluate the various cell types that are actually being used in research, particularly with prospective clinical applications in mind.

### **In the Beginning: Mouse Embryonic Fibroblasts**

Although in 2006 Takahashi and Yamanaka were not the first to achieve or prove cellular reprogramming of somatic cells [7], remarkably, they identified a combination of only four transcription factors (Oct4, Sox2, Klf4, and cMyc, named Yamanaka factors or OSKM), present in embryonic stem cells that could completely reverse somatic differentiated cells into an embryonic pluripotent state [7]. The first generation of iPSCs that Yamanaka's group obtained failed to produce viable chimeras when injected in mouse embryos. Upon changing the selection method for the reprogrammed cells, a collaborative effort with other laboratories allowed Yamanaka and colleagues to develop the second generation of iPSCs, which could successfully form chimeras and therefore give rise to the three germ layers of the embryo. The actual establishment of the first iPSC lines was performed on mouse embryonic fibroblasts (MEFs) and later on adult mouse tail tissue fibroblasts (TTFs). Once 24 genes that were deemed important transcripts for the maintenance of embryonic stem cell (ESC) properties were identified, they transduced various combinations of those genes by retroviral transfection in MEFs, and the resulting cells were screened for pluripotency [7]. As previously mentioned, the exact cocktail of transcription factors needed for the reprogramming event was found: *Oct3/4*, *Sox2*, *c-Myc* and *Klf4*. When transfected with these four genes, their activity was reactivated and the whole transcription program of the cell changed to that of the pluripotent state in both MEFs and TTFs.

Today, the reprogramming of mouse fibroblasts is not the focus of new research on



iPSCs, given their clinical application potential is limited. However, mouse fibroblast-derived iPSCs are still used in other types of experiments, for example to test new methods for increased efficiency or to establish new reprogramming pathways that differ between cell lineages. MEFs are also widely used as feeder cells in iPSC cultures, although they need to be treated beforehand with mitomycin or irradiation to prevent growth.

## **Human Fetal and Neonatal Cells**

### ***Human Neonatal Fibroblasts***

Human neonatal fibroblasts were used as a source for iPSC generation soon after the discovery that younger cells are more easily reprogrammed [10, 11]. These fibroblasts are usually extracted from foreskin samples rather than skin biopsies, which is a safer approach for young individuals. They have the same pros and cons as regular fibroblasts: they require a somewhat long culture time for expansion purposes but then are more easily reprogrammed than other cell types (see below), especially taking into account the young “age” of the cells. They have also been proven to be efficiently reprogrammed even after long-term cryopreservation, which is important in terms of the availability of the samples [12].

### ***Fetal Stem Cells***

Fetal stem cells have also been used extensively as a source for reprogrammed cells. Because they are already stem cells, they are easier to reprogram, have better tissue repair capacity, and sometimes have more rapid growth kinetics than adult stem cells. They can be obtained from newborn and fetal tissues, such as blood, liver, and bone marrow, and also from extraembryonic structures, such as the placenta, cord blood, and amniotic fluid [13, 14].

Fetal stem cells are different from adult stem cells in the sense that they are half way between a pluripotent and a stem cell-like phenotype, presenting markers of both states [14]. However, the initial pool of cells can be very heterogeneous, thus affecting the efficiency of the reprogramming between experiments and making it more difficult to pinpoint the exact nature of the original colony-forming cell [15].

### ***Human Umbilical Cord Endothelial Cells***

Human umbilical cord endothelial cells (HUVECs) present a very accessible source of good quality cells for reprogramming, given the extraction procedure carries no risks whatsoever. Also, these neonatal cells are young and therefore less prone to carrying somatic mutations at the time of isolation. HUVECs can also be

## Reprogramming of Adipose-Derived Stem Cells to Neuronal-Lineage Cells is Regulated by Both Cell Signalling and Redox Status

Sajan George, Anine Crous and Heidi Abrahamse\*

Laser Research Centre, Faculty of Health Sciences, University of Johannesburg P.O. Box 17011, Doornfontein, South Africa

**Abstract:** The generation of specific neuronal-lineages for cellular therapies hold great promise for nervous system disorders. Stem cells can offer regenerative and replacement therapies of the nervous system through cell signalling, which is directed by the addition of cytokines and neuronal growth factors. Adipose-derived Stem Cells (ASCs) are capable of differentiating into neuronal and glial cells through induced cell signalling pathways and altered redox status. In this chapter, we addressed the dynamic changes within ASCs in response to the changes in its *milieu* - a pre-requisite for trans-differentiation *in vitro*. We considered the functional use of ASCs as a regenerative tool in recovering neuronal cells by focusing on ligand expression and their effects on transmembrane receptors. We also discussed various levels of cell signalling capable of modifying epigenetic programming for trans-differentiation processes. Finally, we underlined the fact that harnessing of Reactive Oxygen Species (ROS) and ROS-mediated cellular signalling is a secret recipe for successful differentiation of stem cells *in vitro*.

**Keywords:** Adipose stem cells, Cell signalling, Differentiation, Epigenetics, Growth factors, Glia, Laser, Light, Neurons, Photobiomodulation, Reactive Oxygen Species.

### INTRODUCTION

The most common types of neurological disorders include *spinal cord injuries* caused by accidents, and *stroke* caused by cerebral haemorrhages. These pathologies result from neuronal malfunction or cellular damage that triggers a cascade of signalling events leading to paralysis and cognitive dysfunction. None of the methodologies devised for neuronal differentiation is 'wholly successful'. There is also a need to cogitate on the mechanisms leading to neuroglial transfor-

---

\* **Corresponding author Heidi Abrahamse:** Laser Research Centre, Faculty of Health Sciences, University of Johannesburg P.O. Box 17011, Doornfontein, South Africa; Tel/Fax: +11 559 6550; E-mail: habrahamse@uj.ac.za

mation. Currently there is no research indicating an effective biological or chemical differentiation inducer for Adipose-derived Stem Cells (ASCs), nor the mechanism behind driving ASCs to neurons or glia. Our understanding about various ligands driving the differentiation of ASCs to neurons is very scarce. Researchers have adopted different differentiation approaches or mix-matched them based on literature, where their attempts ended up in ‘neuron-like’ bodies. These undifferentiated ASCs are electrophysiologically inactive and not useful for targeted therapy. This chapter attempted to connect neuroglial differentiation with relevant and recent literature pertaining to cellular changes, whilst focussing on cell signalling which is often controlled by the redox status.

## **NERVOUS SYSTEM**

### **Development and Distinction of Neuronal-Lineage Cells**

Pre-natal development of the central nervous system (CNS) is characterized by the formation of neural plates that give rise to the neural tubes. A highly integrated and spatially distinct neural stem or progenitor population of neuroepithelial progenitor cells (NEPs) exists within these structures. Initially, NEPs undergo symmetric division to expand, but later switch to asymmetric division for giving rise to lineage-restricted progenitors. Neural Precursor Cells (NPCs) is a mixed population of Neural Stem Cells (NSCs) and neural progenitor cells, which give rise to neurons and supporting cells [1]. The last stage of CNS development is marked by dendrite branching, axonal elongation as well as formation of synaptic junctions to facilitate impulse transmission. In the developing nervous system, NSCs undergo asymmetric division to produce glial-restricted progenitors, which generate astrocytes, oligodendrocytes and Schwann cells [2]. Finally, NSCs are also the source of specific- neurotransmitter release cholinergic, dopaminergic and GABAergic neurons. Table 1 indicates the functional as well as anatomical significance of different glial cell types configuring the human CNS.

### **Anatomy of Central and Peripheral Nervous Systems**

The nervous system is broadly divided into two principal parts—CNS and the peripheral nervous system (PNS). The CNS consists of the brain and the spinal cord, while the PNS consists of sensory and motor nerves that interconnect with the periphery. The latter act as a communication system between the periphery of the body and the spinal cord. The CNS decipher sensory input from the PNS and translate it into an appropriate motor response. The nervous system is also classified according to its control over the body functions. The somatic nervous system (SNS) is responsible for all the sensory or cognitive activities followed by the movement of skeletal and ocular muscles. The autonomic nervous system

(ANS) controls all involuntary activities concerning cardiac and smooth muscles as well as endocrine glands.

**Table 1. Glial cell types supporting the central and peripheral nervous systems.**

Cell types	Function
Neuroglia (glia)	helper cells of neurons for anatomical and functional support
Schwann Cells	glial cells that produce myelin sheaths around axons of the PNS
Astrocytes	glial cells that function in the BBB in the piamater of the CNS
Oligodendrocytes	glial cells that produce myelin sheaths on axons of the CNS (white matter)
Satellite Cells	glial cells that are helper cells to sensory and autonomic nerves of the PNS
Ependymal Cells	glial cells that are part of the choroid plexus and produce CSF
Microglia	glial cells that are phagocytic immune cells that find & destroy invaders

NOTE: Schwann Cells, Satellite Cells, Oligodendrocytes, Microglia, Astrocytes, and Ependymal Cells are the six types of neuroglia (glia) cells that support neuronal growth and activity. *Abbreviations: CNS, Central Nervous System; PNS, Peripheral Nervous System; CSF, Cerebrospinal Fluid.*

The nervous tissue consists of neuronal and glial cells, which are the functional and supportive cells of both the CNS and PNS, respectively. Morphologically, neurons have a soma or cell body upon which several extensions emerge and interconnect with the neighbouring cell. These processes, referred as dendrites are the structures that receive sensory input from the surroundings. Each neuron will have at least one of these processes as a prominent extension, referred to as the axon. They are the functional units of neurons that are responsible for the transmission of impulses to neighbouring cells or neurons. It is important to note that a bundle of axons in the CNS is mentioned as tract, while the same in the PNS is a nerve. Similarly, a localized collection of neuron cell bodies is referred to as a nucleus in the CNS and as a ganglion in the PNS.

### **Diseases and Disorders of the Nervous System**

Neurodegeneration is a condition characterized by progressive deterioration of neuronal morphology and functional characteristics due to ischaemia or haemorrhage, deposition of intracellular toxic proteins or accumulation of genetic mutations [3]. Alzheimer's disease and amyotrophic lateral sclerosis is characterized by neurovascular dysfunction resulting in the impairment of the blood–brain barrier function. This evidently result in a lack of nutrition to cholinergic nerve cells and the impairment of clearing neurotoxic molecules resulting in neurodegeneration [3]. Another well-studied condition, Parkinson's disease, is caused by the degeneration of dopaminergic neurons resulting in a gradual dysfunction of the motor neuronal system. Any hypofunction of N-methyl-D-aspartic acid-type glutamate (NMDA) receptors at the cerebral cortical

**CHAPTER 4****Advances in Skin Regeneration and Reconstruction****Ana-Maria Rosca, Raluca Tutuianu and Irina Titorencu\****Institute of Cellular Biology and Pathology “Nicolae Simionescu”, Bucharest, Romania*

**Abstract:** The skin represents the largest and most accessible organ of the body, and it is subjected to numerous aggressions such as infections, physical wounds and diseases. After a moderate-intensity injury, the intrinsic regenerative mechanisms of the skin lead to restoration of the tissue integrity. However, in some pathological cases such as chronic wounds and extensive burns, the healing capacity of the tissue is overwhelmed. In order to resolve these injuries, innovative therapies based on miRNAs as well as paracrine and trophic activities of stem cells combined with biomaterials are currently being developed. This chapter begins with a description of skin biology, followed by the main stages of wound healing including the key cells and molecules involved. Next, we describe the most studied miRNAs relevant for chronic wounds therapies and the proposed methods of delivery. Regarding cellular therapy, the main adult differentiated cells as well as stem cells available from different sources, are presented. Then, we address the commercially available skin substitutes and also the latest innovative approaches, including 3D bioprinting, for combining biomaterials with the activity of the cells previously described, in order to promote wound repair and regeneration. This chapter concludes with current challenges and future perspectives regarding the use of stem cells for skin regeneration.

**Keywords:** Biomaterials, Cellular therapy, Chronic wounds, microRNAs, Skin, Skin biology, Stem cells.

**INTRODUCTION**

The skin is the largest organ of the human body. Situated at the interface between the organism and the exterior environment, it carries out the role of mechanical and waterproof barrier. As a consequence of its position and function, it is often injured as a result of the action of various external factors (mechanical, physical or chemical). Although, in normal physiological conditions, the process of wound healing is extremely effective, resulting in a nearly perfect tissue repair, especially at young ages, there are circumstances in which the repair mechanisms are damaged. The result is either a chronic wound (ulcerative skin damage) or a scar

---

\* **Corresponding author Irina Titorencu:** Institute of Cellular Biology and Pathology “Nicolae Simionescu”, Bucharest, Romania; Tel: (+4021)3194518; E-mail: irina.titorencu@icbp.ro

tissue (hypertrophic or keloid). As a consequence of the prolonged requirement of medical care and elevated rate of reoccurrence, chronic wounds represent a significant burden to the healthcare resources all over the world [1]. Furthermore, chronic wounds represent an important problem of the modern society, as they are a significant cause of morbidity, leading to a poor quality of life, disability, pain, depression and social isolation [2]. This type of skin injury is associated with an intensified inflammatory process, which can be a result of mechanical stimuli (pressure ulcers) or a consequence of other severe dysfunctions, among which diabetes is particularly prevalent in our days.

Burns represent another major type of skin injury, which require special treatment and often result in debilitating scars. The healing of a burn depends on the depth of the wound. The deep second-degree and third-degree burns, where the reticular dermis is affected, result in hypertrophic scars and contraction [3]. Moreover, in severe burns, even though they involve a single organ, almost all systems of the body are influenced, so that it becomes a generalized disorder [4]. Furthermore, sepsis and the accompanying invasive infection are still the primary cause for death after the first 24 hours, with a peak at two weeks after the accident.

Last, but not least, the skin can be affected by genetic diseases. Given the fact that the skin comprises various cell types expressing specific molecules with role in maintaining the structural integrity of the skin, even a single mutation in one of these molecules can disrupt the skin structure, leading to cell separation, blistering, and eventually, wounds [5]. For example, epidermolysis bullosa comprises a group of inherited, disfiguring and painful diseases, which determines skin fragility causing blisters in response to even minor trauma [6].

Next, we will begin with a short description of the skin structure and function, after which the main stages of the wound healing process and the main small non-coding RNAs (microRNAs) will be described. Given the fact that the standard wound care is not effective in severe skin injuries/diseases, we will focus our attention on potential innovative therapeutic approaches such as cellular therapy and the use of available skin substitutes as well as new strategies to improve them.

## **SKIN BIOLOGY**

The skin has many vital functions, by being an immunologically active sensory and excretory organ and also, by preventing loss of excess water and electrolytes, while having an important role in thermoregulation [7, 8].

The integumentary system is formed by the skin and its derivative structures: sweat glands, sebaceous glands and mammary glands, hair, hair follicles, and

nails [9]. The skin is organized in three layers: the stratified cellular epidermis, the underlying dermis, and subcutaneous tissue [10]. The epidermis is a continually renewing stratified epithelium of ectodermal origin, composed of 80% by keratinocytes, which are cells specialized in the synthesis of keratin a fibrous threadlike structural protein with a protective role [2]. These cells are disposed in five distinct layers: stratum basale (basal cell layer), stratum spinosum, stratum granulosum, stratum corneum and stratum lucidum- this last one being present in skin exposed to friction, such as skin on the feet or hands (Fig. 1). Besides keratinocytes, several other cell populations exist in the epidermis: melanocytes, which have the ability to produce melanin and to donate this pigment to the keratinocytes [11], Langerhans' cells, which have immunological functions, and Merkel cells with tactile functions [10].

The **stratum basale (SB or basal layer)** represents a single layer of mitotically active cells which replaces the cell loss on the outer epidermis [12]. The process of cell kinetics in the epidermis is complex and is represented by the balance between growth with differentiation and cell death [10]. In epidermis, the turnover takes between 40-56 days and plays an important role in maintenance of the skin barrier function [13]. Thus, in the basal layer, there are cells that can persist undifferentiated and, in this way, the self-renewing of the basal cell population is preserved. These cells with unlimited capacity for self-renewal and the ability to generate daughter cells that undergo terminal differentiation are named stem cells. They are situated in small clusters in the basal layer of the epidermis. The basal keratinocytes are characterized by the expression of specific keratins: K5 and K14, and contain gap junctions for cell communication, desmosomes for cell-to-cell attachment, hemidesmosomes for connecting with the basement membrane, and an extracellular matrix [14, 15]. The basal layer synthesizes, secretes, and assembles an extracellular matrix (ECM), which ensure the stability of the connections and communication between the epidermis and the dermis [16]. Immediately above the basal cell layer, keratinocytes become more irregular in shape and form the **stratum spinosum (SS or squamous layer)**. This layer consists of 8 to 10 sheets of keratinocytes which express K1 and K10 and have a reduced potential for cell division. In the middle of this layer, the Langerhans cells are located. The intercellular spaces between squamous cells are bridged by abundant desmosomes which promote mechanical coupling between cells of the epidermis and aid in flexibility, enabling the epidermis to better withstand the effects of friction and abrasion [9] (Fig. 1).

The **stratum granulosum (SG or granular layer)** is composed of two or three layers of flatten cells containing basophilic keratohyalin granules consisting of profilaggrin, protein that is eventually cleaved into filaggrin peptides [8].

## MiRNA Mediated Stem Cell Therapy for Cardiac Arrhythmia

Priyadarshan Kathirvelu, Bhuvaneshwari Sampath and Kavitha Sankaranarayanan\*

*Ion Channel Biology Laboratory, AU-KBC Research Center, Madras Institute of Technology campus of Anna University, Chennai, India*

**Abstract:** Arrhythmias are electrical disturbances resulting in irregular heartbeats. Multiple ion channels orchestrate the coordinated propagation of electric stimuli within the heart. Dysfunction of the ion channels, which may result from genetic alterations in ion channel genes or their aberrant expression, can render electrical disturbances predisposing to cardiac arrhythmias. MicroRNA (miRNA) is a type of small RNA belonging to non-protein coding RNAs and is involved in RNA interference, thereby functioning as a regulator of gene expression. Recently, the role of miRNA in cardiac conduction diseases, arrhythmogenesis and their therapeutic potential has been implicated. Stem cell therapies for cardiac arrhythmia have attempted to modulate defective ionic currents by delivering engineered cells. The modulation or engineering of stem cells with appropriate miRNAs could improvise stem cell-based therapies for arrhythmia. This chapter would review the role of miRNAs in cardiac rhythmic disorders and its potential in diagnosis and treatment of cardiac arrhythmia.

**Keywords:** Arrhythmia, Channelopathy, Conduction Disorder, Epigenetic Regulation, Ion Channels, MicroRNA, Regenerative Medicine, Stem Cells, Stem Cell Therapy, SCD, Target Prediction.

### INTRODUCTION

Cardiac arrhythmia is a worldwide serious problem responsible for high rate of cardiovascular mortality and morbidity. An arrhythmia is a condition where the heart beat becomes irregular. Cardiac arrhythmias are significantly associated with increased risks of cardiovascular complications and sudden death [1]. Arrhythmias affect people worldwide, atrial fibrillation alone is estimated to affect 33.5 million people [2]. Rhythmic disturbances of cardiac function are underlying symptoms of a wide range of diseases, disorders or side effects of

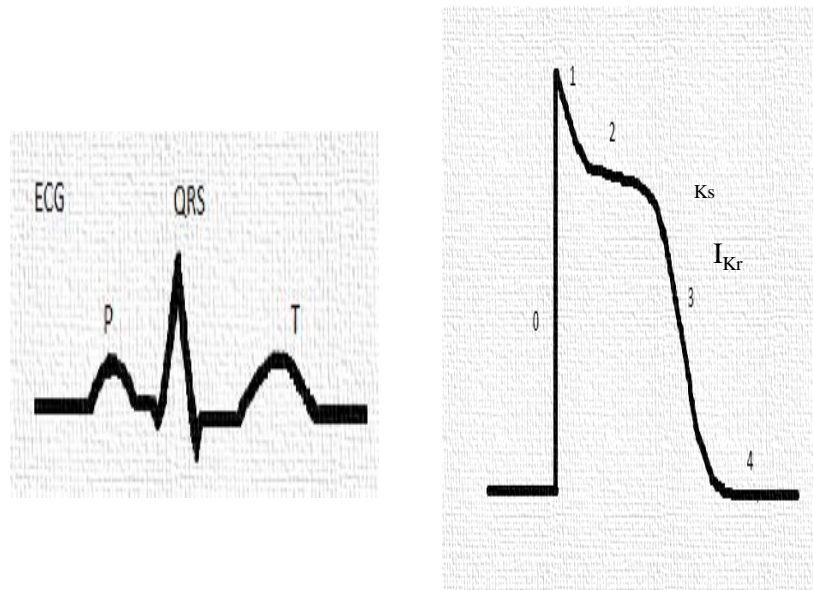
\* Corresponding author Dr. Kavitha Sankaranarayanan: Ion Channel Biology Laboratory, AU-KBC Research Centre, MIT Campus of Anna University, Chromepet, Chennai 44, Tamil Nadu, India; Tel: + 91-044-22232711; E-mail: skavitham@yahoo.com



drugs, which could result in either tachycardia or bradycardia. Arrhythmia are classified as atrial tachycardia, sinus bradycardia or ventricular arrhythmia depending on the origin of the rhythm disturbance. It also may be further classified on the basis of the rate and mechanism (triggered, ectopic, reentry).

Arrhythmias could manifest themselves as ones with mild to serious effects with some being fatal enough to result in sudden cardiac death. Ventricular arrhythmias are the most important cause of sudden cardiac death (SCD). Occurrence of SCD is estimated to be 4 to 5 million cases per year worldwide [3, 4], thereby highlighting arrhythmias and SCD as the most serious cardiovascular diseases worldwide. Arrhythmias do not manifest at any specific age and could be acquired or inherited. In addition to genetics, the occurrence of arrhythmia is also influenced by other factors like smoking, caffeine, drugs, ischemia, infarction, *etc.* Acquired arrhythmias are a manifestation of diverse abnormalities (electrical, structural, metabolic, neurohormonal, or molecular alterations) in multiple pathological conditions (heart failure, hypertension, diabetes mellitus, hyperthyroidism, aging, *etc.*) [5].

The rhythm of the heart beat is controlled by the electrical conduction system (CS) of the heart. The conduction system is responsible for the maintenance of normal blood pressure and ensures proper blood circulation. The electrical activity of the heart is mediated by ion channels and transporters. Ion channels, which are integral membrane protein complexes, facilitate a selective passage of ions across the cell membrane through various gating mechanisms including voltage, pH, ligands *etc.*, thereby being pivotal in the generation of electrical impulses in excitable cells. The coordinated activity of these ion channels is instrumental in the generation and propagation of the cardiac action potential as well as normal ECG pattern Fig. (1). The unique signature pattern of ion channels across different regions of the heart is responsible for the unique action potentials generated by them. The normal cardiac rhythm is regulated by the precise action potential in each type of cell in the various compartments of the heart. The electrocardiogram (ECG) is a result of the cumulative effect of the cellular action potential generated by the meticulously timed action of different ion channels. Dysregulation or functional impairment of ion channels, transporters, intracellular  $\text{Ca}^{2+}$ -handling proteins *etc.* can result in the generation of structural and metabolic substrates, which have the potential to culminate in electrical disturbances predisposing the individual to conduction abnormalities and arrhythmias [6].



**Fig. (1).** The normal ECG pattern and the ionic currents involved in myocardial action potential.

### CARDIAC CHANNELOPATHIES AND ARRHYTHMIA

Electrocardiographic abnormalities are the result of underlying changes in the cellular action potentials which arise due to aberrant cell-to-cell coupling, diseased conditions of the heart, congenital ion channel abnormalities, drug intervention, or electrolyte imbalance [7 - 9]. Primary electrical diseases of the heart refer to rare inherited cardiac arrhythmias in the absence of structural abnormalities of the heart that are associated with mutations in ion channel genes. Wilde and Bezzina (2005) have summarized the ion channel genes that are associated with these inherited arrhythmia conditions [10]. These findings were based on studies of various mutants and highlighting the important contribution of ion channels in maintenance of normal cardiac rhythm. The term cardiac channelopathies is used to refer to ion channel disorders resulting in anomalies of cardiac function, including but not limited to arrhythmias. Molecular studies revealed mutations in genes coding for specific ion channels being responsible for heritable arrhythmogenic disorders such as LQTS, SQTs, Brugada syndrome and idiopathic atrial fibrillation. The findings of genetic basis of the inherited arrhythmia syndromes promoted better understanding of the molecular genetics of cardiac arrhythmias and the role of different ion channels. The development of molecular diagnostic tests has also increased the chances of an early detection of the subjects at high risk of developing arrhythmias.

## Malaria Treatment and Stem Cells

Norma Rivera<sup>1,\*</sup>, Marcela Rojas-Lemus<sup>2</sup>, Nancy G. Flores-Jiménez<sup>1</sup> and Teresa I. Fortoul<sup>2</sup>

<sup>1</sup> Departamento de Microbiología y Parasitología, Facultad de Medicina, UNAM, CDMX 04510, Mexico

<sup>2</sup> Departamento de Biología Celular y Tisular, Facultad de Medicina, UNAM, CDMX 04510, Mexico

**Abstract:** In some countries, Malaria is still a challenge. The highest rates of mortality are reported in sub-Saharan Africa, where children under five years of age, pregnant women and immunocompromised patients are the most vulnerable groups. People living in these endemic areas still do not receive proper antimalarial therapy. Insecticides resistance, antimalarial drug resistance and commercialization of counterfeit and substandard antimalarials, are key factors contributing to complexity in malaria control; trying to find new alternatives to treat and control malaria, some members of the scientific community, have recently started to work in the field of stem cell therapy in experimental malaria models. The purpose of the present chapter is to make a general review concerning various aspects of the use of stem cell therapy and how these findings could improve clinical aspects during malaria pathogenesis and could be used in the field of antimalarial drug design. An overview of the effect of the parasite on the stem cells production in the host, as in hematopoiesis and in neurogenesis, is also described.

**Keywords:** Adult Neurogenesis, Bone Marrow Stromal Cells, Cognitive Dysfunction, Hepatocytes, Hematopoiesis, Hippocampus, Malaria, Malaria Pathogenesis, Malaria Drug Design, Mesenchymal Cells, Memory, Murine Malaria, Neurogenesis, *Plasmodium falciparum*, *Plasmodium vivax*, Stem Cell Therapy.

### INTRODUCTION

Malaria is a disease of great global impact due to the number of deaths it produces annually. The World Health Organization (WHO) in 2015 reported 214 million cases world wide and 438,000 deaths. The most serious situation is in the countries of sub-Saharan Africa, where children under the age of five are parti-

\* Corresponding author Norma Rivera: Departamento de Microbiología y Parasitología, Facultad de Medicina, UNAM, Mexico; Tel: 52 55 56232382; E-mail: normariv@unam.mx

cularly exposed and it is one of the main causes of infant mortality in that region [1].

Due to the limitations in the adoption and implementation of chemoprophylaxis worldwide, in 2014, 306,000 children under the age of five died of malaria and the percentage of pregnant women receiving preventive therapy was less than 20% and only half of the population in endemic areas slept under mosquito nets treated with insecticides [2].

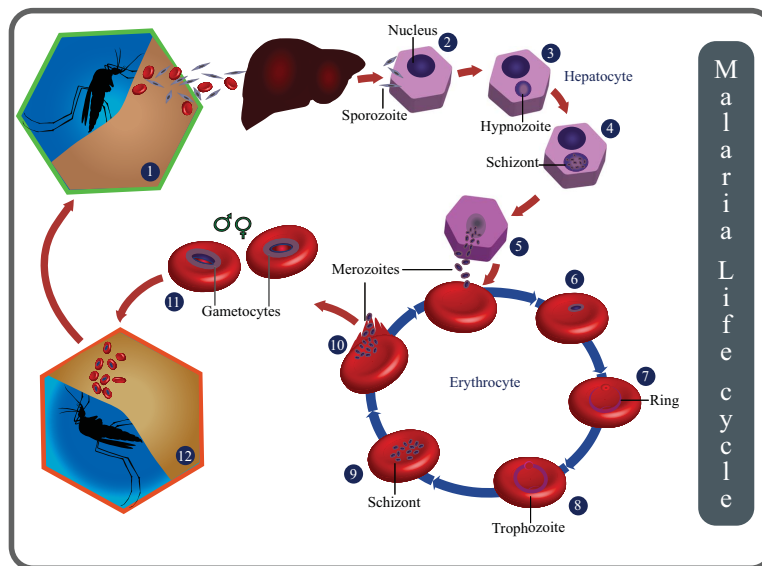
Human malaria is attributed to four species of *Plasmodium*: *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*, which have a particular geographic distribution. *P. falciparum* is distributed in all malaria areas of the world but predominates in sub-Saharan Africa, *P. malariae* has a similar distribution to that of *P. falciparum* but is much less frequent, *P. vivax* predominates in Central America and India, and *P. ovale* is found in Africa and is very rare outside of it [2]. Malaria is transmitted to the human by an *Anopheles* female mosquito that injects the parasites into the host blood stream while feeding.

*Plasmodium vivax* predominates in countries with the lowest incidence of malaria, accounting for more than 70% of cases in countries with less than 5000 cases reported each year. According to the WHO, 2015, the malaria caused by *P. vivax* is concentrated in all Latin America, Oceania and Southeast Asia. In all endemic regions of vivax malaria, severe cases and deaths have been reported. Due to the difficulty in controlling *P. vivax*, its incidence has decreased more slowly than that of *P. falciparum* in places where the two species coexist. *P. vivax* can then persist as the main cause of malaria and constitute the main challenge for its elimination [3].

Malaria life cycle can be observed in Fig. (1).

More than 50 years ago, it was reported that under laboratory conditions, some ape *Plasmodium* parasites were transmitted to humans [4]; it is now known that *Plasmodium knowlesi* is emerging as a very important zoonotic pathogen, which is being exported from endemic areas to other parts of the world through travelers; the infection can be potentially spread through blood transfusions, bone marrow transplantation and congenital infections [5].

Knowledge about the pathogenesis of the parasite that produces malaria has been obtained mostly from non-human animal models such as murine models [6]. The pathogenesis of malaria is complex and is the result of the destruction of the infected erythrocytes and the host's immune-response to the infection. Only the blood stage of the parasite is involved in the pathogenesis of the disease [7].



**Fig. (1).** Malaria life cycle. 1. Female *Anopheles* mosquito injects sporozoites into the host blood stream while feeding. The parasites replicate in the hepatocytes developing schizonts that liberates thousands of merozoites (2-5). *Plasmodium vivax* remains as hypnozoite inside the liver cells (3). Free merozoites invade the red blood cells and start the intraerythrocytic cycle (6-10). In the last schizogony, gametocytes (11) are formed and ingested by a female *Anopheles* which will develop new infective sporozoites (12).

Mice blood smears with different stages of *Plasmodium yoelii yoelii* can be observed in Fig. (2).

In malaria, different pathogenic mechanisms can be observed: block of microcirculation at different organs by sequestration of infected erythrocytes to the endothelium, exacerbated production of proinflammatory cytokines and oxidative stress. The products derived from the parasite during the intraerythrocytic cycle induce the production of proinflammatory mediators such as TNF, IL-1, IL-6 and IFN- $\gamma$ . These mediators induce the production of other cytokines and enzymes that perpetuate the inflammatory cascade. Serum levels of proinflammatory cytokines are increased in patients with complicated malaria or cerebral malaria [8, 9].

In malaria, oxidative stress occurs with increased generation of reactive oxygen species, such as superoxide anion, hydrogen peroxide, hydroxyl radical and peroxynitrite, which are produced by the host's inflammatory cells to control parasitemia, but are also produced directly by the intra-erythrocytic parasite, when in the digestive vacuole it transforms the hemoglobin into methemoglobin. The production of reactive oxygen species in malaria has been demonstrated by

## SUBJECT INDEX

### A

- Abdominoplasty 119  
 Acetylcholinesterase 126  
 Acid 86, 88, 99, 123, 155, 163  
   hyaluronic 155, 163  
   valproic 86, 88, 99, 123  
 Acrylate polymer 89  
 Activity 7, 15, 17, 86, 99, 115, 122, 130, 132,  
   143, 192, 193  
   arrhythmic 99  
    $\beta$ -galactosidase 132  
   biological 86, 130  
   cognitive 115  
   heavy aerobic 7  
   inflammatory immune 17  
   ion channel 192  
   minimal proliferative 15  
   neurotrophic 122  
   pacemaking 193  
   trophic 143  
 Adenoviruses 82, 83, 158  
 Adenylate cyclase (AC) 129, 131  
 Adipocytes 154, 164, 193  
   intradermal 154  
 Adipose tissue 9, 26, 80, 117, 118, 119, 120,  
   132, 134, 149, 164, 171  
   harvest 120  
 Allogeneic 166, 169  
   epidermal 166  
   skin substitutes 169  
 American spinal injury association (ASIA) 10,  
   25, 26, 30, 34  
 Anaplastic thyroid carcinoma 159  
 Angioblasts 39  
 Angiogenesis 13, 19, 133, 152, 154, 155, 158,  
   164, 171, 194, 195  
 Angiopoietins 39, 42  
 Antibodies, xenogeneic 8  
 Antibodies production 152, 225  
 Antigens 92, 95, 101, 166, 225  
   embryonic 92  
   expressing ABH 101  
   tissue-restricted 92  
   viral 225  
 Anti-microbial effects 152  
 Anti-proliferative effect 198  
 Apoptosis 4, 5, 20, 38, 87, 119, 127, 155, 205,  
   223  
   host cell 223  
   neuronal 4  
   showed reduced cardiomyocyte 205  
 Argonaute forms 194  
 Arrhythmias 101, 188, 189, 190, 191, 195,  
   209  
   acquired 189, 191  
   developing 190  
   inherited 191  
   triggered 191  
   ventricular 189, 191  
 Arrhythmogenesis 188, 192, 195, 196, 197,  
   208  
 Arrhythmogenicity 99  
 Ascorbic acid 88, 128  
 ASIA 25, 27, 28, 33  
   impairment Scale (AIS) 27, 28, 33  
   motor scoring 25  
 Assay loss-of-function phenotypes 208  
 Astrocytes 5, 8, 9, 10, 15, 17, 18, 19, 21, 22,  
   23, 24, 41, 42, 115, 116, 117, 127  
   activated 17  
   active 17  
   cortical 15  
   forming 19  
   glial cells 116  
   injecting subgranular zone 17  
   mature 127  
   progenitor 17  
   reactivated resting 15  
   reactive 18  
   reactive resident 22  
   surrounding hypertrophic 5  
 Astrocytic morphology 22  
 Astroglial activation 15  
 Astrogliosis effect 39  
 Atrium 99, 100, 192

porcine 192  
spectrum disorder (ASD) 99, 100  
Autologous 10, 26, 28, 29, 30, 32, 34, 118, 163, 206  
adipose derived (AAD) 10, 26  
BM stem cells 29  
BM transplant 28  
bone marrow 28, 34  
keratinocytes suspensions 163  
mesenchymal stem cells 28  
stem cells 30, 32  
therapy 118, 206  
transplantation 30  
Axonal growth 13, 14, 19, 20, 40, 117, 121  
cultured hippocampal neuron 20  
long-distance 14  
stimulated 19  
Axonal regeneration 17, 19, 24, 25, 35, 36, 37, 42  
and remyelination 25  
hindered 17  
inhibited 19  
promoted 36, 37  
Axons 12, 13, 23, 117, 118  
demyelinated 3, 118  
myelinate 23  
myelinated 23, 117  
remyelinate 13  
supraspinal 12

## B

Bacteriophages 82  
BDNF 40, 99  
secreting fibroblast grafts 40  
signaling pathways 99  
Biocompatible cationic polymer 159  
BMP signalling on dorsal oligodendrocytes 23  
Bombay disease 101  
Bone marrow 8, 28, 29, 30, 94, 118, 132, 133, 193, 220, 221, 224  
host 94  
Derived Autologous Cells 30  
Derived Stem Cells 29  
mesenchymal stem cells (BMMSCs) 8, 224  
stem cells (BMSCs) 8, 28, 29, 118, 132, 133  
stromal cells 193, 220  
transplantation 221

Bone morphogenetic protein (BMPs) 18, 42, 95, 121, 153  
Bovine serum albumin (BSA) 91  
Brain 116, 228  
barrier function 116  
cytokine levels 228  
Brain-derived 19, 40, 117, 121, 122  
neurotrophic factor (BDNF) 19, 40, 117, 121, 122  
neurotropic factor 117  
Breast reconstruction procedures 170  
Brown adipose tissue display 119  
Brugada syndrome 190, 191

## C

Cancer 100, 121, 122, 158, 159, 160, 198, 225  
advanced pancreatic 159  
Cancer cells 198, 207  
breast 207  
Cardiac resynchronization therapy (CRT) 197  
Cardiomyocytes 94, 95, 98, 191, 192, 193, 194, 198, 206, 208  
ischemic 206  
Cardiomyopathy 195  
Cascade 3, 4, 39, 114, 117, 150, 222  
activating 3  
coagulation 150  
immune 4  
inflammatory 39, 222  
Catecholamine responsiveness 193  
Cationic liposomes 159  
Cell  
Cells 11, 24, 27, 38, 40, 78, 93, 94, 117, 120, 151, 171, 194, 220, 224,  
apoptotic 151  
astroglial 120  
cardiac-derived 194  
colony-forming 78  
embryonic 117  
endodermal 93  
grafted 11, 24  
hepatic 94  
hyperexcitable 194  
mesenchymal 27, 171, 220, 224  
myelin-producing 38  
pheochromocytoma 40  
signalling for neuronal differentiation 120  
Cell-based 167, 192  
dressings 167

- therapy for cardiac regeneration 192
- Cell cycle 87, 132
  - arrest 87
  - distribution 132
- Cell death 4, 20, 84
  - oligodendrocyte 4
  - inducer 20
    - preventing 4
    - significant 84
- Cell growth 118, 122, 126
  - inducers 122
  - stable 118
- Cell membrane 3, 4, 84, 146, 159, 189
  - disruption 3
  - function, active 4
- Cell populations 23, 118, 129
  - heterogeneous stromal 118
  - quiescent stem 23
- Cellular 119, 149, 150, 163
  - kinases 119
  - type 149, 150, 163
- Central nervous system, (CNS) 7, 8, 12, 31, 32, 38, 39, 41, 42, 115, 116, 117, 120, 134
- Cerebral 114, 222, 223, 224, 226, 227, 228
  - haemorrhages 114
  - malaria 222, 223, 224, 226, 227, 228
- Cerebrospinal fluid 15, 31, 116, 197
- Channel genes 199, 205, 208, 209
  - associated ion 205
  - regulating cardiac ion 208
  - targeting altered ion 209
  - targeting cardiac ion 208
- Chemical transfection 84
- Chemokine receptor 38
- Childhood neurodisability 227
- Chitosan 89, 170
  - porous 170
- Cholesterol 197, 207, 208
  - based antagomirs 208
  - based antagomir uptake 208
  - conjugation 207
- Cholinergic nerve 116, 122
  - cells 116
  - endings 122
- Cholinergic neurons 10, 122, 126
  - differentiated 126
- Chondrocytes 164, 193
- Chondrogenic 164
- Chronic spinal cord injury 27, 28, 32, 33
  - Repair 32, 33
- Chronic wounds 143, 144, 150, 153, 156, 160, 164, 166, 167, 169, 170
  - treatment of 164, 169
- Collagen 89, 147, 148, 154, 156, 157, 158, 164, 169, 170, 172
  - bovine 170
  - bundles, organized 170
  - deposition 156
  - fibres 148, 154
  - fibrils 148
  - matrix 169
  - reassignment 157
  - wound dressing 164
- Collagenase 120
- Colloid fluids 6
- Combination therapies 35, 43
- Combined multiple algorithms 199
- Commercial 91, 171
  - dermal substitute 171
  - commercial tablemedia 91
- Communication 156, 191, 198, 206
  - cellular 198
  - gene-based 206
  - intercellular 156, 191, 198
- Complexes 84, 159, 170, 189
  - integral membrane protein 189
- Contractile phenotypemyofibroblasts 154
- Corneocytes 146, 149
- Coronary artery disease (CAD) 101
- Corticospinal axons rostral 12
- Cryopreserved human skin allograft 169
- Culture, autologous transgenic keratinocyte 161
- Culture 89
  - systems, animal-free 89
  - treated polystyrene 89
- Cyclic adenosine monophosphate 121, 129, 131
- Cylindrical nanofibers 36
- Cytokines 37, 38, 39, 117, 119, 150, 152, 153, 154, 155, 169, 170, 222, 223, 224, 227, 228
  - anti-inflammatory 117
  - exogenous 119
  - inflammatory 153, 169
  - neurotrophic 117
  - proinflammatory 222, 227, 228
- Cytoskeletal 125, 128
  - dimer 125



rearrangements 128  
Cytotoxicity 98, 130, 208

## D

Damage 83, 96, 114, 117, 224, 226, 228  
cellular 114, 117  
endothelial 223  
genetic 83  
low DNA 96  
neurological 228  
oxidative 117

Damage-associated molecular patterns 151

Deacetylation 123

Deaths 5, 38, 117, 144, 188, 189, 196, 220,  
221, 226

annual 226  
cardiac 189  
induced OPC 38  
neuronal 5, 117

Debris 6, 150, 151, 152

cellular 151  
clearing 150

Decellularized matrices 172

Dendrites 116, 124, 125, 126, 202, 203  
and dendritic spines 202, 203  
emerging 126

Dendritic 125, 128, 202, 203  
morphogenesis 128  
spines 202, 203  
tree 125

Dermal 80, 98, 147, 150, 153, 163, 165, 166,  
168, 169, 171, 172

autologous fibroblasts 163  
compartments 153  
constituents 147  
fibroblasts 80, 98, 150, 165, 166, 168, 169,  
171, 172  
homogenates 172  
papilla cells 171

Dermis 144, 145, 147, 148, 153, 154, 155, 159  
layers 159

papillary 147, 148  
reticular 144, 148

Diabetes mellitus 101, 189, 195

Diabetic 99, 163, 168, 169  
foot ulcers 163, 168, 169  
retinopathy 99

Diacyl glycerol 128, 129

Diffusion tensor imaging 28

Direct reprogramming of somatic cells 166  
Diseases 98, 99, 100, 101, 123, 144, 153, 159,  
160, 174, 188, 197, 198, 206, 207, 208,  
220, 221, 223, 225

autoimmune 98

autosomal recessive neuromuscular 98

cardiac 198

cardiac conduction 188

cerebrovascular 100

chronic obstructive pulmonary 100

congenital 174

coronary artery 101

degenerative 193

diastolic heart 197, 208

eye 100

genetic 144

granulomatosis 101

hematopoietic 8

immunological 100

infectious 225

neurological 100, 123

pulmonary 100

vascular 101

Dismutase 128, 223

superoxide 223

Disorders 3, 99, 100, 114, 118, 134, 188, 190,  
191

autism spectrum 99, 100

autoimmune 134

cardiac rhythmic 188

heritable 191

heritable arrhythmogenic 190

inflammatory spinal cord 3

inherited 191

neurological 114

neuronal 118

DNA 21, 82, 85, 86, 87, 88, 198

bacterial 82

hypomethylation 87

genomic 198

integration 85

methylome changes 88

methyltransferase inhibitor 86

synthesized 21

DNA demethylation 88, 123

enzymes 88

DNA methylation 87, 88, 123

modulators 88

pattern 123

DNA repair 87, 97

- abilities 97
  - repair capacities, reduced 97
  - processes 97
- Dopaminergic 95, 100, 115
  - midbrain 95
- Dopaminergic neurons 116, 122, 126
  - functional 122
- Dopamine transporter 101
- Dorsal 22, 23
  - funiculus incision 22
  - oligodendrocytes 23
  - oligodendrocytes activity 23
- Dysfunction 3, 34, 38, 98, 114, 116, 117, 123, 188, 191, 198, 208
  - cognitive 114, 117, 220, 228
  - gradual 116
  - neurological 117
  - neurovascular 116
  - sphincteric 34
  - urinary 34
  - vascular 3
- Dysregulation 4, 189, 196
- Dystrophin gene 98
- E**
- Early 6, 7, 86, 196
  - afterdepolarization 196
  - decompression 7
  - ectodermal lineage marker 86
  - surgical decompression 6
- Early stage 7, 118
  - cleavage-stage blastomeres 7
  - differentiation 118
- Ectodermal 100
  - dysplasia 100
  - origin 145
- Edema 3, 5, 25, 226
  - increased 25
  - pulmonary 226
- Edge activators 159
- Effect of malaria infection on neurogenesis 225
- EGF 151, 171
  - plasmid DNA-encoding 171
  - epidermal growth factor 151
- EGFR-targeted cationic polymeric 159
- Elastic fibres 148
- Elastin fibres 154
- Electrical activity 43, 134, 189, 191
  - cardiac 191
- Electrical stimulation 1, 2, 42, 43
  - functional 43
- Electrocardiographic abnormalities 190
- Electroneurophysiologic test 28
- Electron transport chain 130
- Electrophysiological feature 99
- Electroporation 84, 85
- Electrospun polycaprolactone 171
- Elements 84, 154, 169, 194, 195
  - cellular 154
  - intact dermal 169
  - main transposable 84
  - miRNA recognition 194
  - miRNA response 195
- Elevated interstitial pressures 4
- Elongation 12, 115, 125, 126
  - axonal 115
  - directed 12
  - neurite 125
  - vessel 154
- Embryoid body (EBs) 93, 94, 102
  - formation assay 102
- Embryonic 1, 7, 9, 76, 77, 90, 96, 117, 124, 167, 171, 192, 193
  - germ cells (EGCs) 76, 96
  - hair buds 171
  - hair folliculogenesis 167
  - stem cells (ESCs) 1, 7, 9, 76, 77, 90, 96, 117, 124, 192, 193
- Encoding, plasmid DNA 225
- Endocrine glands 116
- Endocytosis 198
- Endogenous 2, 42
  - electrical activation 42
  - neural stem cell 2
- Endogenous stem cells for SCI 14
- Endothelial 39, 41, 157
  - cell response 157
  - growth factor 41
  - oligodendrocyte trophic coupling 39
  - precursor cells 39
- Enzyme(s) 82, 96, 127, 128, 134
  - antioxidant 128
  - based procedures 134
  - cellular 127
  - CNPase 127
  - free reagent 96
  - integrase 82
- Ependymal

- cells (ECs) 15, 21, 22, 23, 24, 41, 116, 193
- stem/progenitor cells 1, 14
- Ependymocytes 15
- Epidermal 161, 162, 163
  - basal layer stem cells 161
  - epidermal cells, cultured 162, 163
- Epidermal growth factor (EGF) 7, 37, 41, 42, 124, 127, 132, 133, 147, 151, 153, 154, 165, 171, 172, 206
  - receptor (EGFR) 124, 147, 206
- Epidermis 145, 146, 147, 148, 152, 153, 159, 162, 166, 167, 169
  - avascular 148
  - functional 161
  - integrity 152
  - interfollicular 153, 167
  - stratified 166, 169
  - stratified cellular 145
- Epidermolysis bullosa 144, 153, 162, 163, 166
  - dystrophic 163
  - junctional 153, 162
- Epigenetic changes in neuronal differentiation 123
- Epilepsy 227
- Episomal vector method 102
- Epithelial-mesenchymal transition (EMT) 153
- Epithelium, stratified 145, 152
- Epstein-Barr virus 85
- ER-related stress 38
- Erythrocytes 221, 222, 223, 224
  - infected 221, 222
- Erythropoietin 228
- Excitation 3, 34, 130
  - neural 3
  - triplet state 130
- Excitation energy 130
- Excitotoxic cell death 4
- Excitotoxicity 3, 5
- Exogenous 2, 8, 9, 25, 26
  - neural stem cell 2
  - stem cells for spinal cord injury 25, 26
  - stem cell transplantation 9
  - transplantation methods for SCI 8
- Exosomal membranes 207
- Exosome concentrations 206
- Exosomes 156, 159, 160, 165, 197, 198, 205, 206
  - cell-derived 160
  - secretory 206
- Expression 76, 94, 114, 153, 188, 191, 193, 195
  - aberrant 188, 191, 195
  - connexin 193
  - forced 76
  - keratin 153
  - ligand 114
  - prolonged 94
  - regulating 195
- Extracellular 3, 17, 164, 165
  - glutamate 3
  - signal-regulated kinase 17
  - vesicles 164, 165
- Extracellular matrix 12, 88, 127, 145, 155, 168
  - nerve-related 127
  - molecules 12
- F**
- Factors 3, 12, 13, 23, 24, 25, 37, 88, 95, 117, 119, 126, 127, 143, 153, 154, 167
  - external 119, 143
  - intrinsic 16
  - leukemia inhibitor 88
  - mitogenic 154, 167
  - motogen 153
  - neurotrophic 12, 13, 24, 25, 37
  - neurotropic 117, 127
  - paracrine 126
  - restrictor 23
  - stem cell 95
  - tumor necrosis 3
- Fanconi anemia (FA) 4, 98
- Fas 4
  - mediated apoptosis 4
  - receptors 4
- Fat depots 118, 119, 120
- Feasibility and safety of autologous 32
- Fetal 78, 133
  - bovine serum 133
  - stem cells 78
- FGF 37, 41, 151
  - and PDGF supplementation 37
  - fibroblast growth factor 151
  - growth factors 41
- Fibers, positive 12
- Fibrillar polycaprolactone 172
- Fibrin 150, 154, 155, 163, 164, 172, 173
  - clot 150, 154

- spray 164
- strands 150
- Fibroblast(s) 7, 40, 41, 43, 78, 79, 80, 98, 101, 121, 132, 133, 147, 150, 151, 152, 153, 154, 155, 163, 164, 172, 173, 198
- allogeneic 163
- cardiac 198
- cultured 163
  
- growth factor (FGF) 7, 40, 41, 43, 121, 132, 133, 151, 153, 154
- regular 78
- Fibromuscular dysplasia 101
- Fibronectin 89, 147, 154, 155, 157
- Fibroplasia 152, 154
- Fibrosis 94, 99, 195, 197, 208
  - cardiac 197, 208
- Flow cytometry 102
- Fluorescence-activated cell sorting (FACS) 93, 95
- Fluorescent in situ hybridization 97
- Forkhead box protein 22
- Functional electrical stimulation (FES) 43
- Fungal sterility test 101
  
- G**
- GABAergic production 99
- GABA 42, 126
  - neurons 42
  - synthesis 126
- Gemcitabine 159
- Gene expression 123, 126, 131, 155, 188, 191
  - altered ion channel 191
- Gene regulation 194, 195, 196
  - elucidate 194
- Gene(s) 3, 4, 10, 76, 77, 83, 84, 86, 87, 88, 90, 93, 110, 117, 120, 123, 155, 191, 192, 193, 195
  - active transcription 87
  - antiapoptotic 3
  - conditional growth-promoting 10
  - fusion sarcoma 101
  - mammalian miRNA 195
  - mesodermal-specifying 86
  - mutated 191
  - neuronal 123
  - oxidative stress mediating 3
  - somatic 88
  - stem cell transcription factor 83
  - therapy strategy 192
  - transgenic 117
  - translation 194
- Gene targets 195, 196, 205
  - ion channel 205
  - multiple 195
- Genetic 2, 21, 23, 101
  - fate mapping (GFM) 2, 21, 23
  - fidelity and stability 101
- Gene transfer 192, 208
  - cardiac 208
- Glia 4, 11, 15, 42, 114, 115, 116, 120, 121, 125, 127, 133, 200
  - progenitor (GP) 15
  - radial 42, 120
- Glial cells 15, 16, 20, 35, 114, 116, 119, 120, 123, 124, 131, 224
  - mature 15
- Glial fibrillary 8, 23, 24, 124, 125, 127
  - acidic protein (GFAP) 8, 23, 24, 124, 125, 127
- Glial scar 1, 2, 4, 6, 15, 18, 22, 23, 24, 117, 118
  - chronic 1
  - formation process 18
- Glial scar post 16, 24
  - injury 24
- Gliogenesis 20, 120, 123
- Gliososis 20, 36
  - decreased 20
- Glucocorticoids 38, 226
  - synthetic 38
- Glutamate 4, 126
  - receptors 4
  - transporter 126
- Glutamic acid decarboxylase (GAD) 126
- Glutaminase 126
- Glutamine synthetase 126
- Glutathione 90, 128
  - reduced 128
- Glutathione 128, 223
  - content 128
  - peroxidase 223
  - reductase 128
- Glycoproteins 121, 147, 148
  - adhesive 147
- Glycosaminoglycans 154
- Granule cells, hippocampal 14
- Granulosum 145, 146, 147

stratum 145, 146, 147  
Green fluorescent protein (GFP) 22, 23, 208  
Growth 28, 40, 42, 117, 118, 125, 127  
  abnormal 28  
  axon 42  
  cellular 127  
  enhanced cholinergic fiber 40  
  inhibitory molecules 118  
  neuron 125  
  stimulate nerve 117  
Growth factors 1, 2, 7, 12, 39, 40, 42, 88, 94,  
  114, 117, 119, 121, 127, 131, 132, 133,  
  134, 150, 151, 154, 165, 169, 170, 171  
acidic Fibroblast 121  
cell 118  
epidermal 7, 127, 133, 165, 171  
fibroblast 7, 133  
hepatocyte 94, 165  
keratinocyte 165  
neuronal 114  
neurotrophic 12  
transforming 42  
vascular endothelial 39, 117, 165  
GTPases 128

## H

Haemorrhage 116, 117  
Haemostasis 150, 151, 155  
Hallucinations 227  
Healing process 16, 155, 156, 163, 165, 171  
  efficient wound 163  
  skin wound 165  
Heart 189, 195, 198, 206  
  failure 189, 195, 198  
  ischemia 206  
Hematopoiesis 220, 224  
Hematopoietic 35, 94, 95, 99, 165, 167, 168,  
  225  
  cell types 165  
  cytokines 94, 95  
  stem cells (HSCs) 35, 94, 99, 165, 167,  
  168, 225  
Hemidesmosomes 145  
Hemoglobin 222, 224  
  digestion 224  
  variants 224  
Hepatic organoids (HOs) 99  
Hepatitis virus 38  
Hepatocellular carcinoma 197

Hepatocyte growth factor (HGF) 94, 165  
Hexavalent chromium 96  
Hippocampal 28, 120  
  dentate gyrus 120  
  microglial activation 228  
Hippocampus neurogenesis 228  
Histocompatibility 8  
Histone acetylation 123  
HIV and nucleic acid 101  
Holoclones 161, 162  
Homeostasis 4, 127, 128  
  maintaining glutamate 4  
Host 158, 228  
  cells, hippocampal 228  
  genomic DNA 158  
Human 78, 100, 157, 164  
  epidermal keratinocytes (HEKs) 157  
  Fetal and Neonatal Cells 78  
  fibroblast-derived dermal substitute 164  
  haploid germ cells 100  
Human fibroblasts 77, 79, 83, 88, 93, 102, 169  
  embedded 169  
Huntington disease (HD) 99  
Hypertrophic scar 157  
  fibroblasts 157  
  formation 157  
Hypertrophy 4, 195, 198  
  cardiac 195, 198  
Hypertrophy heart 195  
Hypoexcitability 101  
Hypoglycemia 227  
Hyporeflexia 227  
Hypotension 4, 6  
Hypotonia 34

## I

Immature excitation-contraction 193  
Immortalized keratinocyte 169  
Immune response 19, 83, 85, 97, 99, 152, 158,  
  198, 223, 224  
  adaptive 152  
  innate 83  
Immune system 150, 224, 226  
  innate 150, 226  
Immunity 120, 224, 225  
  adaptive 225  
Immunodeficiency 228  
Immunohistochemical analysis 36  
Immunohistochemistry 93

- Immunomodulatory effect 7  
Immunopathogenesis 227  
Induced pluripotent stem cells 2, 10, 76, 77,  
117, 165, 168, 205  
Induction, tamoxifen 22  
Infarction 189  
Infections 144, 192, 221, 227  
bacterial 192  
congenital 221  
invasive 144  
severe malaria 227  
transmitting viral based 192  
Inflammatory cells release 154  
Injury 35, 134, 191, 197, 227  
ischemic 227  
ischemic brain 134  
life-threatening 134  
myocardial 191, 197  
peripheral nerve 35  
Integrin receptors 89  
beta-1 42  
Intracellular cAMP concentration 121  
Intrahepatic cholestasis 99  
Intrathecal infusion 37
- J**
- Janus Kinases (JNK) 129
- K**
- Keratinocyte growth factor (KGF) 151, 165  
Keratinocytes 63, 80, 145, 147, 149, 150, 152,  
153, 154, 156, 160, 161, 162, 163, 165,  
166, 168, 170, 172  
activation 153  
basal 145, 147, 153, 161  
epidermal 80, 166, 170  
migration 152, 153, 156, 165  
proliferation 153, 156  
root sheath 162  
suprabasal 150  
suspension 163  
Keratins 145, 147, 153, 171  
Knockout serum replacement (KSR) 90, 94
- L**
- Langerhans cells 145, 149, 152  
Large DNA fragments 83, 84  
integrating 84  
Lesion, damaged DNA 96  
Leukemia 39, 88, 94  
inhibitor factor (LIF) 88, 94  
inhibitory factor 39  
Leukocytes, attracted peripheral 4  
Lipids 84, 90, 146, 197  
cationic 84  
neutral 146  
Low affinity growth factor (LAGF) 12  
Lower spinal cord injuries 6  
Low-Intensity Laser Irradiation (LILI) 130,  
131, 133, 134  
Lymphoblast 85  
Lymphocytes 4, 79, 80, 94, 147, 150, 152, 204  
Lymphotoxins 223
- M**
- Macrophage 152, 165  
inflammatory protein (MIP) 165  
phenotype 152  
population 152  
Magnetic 26, 27, 28, 31, 32, 33, 95, 98  
-activated cell sorting (MACS) 95, 98  
Resonance Imaging (MRI) 26, 27, 28, 31,  
32, 33  
separation methods 95  
Malaria 220, 221, 223, 224, 225, 227, 228  
elimination 223  
falciparum 227  
infection 224  
Infection on Neurogenesis 225  
murine strain 228  
pathogenesis 220, 221  
Malignant hyperthermia 100  
Mammary glands 144  
Matrix 35, 154, 155, 170, 171, 172, 173  
collagen-based 154  
collagen-fibrinogen 173  
denatured acellular dermal 171  
fibrin-collagen 172  
human acellular dermal 170  
porcine acellular dermal 171  
synthesized 154  
Matrix components, extracellular 147, 151,  
154, 155, 167  
Mechanisms 120, 143, 189, 222  
cellular signalling 120

- gating 189
  - intrinsic regenerative 143
  - natural protective 18
  - pathogenic 222
  - Mesenchymal 8, 9, 10, 26, 27, 28, 30, 117, 118, 122, 131, 132, 133, 158, 164, 193, 206, 224
    - BM cell 31
    - origin 117, 131
    - stem cells (MSCs) 8, 9, 10, 26, 27, 117, 118, 122, 132, 133, 158, 164, 193, 206, 224
    - stem cell transplantation 28, 224
    - stromal cells 8, 30
  - Metalloproteinase 151
  - Methemoglobin 222
  - Methylation 88, 123
  - Methylmercury 96
  - Methylprednisolone sodium succinate 7
  - Microarray analysis 120
  - Microbiological sterility 101
  - Microenvironment 11, 17, 19, 89, 131
    - functions 19
    - nurturing 17
  - Microextrusion 172
  - Microglia 4, 6, 21, 38, 41, 116
    - activated 4
    - surrounding 4
  - Microglia 4, 6, 116
    - and macrophages 4, 6
    - glial cells 116
    - proliferation 4
  - MicroRNAs 124, 143, 144, 155, 158, 159, 160, 188, 194, 195, 196, 197, 199, 206
    - delivering 206
    - delivery of 158, 159
    - functional 160
    - therapeutic 160
  - Migration 10, 16, 17, 18, 23, 37, 42, 43, 98, 151, 152, 154, 156, 157, 165, 168
    - cellular 98
    - fibroblast's 156
    - graft 10
    - inhibiting NSC 17
    - involved astrocyte 18
    - neuroblast 42
    - preventing oligodendrocyte 23
    - quantified directional 43
  - Mineralocorticoid receptors 38
  - miRNA response elements (MREs) 195
  - Mitogen activated protein kinases (MAPK) 128, 129
  - Modifying epigenetic programming 114
  - Modulating signalling pathways 127
  - Molecules 12, 35, 86, 100, 118, 128, 130, 143, 144, 193, 194
    - expressed cell adhesion 12
    - key signalling 128
    - multiple bioactive 118
    - neural cell adhesion 12
    - peptide amphiphile 35
    - trafficking-related 193
  - Monocytes 4, 151, 152
  - Motor evoked potentials (MEP) 19, 32, 33, 34
  - Mutagenesis 84
  - Mutations 76, 78, 80, 87, 96, 97, 98, 101, 116, 121, 159, 190, 191, 199
    - avoiding 97
    - functional 87
    - genetic 116
    - missense 101
    - somatic 78
  - Myelinating 12
  - Myeloperoxidase 150
  - Myoblasts 164, 194
    - grafted 194
  - Myocardial infarction 194, 197, 206
  - Myocardocytes 208
  - Myocardium 192, 194
    - infarcted 194
    - quiescent 192
  - Myocardium structure 191
  - Myocytes 193, 199, 202, 203
    - cardiac 199
    - porcine 193
    - ventricular 202, 203
  - Myofibroblasts 155
- ## N
- Nanog, pluripotency proteins 93
  - National acute spinal cord injury study (NASCIS) 7
  - Near Infrared region (NIR) 129
  - Neovascular effects 197
  - Neonatal cells 78, 80
  - Neon Transfection System 85
  - Nerve 34, 40, 116, 117, 122, 132, 134
    - autonomic 116
    - damaged 132, 134

- growth factor (NGF) 40, 117, 122
  - impulses 34
  - Nerve fiber growth 12, 17
    - long distance 17
  - Nerve fibers 25, 34
    - injured 25
  - Nerve regeneration 35, 118, 159
    - peripheral 35
  - Nervous system 7, 39, 115, 116
    - developing 115
    - peripheral 7, 39, 115, 116
    - somatic 115
  - Nervous system 100, 114, 134
    - diseases 100, 134
    - disorders 114
  - Neural 11, 14, 18, 37, 43, 95, 99, 115, 121, 122, 123, 124
    - cortical organoids 99
    - patterning 121, 122
    - precursor cells (NPCs) 18, 37, 43, 115, 123, 124
    - progenitor (NPs) 11, 14, 95, 115
  - Neural cells 11, 16
    - grafted human 11
    - post injury 16
  - Neurobiological indices 12
  - Neurocognitive deficits 227
  - Neurodegeneration 116
  - Neurogenesis 14, 19, 20, 38, 39, 98, 120, 121, 122, 123, 128, 220, 225
    - demonstrated active 39
    - embryonic 120
    - post-natal 39
    - vertebrate 122
  - Neurogenesis in Spinal Cord 14
  - Neurogenic shock 3
  - Neuronal 11, 25, 39, 116, 124, 125, 134
    - growth 39, 116
    - lineage cells 124, 125
    - phenotypes 11, 122
    - progenitors 124, 134
    - protection 25
  - Neuronal circuitry 14, 37
    - disrupted 37
  - Neuronal cytoskeleton 4
  - Neurons 8, 9, 10, 11, 12, 14, 15, 35, 115, 116, 121, 122, 123, 124, 125, 126, 134, 199, 200, 202, 203
    - cholinergic basal forebrain 122, 126
    - cholinergic phenotypic 11
    - cortical 203
    - dorsal root ganglion 12
    - immature 15, 125
    - peripheral 199, 200
    - sensory 122, 123
  - Neuropathic pain 27
  - Neuroprotection 38
    - promoted 38
  - Neuroregeneration, affected 6
  - Neurosphere-initiating cells 21
  - Neurotoxicity 100
  - Neurotransmission 3, 126
  - Neurotransmitter(s) 126, 134
    - exchange 134
    - monoamine 126
    - receptors 134
    - release activities 122
  - Neurotrophic factors post injury 1
  - Neurotrophins 39, 40, 122, 126
  - Nuclear receptor modulators 87
  - Nucleases 83
  - Nucleofection 85
  - Nucleotidase 164
  - Nucleotide activation 20
- O**
- Olfactory ensheathing cells(OECs) 1, 12, 13
  - Oligodendrocytes 4, 5, 9, 10, 11, 14, 15, 17, 18, 21, 22, 23, 24, 40, 42, 127
    - immature 127
    - mature 9, 22, 40
    - myelinating 22
    - ventral 23
  - Oligodendrocyte lineage 15, 22, 38, 40
    - cells 40
    - identified 22
  - Oligodendrocyte progenitor cells (OPCs) 8, 9, 10, 15, 23, 38, 40, 41, 42
  - Oligodendrogenesis 38
  - Oncogenesis 85
  - Open reading frame (ORF) 194
  - Organogenesis 168, 169
  - Osteoblasts 164, 202, 203
  - Osteogenic 132, 133
    - differentiation media 132, 133
    - scaffolds 133
    - supplements 132
  - Oxidase 127, 129
  - Oxidative stress in malaria 223



**P**

- Pacemaker channels, engineered novel  
synthetic 192
- Paracrine effect 164, 167
- Parasite 220, 221, 222, 224, 225  
ape Plasmodium 221  
intra-erythrocytic 222  
liver stages 225
- Parkinson's disease 116, 134
- Partially reprogrammed cells 92
- Pathogen 83, 151, 221  
respiratory 83  
zoonotic 221
- Pathogenesis 221, 227
- Pathogenic 151, 166  
gene alteration 166  
microorganisms 151
- Pathways 17, 41, 87, 89, 120, 121, 122, 129,  
130, 132  
cell senescence 132  
default neural differentiation 121  
energy transfer 130  
integrin 89  
phosphatidylinositol 3-kinase 41  
tyrosin kinase receptor 87
- Pattern, microRNA signature 124
- Peptides 12, 89, 98, 133, 145, 159, 206  
filaggrin 145  
gene-related 12  
synthetic 89  
truncated 89  
tumor 98
- Peripheral 6, 7, 8, 39, 76, 79, 80, 81, 82, 85,  
115, 116, 122, 127  
blood mononuclear cells (PBMCs) 76, 79,  
80, 81, 82, 85  
nervous system (PNS) 7, 8, 39, 115, 116,  
122, 127  
vasoconstriction 6
- Peroxidation, reducing 7
- Phagocytosis 151, 152, 224
- Phenotype 78, 100, 127, 152, 154, 155, 164  
contractile 155  
epithelial 164
- Phosphodiesterase 121
- Phospholipase 129
- Phosphorylation, induced 128
- Photobiomodulation 114, 129, 131
- Photoreceptors 94
- Plasmodium* 220, 221, 222, 224, 226  
*berghei* 224, 228  
*chabaudi* 224  
*falciparum* 220, 224, 226  
*vivax* 220, 221, 222
- Plasticity 13, 125, 164, 225  
synaptic 13, 125
- Platelet-derived growth factor (PDGF) 21, 40,  
41, 124, 127, 150, 154, 164  
-B (PDGFB) 164  
receptor (PDGFR) 21
- Pluripotency genes 86, 88, 92
- Pluripotent 76, 77  
cell extracts 76  
state 77
- Polyethyleneimine 84
- Polymerase chain reaction (PCR) 93, 97
- Polymers 84, 89, 159, 170, 172, 208  
cationic 84, 159, 208  
natural 170, 172  
synthetic 170
- Polymer scaffolds 35, 36, 37  
biodegradable 35, 36
- Polymorphism 97, 101  
single nucleotide 97
- Progenitor 2, 41, 43, 94, 95, 115, 121, 226  
endogenous 41  
glial-restricted 115  
hematopoietic 94, 95  
lineage-restricted 115  
tripotential 43
- Progenitor cells 14, 41, 95, 102, 115, 150,  
165, 167  
endogenous 41  
hematopoietic 102  
neural 115  
neuroepithelial 115  
smooth muscle 95
- Progeny 21, 22, 42  
ependymal 22  
mature 21  
producing persistent neuronal 42
- Progressions 123, 158, 160, 173  
tumour 160
- Protection 149, 206, 224  
cardiovascular 206
- Proteins 22, 38, 87, 89, 91, 92, 121, 124, 125,  
127, 128, 145, 146, 153, 156, 191, 193,  
194, 195, 197  
basic helix-loop-helix 127

bone morphogen 153  
calcium-binding 128  
critical cardiac 193  
cross-linked 146  
encode 195  
green fluorescent 22  
growth factor binding 38  
intermediate filament 124  
kinase A (PKA) 128  
  non-channel scaffolding 191  
single spanning transmembrane 121  
Proteoglycans 1, 4, 24, 18, 24, 37, 89, 148,  
  154  
  chondroitin sulfate 1, 4, 18, 24, 37  
  heparan sulphate 89

## R

Ras/mitogen-activated protein kinase  
  signalling 157  
Regeneration 43, 111, 157, 206  
  affected spinal cord 11  
  myocardial 206  
  neural 43  
  skin attachment 157  
Regenerative medicine 7, 27, 97, 100, 117,  
  118, 130, 166, 169, 188, 192  
Regulation, posttranscriptional 18, 155  
Remyelination failure 38  
Repression 155, 194, 196, 197, 199  
  post transcriptional 199  
  post-transcriptional 196  
  translational 155  
Repressive chromatin marks 87  
Reprogramming 77, 80, 96, 198  
  cellular 77, 160, 193, 220, 223  
  event 77  
Resistance 160  
  antimalarial drug 220  
  emerging Plasmodium 223  
  high input 193  
  insecticides 220  
Retinoic acid (RA) 17, 86, 96, 122, 123, 132  
Retinoid X receptors (RXR) 122  
Retroviral vectors 102, 158  
  classical integrative 102  
RNA 86, 188, 194, 206, 207  
  -binding proteins 86, 194  
  drug delivery system 206  
  interference 188

  molecules 207  
RNA-induced silencing 156, 194  
  complex (RISC) 156, 194  
RNA polymerase(s) 123, 155  
  II 155, 194  
  III 155  
RNAs 18, 93, 123, 144, 159, 188, 195, 198,  
  206  
  competing endogenous 195  
  degradation 206  
  long non-coding 18, 195  
  main small non-coding 144  
  non-coding 198  
  non-protein coding 188  
  regulatory 123  
  short hairpin 93  
  silencing 159  
  small interfering 206  
Rostral migratory stream (RMS) 225, 226  
Ryanodine receptor 191

## S

Sarcoma kinase 129  
Scaffold 35, 36, 37, 168, 169, 170  
  acellular 168  
  bioresorbable 169  
  cellular bioengineered 168  
  composite 170  
  multichannel 35  
  polyglycolic acid 35  
  single lumen 35  
Scar 19, 144, 154, 157, 164  
  astrocytic 19  
  hypertrophic 144, 154, 157, 164  
Scar formation 11, 13, 16, 17, 18, 20, 37, 157,  
  164, 174  
  attenuate 164  
  chronic astrocyte 18  
  glial 11, 16, 20, 37  
  nil astrocyte 18  
Schizophrenia 117  
Schwann cells (SCs) 1, 12, 36, 115, 116, 127,  
  146, 159  
Sebaceous glands 144, 148, 149, 153, 163  
Serious adverse events (SAEs) 31, 32  
Severe malaria treatment 228  
Sickle anemia 101  
Signaling pathways 17  
Signalling 121, 128, 129, 130, 169, 191

- neuro-hormonal 191
  - regulating Wnt/ $\beta$  catenin 169
  - Signalling pathways 114, 123, 124, 128, 129, 131
    - cellular 131
    - induced cell 114
  - Skin 146, 150, 158, 159, 167, 168, 170, 172
    - hairy 150
      - healing process 170
    - healthy 172
    - lesions 167
      - palmoplantar 146
    - planar hair-bearing 167
    - porcine 159
      - regeneration therapy 168
      - therapy 158, 167
  - Skin cells 160, 167
    - differentiated 172
  - Skin grafts 162, 163
    - split thickness 163
  - Somatic nervous system (SNS) 115
  - Somatosensory evoked potentials (SEP) 19, 32
  - Spinal cord 1, 2, 3, 4, 6, 11, 12, 14, 15, 16, 18, 21, 22, 23, 24, 33, 35, 37, 39, 42, 115
    - injured 1, 18, 24, 37
    - intact 10, 14, 15, 16, 23
    - non-injured 11
    - parenchyma 15
      - thoracic 12
    - transected thoracic 12
      - repair 35
      - upper 6
  - Spinal cord injury 1, 2, 5, 43, 117
    - pathophysiology 5, 117
      - chronic 43
    - understanding of 1, 2
  - Spinal muscular atrophy (SMA) 98
  - Split-thickness allograft 169
  - Stem cell 1, 2, 8, 10, 11, 28, 33, 35, 77, 100, 114, 118, 120, 133, 165, 168, 171, 224, 225
    - adipose 114, 120
    - adipose derived 1, 10
    - adipose derived mesenchymal 171
    - adipose-derived mesenchymal 168
    - atypical 224
    - bone marrow 8, 28, 118, 133
    - haematopoietic 168
    - haploid 100
    - hematopoietic 35, 165
    - human adipose 118
    - human brain-derived 11
    - human CNS 11
    - human embryonic 77
    - human hair follicles 171
    - human hematopoietic 225
    - marrow-derived mesenchymal 168
    - tissue-derived mesenchymal 33
    - transgenic epidermal 162
  - Stem cell therapy 25, 29, 34, 119, 131, 188, 191, 192, 194, 220, 224, 228
    - in spinal cord injury 29
  - Stem cell transplantation 24, 25, 29, 32, 35
    - neural 32
    - status post 25
  - Stromal-vascular fraction (SVF) 119
  - Sudden cardiac death (SCD) 188, 189
  - Suppression 87, 192, 194, 208, 228
    - temporary 228
  - Synapse formation 42, 126
  - Synaptic junctions 115, 127
    - neuromuscular 127
  - Synaptogenesis 121, 126
  - Synaptophysin 126
- ## T
- Tachycardia 189
  - Tachycardia remodelling 191
  - Tail tissue fibroblasts (TTFs) 77, 82
  - Tamoxifen-dependent Cre 22
  - Tanycytes 15
  - Target cell 121, 207
    - surface 121
    - types 207
  - Target genes 84, 194
    - suppress 194
  - Target miRNA 208
    - silence 208
  - Targets 121, 156, 195, 199, 208
    - direct 156
    - natural 208
    - potential 199
    - single 195
    - transcriptional 121
  - Therapies 1, 6, 25, 115, 160, 164, 165, 167, 169, 173, 192, 193, 209, 220
    - antimalarial 220
    - biological 192

- immuno-suppressive 193
  - regenerative 164, 165
  - supportive 6
  - Tissues 8, 6, 7, 11, 18, 78, 97, 116, 130, 131, 132, 143, 144, 147, 152, 154, 168, 169, 192, 193, 194, 197, 201, 205, 208
    - cardiac 192, 208
    - connective 147
    - damaged 197
    - differentiated 169
    - fetal 78
    - harvested 132
    - human spinal cord 11
    - injured spinal 8
    - ischemic 97, 197, 205
    - lymphoid 152
    - nervous 1, 116
    - neural 6, 7, 201
    - neuronal 18
  - TNF $\alpha$ -tumour necrosis factor alpha 151
  - Toll-like receptor (TLRs) 152
  - Transcription factors 2, 10, 15, 18, 42, 43, 77, 87, 118, 119, 121, 123, 127, 131
    - bipartite 123
    - deleting STAT3 18
    - inducing 131
    - oligodendrocyte 15, 127
    - pluripotency-associated 86
    - regulating 127
    - stem cell 119
  - Transcripts 38, 77, 155, 194
    - messenger RNA 38
  - Transduction 82, 83, 85
    - retroviral 85
    - retroviral-mediated 82
    - viral 83
  - Transfection 76, 77, 84, 85, 102
    - laser-based 84
    - physical 84
    - retroviral 77
  - Transfer of bone marrow derived stem Cells 29
  - Transferrin 89, 90, 95
  - Transferring zoonotic pathogens 88
  - Transfersomes 159
  - Transglutaminase 147
  - Transition 87, 152, 153, 156
    - epithelial-mesenchymal 153
    - impaired 152
    - mesenchymal 87
  - Translation 2, 166, 194
    - repress 194
  - Translocation 86, 131
  - Transmembrane receptors 114, 121
    - seven-pass 121
  - Transmission 115, 116, 117, 134
    - impulse 115, 117, 134
  - Transplant 13, 28, 97, 162
    - olfactory ensheathing cell 13
  - Transplantation 2, 9, 10, 12, 20, 24, 25, 26, 33, 34, 36, 37, 76, 162, 166, 167
    - acute 20
    - allogenic cell 8
    - autologous BMSC 25
    - derived keratinocytes 167
    - direct intra-spinal cell 24
    - exogenous 24
    - expanded mesenchymal stem cells 26
    - follicular unit 162
    - hair follicle 162
  - Transporters 126, 189, 191
    - choline 126
    - vesicular acetylcholine 126
    - vesicular glutamate 126
  - Tranlylcypromine 86, 88
  - Trauma 24, 132, 144
    - minimal surgical 132
    - minor 144
  - Tumorigenesis 82, 160
  - Tumor 3, 87, 222, 227, 228
    - necrosis factor (TNF) 3, 222, 227, 228
    - suppressor 87
  - Tyrosine kinases 42, 128, 129
- ## V
- Vaccines 225
    - anti-cancer 225
  - Valvopathies 101
  - Vascular endothelial 39, 40, 41, 117, 120, 151, 154, 158, 165
    - cell types 120
    - growth factor (VEGF) 39, 40, 41, 117, 151, 154, 158, 165
  - Vectors 82, 83, 85, 192
    - episomal 76, 85, 93, 102
    - gene therapy 225
    - single cassette reprogramming 83
  - VEGF 40, 151
    - family molecules 40

-vascular endothelial growth factor 151

## **W**

Wallerian degeneration 4

Water storage 149

Wavelengths 129, 130, 132, 133

higher 130

lower 130

Weighted gene coexpression analysis 19

White adipose tissue 119

White matter 12, 14, 38, 40

function 40

parenchyma 14

tracts 12, 38

World health organization (WHO) 220, 221,  
226

Wound closure, accelerating 165

Wound contraction 154, 156, 173

reduced 173

Wound dressing 169

Wound healing 143, 152, 153, 155, 156, 160,

162, 163, 164, 165, 168, 170, 172

chronic 160

therapy 158, 163

Wound healing process 143, 144, 150, 153,

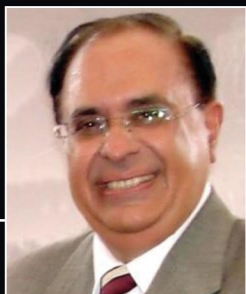
156, 160, 164, 169, 173, 206

Wounds therapies 143, 171

chronic 143

## **Z**

Zonesthesia 25



**ATTA-UR-RAHMAN, FRS**

---

Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/ Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.



**SHAZIA ANJUM**

---

Dr. Shazia Anjum is the Professor of the Chemistry Department and the Director of Cholistan Institute of Desert Studies, the Islamia University of Bahawalpur, Pakistan. She is experienced medicinal and natural product chemist. She has authored and co-authored more than 116 research papers (Impact Factor: 208) and a US patent. She has edited 09 books and has published 03 chapters in international books. She has accomplished the synthesis of several naturally occurring aminoglycosides that can be used as antibiotics. Dozen of students have completed their MS degrees under her supervision and couple of others are pursuing for their MS/PhD degrees.

As recognition of her contributions to science, she has been awarded with 03 International awards like Fellowship from Islamic World Academy of Sciences, Postdoctoral fellowship from Ministry of Culture and Education, Spain and a Young Chemist Award from Third World Academy of Sciences, Italy. She also has several national awards on her credit.