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Frontiers in Stem Cell and Regenerative Medicine Research Volume 4

Editors:
Atta-ur-Rahman, *FRS*
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Frontiers in Stem Cell and Regenerative Medicine Research

(Volume 4)

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Volume # 4

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CONTENTS

PREFACE	i
LIST OF CONTRIBUTORS	iii
CHAPTER 1 RETRODIFFERENTIATION: FROM CONCEPT TO BEDSIDE STEM CELL THERAPY	3
<i>Kj co "Uergj "Cdwlcfc{gn</i>	
INTRODUCTION	4
HEALING MECHANISMS IN RESPONSE TO TISSUE INJURY IN ADULT HUMAN	6
COMPENSATORY REGENERATION	8
EPIMORPHIC REGENERATION	11
POSITIONAL INTEGRATION AND MOLECULAR MECHANISMS OF REGENERATION	12
ORIGIN OF BLASTEMA	13
REPROGRAMMING THE DIFFERENTIATED STATE	14
RETRODIFFERENTIATION OF HUMAN LEUKOCYTES	15
PHENOTYPES OF THE RETRODIFFERENTIATED STEM CELL STATE	17
CLINICAL APPLICATION OF RETRODIFFERENTIATED STEM CELLS	22
CONCLUDING REMARKS	24
CONFLICT OF INTEREST	26
ACKNOWLEDGEMENTS	26
REFERENCES	26
CHAPTER 2 THE MESENODERM: A WELLSPRING OF CELL LINEAGES FOR REGENERATIVE MEDICINE	36
<i>Defy kDODqwo gjj go . "Ugrj gp "LOCuapf gt. "Ej tkarj "J co o cpu "O ctkgwc "ROVcpwf kuciat q. "F co kgp "VOO ONg. "Mst vY ONODt ki f gp "and "Uwct vVOHt cugt</i>	
INTRODUCTION	37
The Germ Layers	39
The Mesendoderm	40
Mesoderm Differentiation	43
Endoderm Specification	43
In vitro Models of Mesendoderm Formation	45
<i>Embryonic Stem (ES) Cell Differentiation as in vitro Model of Mesendoderm Development</i>	46
<i>Induced Pluripotent Stem Cells as a Novel Source of Mesendodermal Progenitors for Regenerative Medicine</i>	49
Modelling Interactions Between Endoderm- and Mesoderm-derived Cell Types Using Pluripotent Stem Cells	50
<i>Differentiation of Pancreatic β-cells as a Treatment for Diabetes</i>	50
Developing New Systems for Regenerative Medical Intervention During Liver Disease	52
Endodermal and Mesodermal Derivative Lineages in Treatment for Disease of the Genitourinary Tract	54
Development of the Bi-potential Gonad and Reproductive Tracts	54
Development of Kidney Organoids from Human Embryonic and Induced Pluripotent Stem Cells as a Model of Kidney Development	55
The Urogenital Sinus and Accompanying Organs	56
Differentiation of Urothelium from Mouse, Human and Adult Stem Cells	57
Primordial Germ Cell Development	59
In vitro Generation of PGCs and Regenerative Medicine	60
Adipogenesis and Differentiation of Adipocytes from Stem Cells	61
Mesendoderm and Tissue Engineering for Regenerative Medicine	62
<i>Introduction to 3D Printing</i>	62

3D Printing Technologies	63
3D Printing of Biomaterials in Tissue Engineering	66
Selecting the Biomaterial for 3D Bioprinting	67
Applications of Scaffolding in Mesendodermal Tissues	75
Stem Cells, 3D Printing and Bone Healing	75
Stem Cells and 3D Bioprinting of the Trachea	76
3D Bioprinting of Stem Cells for the Treatment of Cardiac Disease	77
Bioengineering Blood Vessels	78
3D Stem Cell Bioprinting in an Undergraduate Research Laboratory	79
Future Directions in Tissue Engineering	82
CONCLUDING REMARKS	84
CONFLICT OF INTEREST	84
ACKNOWLEDGEMENTS	84
REFERENCES	85

CHAPTER 3 HEMATOPOIESIS AND REGENERATIVE MEDICINE 101

<i>Ej cpwifc 'MØEqrppg. 'Xgtqpkc 'KOCpvcu 'Lk' 'J cq' 'I gq. 'J gpt{ 'Y lntc o u 'Ej gngc 'Rlri tlo 'and 'Uwctv'VOHt cugt</i>	
INTRODUCTION	102
AN INTRODUCTION TO HEMATOPOIESIS	103
Hematopoiesis is Dependent Upon the Hierarchical Production of Mature Cells from Rare Stem Cells	105
Identifying and Characterising Hematopoietic Stem Cells	107
Embryonic Hematopoiesis	108
The Yolk Sac is the Initial Site of Blood Production	110
The Dorsal Aorta as a Critical Hematopoietic Niche	111
The Placenta is a Blood-production Site	112
The Fetal Liver: A Niche for Expansion of Blood Stem and Progenitor Cells	112
The Fetal Spleen: A Newly Recognized Fetal Blood Producing Niche	113
THE HEMATOPOIETIC NICHES	113
Embryonic Hematopoietic Niches	114
The Adult Bone Marrow Hematopoietic Niche	114
Adult Peripheral Hematopoietic Niches: The Thymus Provides a Niche for T Cell Maturation	118
Adult Peripheral Hematopoietic Niches: The Splenic Niche During Stress	119
HEMATOPOIETIC STEM CELL TRANSPLANTATION	121
A Classical Case Study in Regenerative Medicine	121
A History of Bone Marrow Transplantation	121
Sources of Hematopoietic Stem Cells	123
The Human Umbilical Cord: A Source of Therapeutic Stem Cell Populations	124
Complications of Hematopoietic Stem Cell Transplantation	125
FUTURE DIRECTIONS AND THE POTENTIAL OF REGENERATIVE MEDICINE	126
Generating Hematopoietic Stem and Progenitor Cells from Pluripotent Stem Cells in vitro	126
<i>Pluripotent Stem Cells</i>	126
<i>Embryonic Stem Cells</i>	126
Induced Pluripotent Stem Cells and Hematopoietic Development	128
Regenerative Medicine for Red Blood Cell Transfusion: Generation of Mature Erythroid Cells from Patient-derived Hematopoietic Progenitors	129
Utilizing Primary HSPCs as a Source for Ex vivo Erythroid Cell Generation	131
Pluripotent Stem Cells as a Source for Ex Vivo Erythroid Cell Generation	132
New Directions to Improve Yield of Ex Vivo Erythrocyte Production	133
Application of Hematopoietic Regenerative Medicine to Human Disease	134
<i>Regenerative Medicine Utilizing Cell-based Gene Therapies; The Future is Here</i>	134
<i>Bio-engineering Hematopoietic Cells, Tissues and Organs for Regenerative Medicine</i>	136

<i>Bioengineering the Primary Hematopoietic Organ in Adults - Factors to Consider for an Ex Vivo Bone Marrow Model</i>	136
<i>3D Bioprinting and "Organ-on-a-chip" Technologies</i>	138
<i>Engineering Hematopoietic and Lymphoid Organs from Pluripotent Stem Cells</i>	141
<i>Bioengineering the Thymus</i>	141
<i>Bioengineering the Spleen</i>	142
<i>Artificial Lymph Nodes</i>	143
CONCLUDING REMARKS	143
CONFLICT OF INTEREST	144
ACKNOWLEDGEMENTS	144
REFERENCES	144
CHAPTER 4 CELL-BASED THERAPY IN VETERINARY MEDICINE	170
<i>Ej cf 'O cnk 'Vj qo cu'Tco qu'and'Hctkdqt/'Kcf {ct</i>	
RECENT ADVANCES AND APPLICATIONS OF CELL THERAPY	170
CELL THERAPY AND REGENERATIVE MEDICINE	174
FUNCTIONAL MODELS OF CELL THERAPY AND REGENERATIVE MEDICINE	177
IMPLICATIONS OF CELL THERAPEUTIC APPLICATIONS	183
Quality of Life and Anti-aging	184
MANUFACTURING CELL-BASED PRODUCTS	185
STEM CELLS, PROGENITOR CELLS AND BLOOD DERIVED PRODUCTS	188
THERAPEUTIC APPLICATIONS IN VETERINARY MEDICINE	190
Veterinary Clinical Studies	192
AGING AND REGENERATIVE POTENTIAL	195
DEBILITATING DISEASES IN COMPANION ANIMALS	197
ARTHRITIS AND JOINT FAILURE AS A MODEL FOR CHRONIC DISEASES	199
CURRENT CLINICAL MANAGEMENT AND STEM CELL THERAPIES	202
ORGAN FAILURE AND TISSUE ENGINEERING	209
LIMITATIONS AND CHALLENGES OF CELL-BASED THERAPY	211
Reality vs. Fantasy	211
Technical Challenges	212
Regulatory Encounters	213
FUTURE IMPLICATIONS	216
CONFLICT OF INTEREST	218
ACKNOWLEDGEMENTS	218
REFERENCES	218
CHAPTER 5 FROM TRIALS TO THERAPEUTICS: ARE MESENCHYMAL STEM CELLS PROMISING IN CELLULAR THERAPY?	234
<i>I cpcrcvj k'O 0Dj cv'Rqqlc'Uj cj crwtmct 'and'Tcuknc'I 0Dj cv</i>	
INTRODUCTION	235
THERAPEUTIC APPLICATIONS	237
Therapeutic Debut: Taking the First Step	237
<i>Migratory Homing</i>	237
<i>Paracrine Effects</i>	238
<i>Regenerative Prowess: Role in Tissue Repair and Organ Rescue</i>	239
<i>Battling Immune Assaults: Role in Immune Mediated Disorders</i>	242
DISCUSSION	246
CONCLUSION	250
FINANCIAL SUPPORT	250
CONFLICT OF INTEREST	250
ACKNOWLEDGEMENTS	251
REFERENCES	251
SUBJECT INDEX	263

PREFACE

There continues to be tremendous progress in the field of stem cell and regenerative medicine research. The developments promise to change the face of medicine. This 4th volume of ‘*Frontiers in Stem Cell and Regenerative Medicine Research*’ should be of considerable interest to the readers as it presents state-of-the art reviews written by renowned experts in this fast moving field.

Ilham Saleh Abduljadayel presented a comprehensive review in chapter 1 on epimorphic regeneration and retrodifferentiation. Both processes have the capacity to recreate and reconstruct tissue with precise positional integration of cells in such a way that will enable healing without scars. In chapter 2 Fraser *et al.* extensively reviewed the unique genetic programmes that lead to mesendoderm formation and the pathways leading to mesoderm and endoderm specification. They also present examples where mature cell types from both germ layers interact to support their mutual development. These programmes are being employed to direct the differentiation of pluripotent cells *in vitro* into mesendoderm derived cells and tissues. Fraser *et al.* also reviewed the role of stem, progenitor and supportive cells within the hematopoietic tissues as essential elements of regenerative medicine in chapter 3.

Cell-based therapy is an emerging field in veterinary medicine that has been used for developing new therapies for degenerative diseases. In chapter 4 Izadyar *et al.* described different cell based therapies, their risks and benefits and their possible therapeutic use for veterinary medical applications. Mesenchymal stem cells (MSCs) are the most favored cellular candidates for regenerative therapeutics. Bhat *et al.* discussed how MSCs contribute to therapeutic efficiency include facilitating secretion of bioactive factors, induction of cellular recruitment and retention of progenitor faculties in the last chapter.

Knowledge of stem cell and regenerative medicine research continues to move ahead on many fronts. We hope that the readers will enjoy reading about the latest and stimulating development in this hot area in the 4th volume of this series.

We are pleased to place on record our heartfelt thanks to all the authors for their contributions. We are also grateful to the editorial staff of Bentham Science Publishers, particularly Dr. Faryal Sami, Mr. Shehzad Naqvi and Mr. Mahmood Alam for their constant support and great help.

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Retrodifferentiation: From Concept to Bedside Stem Cell Therapy

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Abstract: Epimorphic regeneration is a process by which damaged tissues or severed body parts are restored to the original. This type of sophisticated regeneration is observed in urodeles and fetal mammals. For example, through this process, an amputated limb of a salamander can be restored, by re-growing an exact replica, irrespective of its age. During limb epimorphic regeneration: committed mesenchymal cells at the stump site dedifferentiate, forming a cluster of heterogeneous population of stem cells, known as the blastema. Upon blastema integration, positioning and expansion, constituent cells embark on redifferentiation and remorphogenesis to restore the lost appendage. Similar to epimorphic regeneration is retrodifferentiation in human leukocytes. In response to ligation of monomorphic regions of MHC class II antigens with monoclonal antibody CR3/43, human leukocytes retrodifferentiate into a variety of heterogeneous stem cell types belonging to the mesoderm, ectoderm or endoderm lineage, depending on culture media and conditions. During this process, leukocytes lose lineage-associated markers home and undergo homocytic aggregation, upregulate expression of stem cell antigens, and subsequently redifferentiate to give rise original tissue or, transdifferentiate into a different tissue altogether. The hematopoietic retrodifferentiated stem cells have been shown to engraft an animal host in two proofs of principle clinical studies, demonstrating long-term engraftment and safety in acquired aplastic anaemia, while transient amelioration of beta thalassemia major was also observed. Binding of MHC class II antigens on leukocytes with the monoclonal antibody CR3/43 appears to emulate stress and injury in human tissue *in vitro*, similar to limb amputation in salamander. The ease by which various stem cell types can be generated from human peripheral blood has allowed the design of various kits to guarantee the specificity, sterility and efficacy of stem cells production for various

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clinical and research applications. The robustness and efficacy of the retrodifferentiation process in generating unprecedented quantities of stem cells belonging to the three germ layers will enable organ and tissue reconstruction *ex vivo*, using bio-printing and various scaffold materials. Epimorphic regeneration and retrodifferentiation both have the capacity to recreate and reconstruct tissue with precise positional integration of cells in such a way that will enable us to heal without scars and to understand how to maintain tissue integrity and architecture in the face of a hostile environment.

Keywords: Axolotl, Bioprinting, Blastema, Bone, Dedifferentiation, Ectoderm Endoderm, Epimorphic Regeneration, Hematopoietic, Hepatocytes, Histogenesis, Human leukocytes, Mesenchymal, Morphogenesis, Neurons, Pluripotent, Positional integration, Regeneration, Retrodifferentiation, Salamander, Scaffolding, Stem Cells, Tissue Repair, Transdifferentiation.

INTRODUCTION

The ability to regenerate an entire complex tissue, organ or appendage upon damage is almost nonexistent in higher vertebrates, for instance in an adult human. This is because neither all tissues in the human body are endowed with stem cells that have the ability to proliferate and differentiate to replenish damaged or spent cells nor the adult human body possess sophisticated regenerative processes that enable replacement of body parts lost to severe injury. Most injuries are dealt with simply utilizing repair mechanism which entails closure of the injured site by deposition of fibrous tissue instead of cells. This leads to altering organ geometry and architecture including deterioration in function. In stark contrast, amphibians and particularly a selected group of urodele salamander can re-grow body parts, such as an amputated limb, even when old, in a process known as epimorphic regeneration. In this process, complex mechanisms, including dedifferentiation, innervation, positional integration and re-morphogenesis occur to restore the severed appendage. During the dedifferentiation phase, fully mature specialised cells from various positions around the circumference of the amputate, belonging to the mesenchymal lineage home to the stump site and dedifferentiate. This leads to the formation of a cluster of heterogeneous population of stem cells, known as the blastema. Homing and integration of mesenchymal cells occur according to positional values. This

facilitates alignment and arrangement of cells of different lineages, in a configuration that upon re-morphogenesis permits restoration of the original geometry and architecture of the limb. Elucidation and understanding of epimorphic regeneration, including harnessing similar mechanisms in human, has tremendous applications in regenerative medicine than mere production of stem cells which at best proliferate and differentiate *ex-vivo*, but may fall short of positional integration or morph into tumors when transplanted into humans. The process which has been termed retrodifferentiation [1] is similar to the process of cellular dedifferentiation which facilitates blastema formation in salamander [2].

Retrodifferentiation of human leukocytes into a variety of pluripotent stem cell classes occurs in response to ligation of the monomorphic region of the major histocompatibility complex beta chain, using a monoclonal antibody (clone CR3/43) [3]. Each stem cell type generated is determined by the type of culture media and conditions utilized during retrodifferentiation. Similar to mesenchymal cell dedifferentiation in salamanders, leukocytes lose lineage associated markers, undergo homing and homocytic aggregation, and form heterogeneous stem cell colonies which subsequently redifferentiate into cellular components of the original tissue. Unlike salamander regeneration, retrodifferentiation is capable of transdifferentiation and histogenesis giving rise to entirely different tissues. In this process, mature mononuclear leukocytes can be converted into a variety of stem cell types belonging to the three germ layers: mesoderm, endoderm or ectoderm. Three hour human male retrodifferentiated haematopoietic stem cells (RHSC) have been shown to engraft in minimally irradiated NOD/SCID female mice [4]. Furthermore, 3 hr autologous RHSC were capable of long term engraftment in severe acquired aplastic anemia patients without any form of pre-conditioning therapy [5]. While in beta thalassemia major [6], a genetic blood disorder, the autologous RHSC were only able to ameliorate the course of the disease for six months. The ease by which any stem cell type can be prepared from human peripheral blood *via* retrodifferentiation, enabled the development of kits for the treatment of haematological and degenerative disorders, as a bed side stem cell therapy. In this manner, and in combination with leukopheresis and washing devices, the automation of stem cell production, will guarantee efficiency, sterility and specificity of stem cell infusate. Most importantly, retrodifferentiation

The Mesendoderm: A Wellspring of Cell Lineages for Regenerative Medicine

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Abstract: Regenerative medicine is centred around the premise that progenitor populations can be engineered to give rise to mature cell lineages forming a complex tissue architecture which in turn produces functional organs. The potency of the starting progenitor population is therefore a critical consideration. The mesendoderm is a rare population of cells present in the embryo only at gastrulation. This bipotent population gives rise to the mesoderm and the definitive endoderm and all mature cell types derived from these germ layers. Mesodermal progenitors generate cardiac, smooth and skeletal muscle, as well as the blood and vascular lineages, bone and connective tissue cells. The endoderm is the source of numerous cell lineages with potential utility for regenerative medicine including hepatocytes, pancreatic lineages and the epithelial cells of the respiratory, gastrointestinal and reproductive tracts. The development of numerous organs is dependent upon mesoderm-derived lineages interacting with endodermal-derived cell types. The kidney, adrenal gland, pancreas and genito-urinary tract development all require interactions between mesodermal and endodermal derivative cell types. Here, we describe the unique genetic programmes that lead to mesendoderm formation, the pathways leading to mesoderm and endoderm specification and examples where mature cell types from both germ layers interact to support their mutual development. We will also show how these programmes are being

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harnessed to direct the differentiation of pluripotent cells *in vitro* into mesendoderm-derived cells and tissues which can be used to improve the quality of human life. Finally, we will discuss considerations for combining stem cell differentiation with tissue engineering through 3D bioprinting modalities.

Keywords: 3D bioprinting, Embryonic development, Embryonic stem cells (ESC), Endoderm, Germ layer specification, Induced pluripotent stem cells (iPSC), Mesendoderm, Mesoderm, Regenerative medicine, Tissue engineering.

INTRODUCTION

The complex adult mammalian body is derived from three simple structures early in embryogenesis termed the germ layers. These are: the ectoderm, which forms the skin and central nervous system; the endoderm which gives rise to the epithelial tissues of the viscera such as the respiratory, gastrointestinal and genitourinary tracts; and the mesoderm, which forms all of the connective tissue, blood, vessels and muscle tissues. These three germ layers, can be first distinguished at the developmental stage termed gastrulation. However, it has been proposed for some time that the mesoderm and endoderm arise from a single cell type with the potential to form both lineages. This cell type, termed the mesendoderm, can be identified in simpler animal models such as the frog embryo, and an equivalent cell type can be generated from mammalian pluripotent stem cells in culture. The mesendoderm is, in the end, responsible for the formation of essentially vast amounts of the body except for the brain, skin (derived from the ectoderm) and other tissues derived from a structure arising later in embryogenesis termed the neural crest.

All of the epithelial tissues contain mesoderm-derived lineages. For example, the gastro-intestinal epithelial tissue has a mesoderm-derived connective tissue component essential in maintaining structural integrity. Indeed, it is now clear that, in many organs, extensive cross-talk must take place between endoderm-derived tissues and mesodermal-derived structures during embryogenesis of organogenesis to proceed. The developing pancreas and liver (endoderm) require signals from underlying blood vessels (mesoderm) to form [1, 2]. Removal of the blood vessels leads to a loss of appropriate signals and failure of pancreatic

development. In contrast, most mesoderm-derived organs lack epithelial structures. For example, the heart, skeletal muscle and bone marrow do not contain endoderm-derived cell types (Table 1).

Table 1. Organs and cells derived from the mesendoderm.

Organ	Endoderm-derived Lineages	Mesoderm-derived Lineages
Salivary gland	Serous, mucosal and seromucosal epithelial cells	Connective tissue fibroblasts, macrophages endothelial cells, adipose cells
Trachea	Goblet cells columnar epithelial cells	Tracheal cartilage, lymphoid cells, macrophages
Lungs	Type I and II alveolar cells Clara/club cells, Goblet cells	Endothelial cells alveolar macrophages
Stomach	Surface mucous cells mucous neck cells entero-endocrine cells chief cells, parietal cells	Smooth muscle, adipocytes, endothelial cells fibroblasts, lymphoid cells
Liver	Hepatocyte cholangiocyte	Sinusoidal endothelial cell Kupffer cell, hepatic stellate cell
Gastrointestinal tract	Gastric epithelium glands (pyloric, cardiac, fundus)	Mesentric connective tissue fibroblasts smooth muscle, endothelial cells, lymphoid cells
Pancreas	Acinar cells, centroacinar cells pancreatic α , β and δ cells	Capillary endothelial cells connective tissue fibroblasts
Kidney	Tubular epithelial cells	Glomerular endothelial cells, mesangial cells podocytes, capsular stromal fibroblast
Prostate	Cuboidal epithelial cells columnar epithelial cells	Prostatic stroma fibroblasts, smooth muscle connective tissue
Urinary bladder	Urothelium	Smooth muscle, hematopoietic cells, endothelial cells
Bone		Osteocytes, osteoblasts, chondrocytes, endothelial cells, hematopoietic cells, adipocytes
Thymus	Cortical thymic epithelial cells medullary thymic epithelial cells	Thymocytes (developing T lymphocytes) dendritic cells, thymic macrophages
Spleen		Capsule stromal fibroblasts, erythrocytes lymphocytes, sinusoidal endothelium macrophages
Gonads		Leydig cells, Sertoli cells, follicular cells thecal cells

Hematopoiesis and Regenerative Medicine

Chanukya K. Colonne¹, Veronica I. Antas¹, Jia Hao Yeo², Henry Williams¹, Chelsea Pilgrim¹ and Stuart T. Fraser^{1,2,*}

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Abstract: The hematopoietic, or blood-producing, system resides in the bone marrow of adult mammals. This system regulates the production of billions of new blood cells per day in healthy adult humans. Even slight perturbations of this production can lead to severe pathological conditions. One of the first applications of cellular regenerative medicine in clinical practice was the transplantation of bone marrow cells to generate a new, healthy blood production system in compromised patients. The success of bone marrow transplantation is dependent upon the potency of stem cell and progenitor populations within the adult mammalian bone marrow. The utility of hematopoietic stem cell (HSC) transplant has been extended to the treatment of a broad range of hematological diseases and disorders, as well as in the regeneration of the blood-producing tissue following radiation or chemotherapy. There is a strong push towards the development of vast numbers of mature blood cells *in vitro*. An *in vitro* system resulting in the consistent, large-scale production of patient-specific mature erythrocytes from HSCs or erythroid progenitors could alleviate the pressure felt by blood donation agencies. The cells that support blood cell production in the bone marrow and other organs, known collectively as the hematopoietic niche, are critical in blood cell lineage regeneration. The development of novel regenerative therapies to treat myelodysplastic syndromes, anemia, leukemia and other blood diseases deserves attention. Stem, progenitor and supportive cells within the hematopoietic tissues are essential elements of regenerative medicine. The utility, limitation and promise of these populations in regenerative medicine are described here.

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Keywords: Bioengineering, Blood, Bone marrow, Embryo, Hematopoiesis, Niches, Regenerative Medicine, Stem cells, Transplantation.

INTRODUCTION

A healthy adult human produces over 2 million new red blood cells per second or nearly 2 billion per day. This extraordinary rate of cellular production is dependent upon a hierarchy of stem, progenitor and maturing cell types forming in the hematopoietic organs. Hematopoietic stem cells (HSCs) are very rare cells capable of giving rise to all of the major blood cell types when transplanted. These characteristics have led to HSCs being one of the cell types most frequently transplanted for clinical treatment. Once HSCs have been transplanted from donor to recipient, these cells home to the bone marrow where they reside and give rise to the massive number of blood cells required to maintain human health. HSCs also give rise to a broad variety of blood cell lineages. These range from gas transporting erythrocytes (the most common form of blood cell in mammals) to megakaryocytes producing platelets; granulocytes (neutrophils, eosinophils and basophils) offering immune protection against bacteria, fungi and parasites; and the lymphocytes capable of forming an immunological memory of pathogen exposure. Specialized tissue macrophages and dendritic cells are also derived from HSCs. HSCs therefore have a profound capacity for regenerating the blood compartment, which comprises approximately one fifth of all cells in the healthy adult human. The remarkable capacity of HSCs to give rise to the entire hematopoietic system in recipient animals and patients has led to utilization of these cells in regenerative medicine. HSC transplantation can be performed from transplanting a patient's own stem cells (autologous transplants) or from transplanting a donor's cells (allogeneic transplants). Both these techniques are used commonly in medicine today and are often the only life saving or prolonging treatment available to these patients.

Significant challenges lie ahead in hematopoietic regenerative medicine, and we will discuss some of these in this chapter. In contrast to other stem cell types, such as embryonic or induced pluripotent stem cells, we cannot currently maintain HSCs *in vitro* in the stem cell state for an indefinite period. There are also

significant challenges in finding appropriately matched HSCs for transplantation, and mitigating the many complications associated with HSC transplantation. Sourcing matched volunteers for blood donations for red blood cell and platelet transfusions is a challenge globally. In some clinical cases, the problem is due to defects in the hematopoietic niche, the supporting cells which maintain HSCs as stem cells. Developing novel systems to obtain patient-specific HSCs and progenitors as well as novel methods for modifying and enhancing the HSC niche, will dramatically improve the health outcomes of a vast number of patients suffering from hematopoietic and related diseases.

Here, we will discuss the link between blood cell generation and regenerative medicine. In contrast to other systems, the hematopoietic system is more diffusely scattered throughout the body. Regenerative therapeutic treatment will vary according to patient needs and may include regeneration of failing bone marrow, replacement of a deficient or defective thymus to produce T cells; re-construction of a spleen or other hematopoietic tissue; or the generation of mature circulating cells from an *ex vivo* or *in vitro* expanded progenitor population such as functional red blood cells, mature platelets or granulocytes to supplement immunodeficient individuals.

This discussion will proceed in four sections. Firstly, the hematopoietic system will be introduced. Secondly, the niches which regulate blood cell generation and constant production will be described. The application of HSC transplantation to the treatment of a range of human diseases is one of the major forms of regenerative medicine and will be discussed at length in the third section. Finally, focusing all of these studies onto future directions, we will discuss the application of novel technologies such as induced pluripotent stem cells and tissue engineering of blood producing tissues to the treatment of hematological disorders.

AN INTRODUCTION TO HEMATOPOIESIS

Hematopoiesis is the production of blood cells initiated in the early embryo and maintained throughout life. Maintenance of a homeostatic state requires the genesis and consistent life-long production of a broad palette of blood cell types.

Cell-based Therapy in Veterinary Medicine

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Abstract: Cell-based therapy is a growing field in veterinary medicine and has created a lot of hope and excitement for developing new therapies for degenerative diseases that otherwise cannot be treated by traditional medical approaches. Clinical studies in dogs, cats and horses show promising results indicating that stem cells and other cell-based products may facilitate tissue repair and improve quality of life in companion animals. In this review, different cell based therapies, their risks and benefits and their possible therapeutic use for veterinary medical application will be discussed.

Keywords: Companion animals, Degenerative diseases, Stem cells, Veterinary medicine.

RECENT ADVANCES AND APPLICATIONS OF CELL THERAPY

Cell therapy is the administration of live cells to the body of a recipient for treatment of a medical condition. It could be for replacement of absent cells like infusion of red blood cells to overcome anemia, administration of platelets for emergency thrombocytopenia, or application of T lymphocytes for regulation of the immune system and cancer therapy. This type of cell therapy is called cell replacement therapy and is commonly used in medical and veterinary medical protocols. Cell therapy can also be used for regenerative medical applications. In that case, stem cells and progenitor cells with the ability to produce other cells will be used. A good example is the administration of bone marrow cells, which contain hematopoietic stem cells for regeneration of the blood. This therapy can help reestablish hematopoiesis and regenerate blood in patients undergoing

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cytotoxic treatments such as chemotherapy or radiotherapy. Cell products with regenerative potential can regenerate cells, tissues and organs, to restore or establish normal function. In addition to live cells, regeneration could also be triggered by proteins and growth factors, extracellular matrices, scaffolds and small molecules, but these effects are generally transient, and repeated treatments are required.

The nomenclature to identify and describe various cells is to use the cluster of differentiation (abbreviated as CD) distinction. It refers to protein structures (or antigens) embedded on the outer membrane of cells. The system was first described to identify basic immune cells and since has been applied to many cell types relevant for the immune system. Over the past 30 years, data generated by the Human Leukocyte Differentiation Antigens Workshops have led to the characterization and formal designation of more than 400 CD molecules. These CD molecules are commonly used as cell markers, allowing the identification and isolation of leukocyte populations, subsets and differentiation stages. Some of these markers are commonly expressed by other cells including stem cells (Table 1).

Table 1. Some of the important CD molecules and their expression profile.

CD1	The first-named CD; this complex glycoprotein is expressed in immature T-cells, some B cells and other, specialized immune cells in the skin.
CD3	A multimeric protein complex, known historically as the T3 complex, and is part of the T cell receptor.
CD4	A molecule on a mature “helper” T lymphocyte cell surface.
CD8	A molecule on a mature “cytotoxic” T lymphocyte cell surface.
CD19	A molecule on a mature B lymphocyte cell surface.
CD34	A monomeric cell surface antigen that is selectively expressed on hematopoietic progenitor cells.
CD90	Also known as Thy-1. CD90 is expressed on neuronal cells, a subset of CD34+ cells, activated endothelial cells and mesenchymal stem cells.

The types of cells used in cell therapy can be mature cells, such a T-cells or dendritic cells, to adult stem cells isolated from a fresh tissue source. An up and coming exciting use of mature cells is that of regulatory T-cells (Tregs) in therapeutic applications. CD4+Foxp3+ Tregs are long-lived cells that suppress

immune responses *in vivo* in a dominant and antigen-specific manner. Tregs confer long-term protection against auto-inflammatory diseases in mouse models and have been shown to be effective in suppressing alloimmunity in models of graft-*versus*-host disease [1]. CD4⁺ Foxp3⁺ Treg therapy is now at the point to evaluate its safety and efficacy within preclinical testing in humans [2, 3].

Another interesting mature cell type being explored for cell therapy is the dendritic cell. Dendritic cells are highly specialized, bone marrow-derived antigen-presenting cells that induce or regulate innate and adaptive immunity. In general, dendritic cells express CD11b and CD11c, although there are many more markers to identify subsets of dendritic cells. Since the mid-1990s, dendritic cells have been used in clinical trials as cellular mediators for therapeutic vaccinations of patients with cancer. As sentinel members of the innate immune arm, dendritic cells secrete protective cytokines (Table 2) in response to signals of inflammation [4]. Interleukins (ILs) are specific types of cytokines that are produced by leukocytes for regulating immune responses. IL-6 and IL-12 are particularly important because they play roles in establishing a local immune response. For example, IL-6 secreted from dendritic cells has immunosuppressive properties and IL-12 augments CD8 T cell activation. Dendritic cells capture process and present antigens *via* the major histocompatibility complex to naïve T-cells at lymphoid organs, thereby inducing adaptive CD4⁺ and CD8⁺ T-cell-mediated immune responses [5, 6]. Dendritic cell based therapeutic immunotherapies with oncogene inhibitors in patients appear to be the method of choice. Human clinical trials investigating targetable tumors are underway in renal cell carcinoma, prostate cancer, breast cancer and melanoma [7, 8].

Table 2. Some of the important Cytokines produced and their function.

Cytokine	Full Name	Characteristic
IL-2	Interleukin-2	Promotes T cell expansion, used in immunotherapy to support large numbers of tumor-infiltrating lymphocytes with anti-cancer activity.
IL-6	Interleukin-6	Multifunctional cytokine involved in modulating various physiological events, such as cell proliferation, differentiation, survival, and apoptosis.
IL-10	Interleukin-10	Produced by cell types that mediate anti-inflammatory activities, induce regulatory T-cells, and are involved in immunosuppression and tissue repair.

From Trials to Therapeutics: Are Mesenchymal Stem Cells Promising in Cellular Therapy?

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Abstract: Mesenchymal stem cells (MSCs) are today, the most favoured cellular candidates for regenerative therapeutics. Though discovered early in the 1960s, only recent decades have witnessed extensive research involving MSCs. MSCs, termed as multipotent mesenchymal stromal cells in 2006, by the International Society of Cellular Therapy have gained greater acceptance in view of their ubiquitous presence in tissues, exemption from ethical concerns, clonogenic potential, trilineage differentiation, versatile plasticity and ability to orchestrate host tissue interactions. Biological properties of MSCs that contribute to therapeutic efficiency include facilitating secretion of bioactive factors, induction of cellular recruitment and retention of progenitor faculties. Researchers, however continue to be intrigued by variability in the *in vivo* identity of MSCs which is influenced by various factors that include tissue of origin, age of MSCs, number of isolates and isolation efficiency, associated metabolic disorders, foetal or adult status, gene expression, protein and transcription factors and allogenic or autologous extract. Although early results in clinical studies are promising, transformation of MSCs into a mature clinically viable option would mean a patient wait.

Keywords: Cellular therapy, Critical limb ischemia, Crohn's disease, Graft *versus* host disease, Mesenchymal stem cells, Osteogenesis imperfecta, Telomere, Tissue repair, Wharton's jelly, Wound healing.

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INTRODUCTION

Successive failures of embryonic stem cells and induced pluripotent stem cells have potentiated the research utilization of mesenchymal stem cells (MSCs). As defined by the International Society of Cellular Therapy, these multipotent, plastic adherent spindle-shaped cells can be propagated through multiple passages in cell culture and differentiated into osteogenic, adipogenic and chondrogenic lineages under permissive conditions [1]. Conventionally isolated from the bone marrow, over the past couple of decades, the isolation of MSCs has been possible from virtually every tissue [2] exhibiting similarity in morphology and, to a certain extent in surface marker profile [3]. Culture-expanded MSCs may lose some of these markers but continue to remain multipotential [3].

By virtue of a variety of biological properties exerted either individually or in combination MSCs have contributed to therapeutic effects in a variety of disease conditions (Fig. 1). The distinguishable properties include capability to: differentiate into different cell lineages, homing and migration to sites of inflammation and injury, secrete bioactive molecules and promote repair, produce immunomodulatory effects by interacting with the immune cells [4].

Though all MSCs were previously regarded as having low immunogenicity, in view of the low expression of MHC class I and II along with other co-stimulatory molecules such as CD40, CD80, and CD86, recent studies have suggested that allo MSCs may not be as immune-privileged [5] as previously reported except for a few foetal origin MSCs [6], such as those from Wharton's jelly [7].

Owing to the ease of isolation and expansion, MSCs have been studied and have undergone trials in a diverse range of clinical conditions ranging from graft *versus* host disease, autoimmune diseases such as Crohn's disease, cardiovascular diseases such as acute myocardial infarction, stroke and orthopaedic applications including bone and cartilage repair [8]. Primitive MSCs isolated from foetal and perinatal tissues, umbilical cord, placenta, and amniotic fluid have been found to possess longer telomeres [9], higher proliferative potential [10], greater colony-forming capacity, and ability to readily differentiate into bone and muscle [11] and in addition, into non-mesenchymal cells such as neural [12] and hepatic cells

[13]. Increasing age of the MSC may limit the ability to be expanded, leading to rapid senescing in culture and restricted differentiation capacity. In addition, differentiation capabilities, growth kinetics, and yield vary significantly between MSC cell populations from different tissue sources, impacting their clinical utility [14].

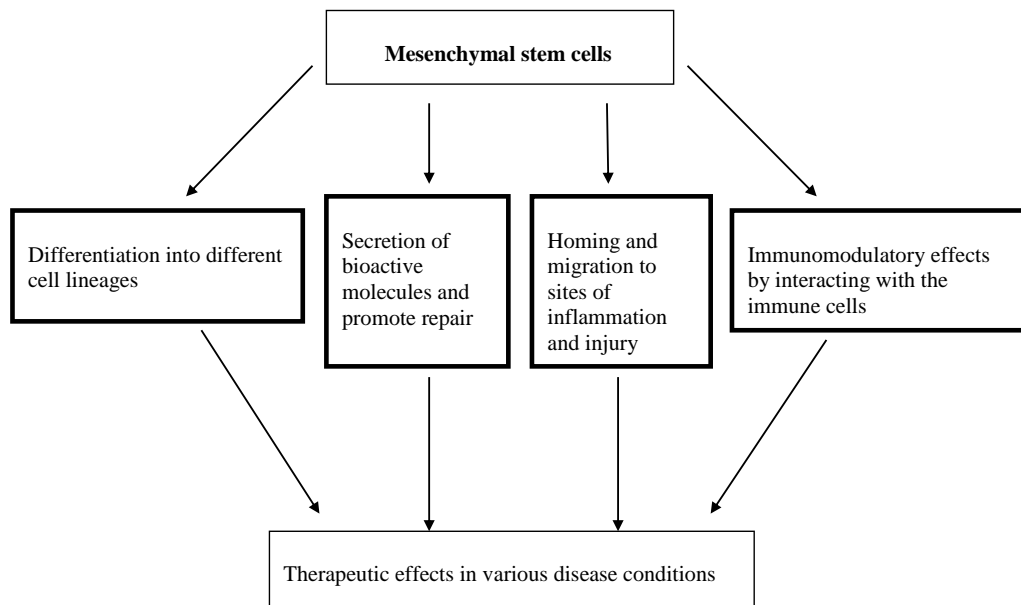


Fig. (1). A schematic diagram of the biological properties of MSCs.

Safety profile of MSCs has been encouraging with no reports of any major health concern in the various human disease settings and clinical trials conducted [15]. Further studies to evaluate tumor formation and genomic integrity are though necessary, the results from current studies have demonstrated no solid evidence of malignant growth or cellular transformation induced by chromosomal inconsistencies [16]. However there is concern about acquired mutations that may induce transformation as a result of prolonged culture.

The lack of standard validated protocols for cell isolation, expansion, and quality control hinder the monitoring of the clinical effectiveness of MSC-based therapy [14]. The absence of governmental regulatory policies at both local and global levels may impact the advance of MSC-based therapeutics into the clinic [17].

SUBJECT INDEX

A

Abnormal forces 198
 Acinar cells 38, 50
 exocrine 50
 Acquired aplastic anemia patients, severe 5
 Activin 44, 58
 Acute kidney ischaemia (AKI) 240
 Adipocyte differentiation 61, 62
 brown 62
 Adipocytes 17, 38, 61, 62, 116, 175, 179, 189
 Adipogenesis 61
 Adipose-derived stromal cells 238
 Adipose tissue 61, 119, 179, 182, 189, 192,
 197, 204, 205, 241, 243, 246, 247, 248
 human 243
 Adipose-tissue-derived MSCs display 244
 Adult bone marrow hematopoietic niche 114,
 116
 Adult cells, reprogrammed fully-differentiated
 23
 Adult organ tissues 247
 Adult stem cell genome 196
 Adult stem cell release 197
 Adult stem cells 57, 171, 173, 175, 195, 196,
 197, 210
 Agarose rods 79
 Agencies, regulatory 176, 181
 Agents 70, 71, 205, 208
 decellularisation 70, 71
 modifying 205, 208
 Aggregation, homocytic 3, 5, 16, 17, 18, 22
 Aging 141, 177, 184, 185, 195, 196, 197, 212
 circulating stem cells 197
 Aging patients 198
 Aging process 185, 196
 AGM cells 111, 112
 AGM hematopoietic cells 111
 AGM region 111, 114
 AGM stromal cells 111
 Albumin 22, 24, 53
 Alginate 69, 81
 autoclaved 81
 non-autoclaved 81
 Allogeneic cell therapy products 186, 187

Allogeneic products 215, 216
 Allogenic MSCs 181, 194, 239, 247, 248
 Amniotic fluids 136, 235, 246, 248
 Anemia 23, 101, 135, 170, 207, 218
 severe 23, 135, 207
 Angiogenesis 173, 178, 210, 238, 246, 248
 Anti-aging 184
 Antibodies 20, 21, 129
 Antigen-activated CD4+ T-cells stimulate
 monocytes 202
 Antigen-presenting cells 172, 183
 marrow-derived 172
 Antigens, dendritic cells screen 119
 Aorta-gonad-mesonephros (AGM) 52, 109,
 111, 112
 Apical epithelial cap (AEC) 11, 13
 Aplastic anemia 23, 106, 121
 Apoptosis 7, 45, 71, 73, 172, 173, 184, 196
 Arthritis 192, 199, 201, 200, 202, 206, 242,
 250
 inflammatory 200, 202
 rheumatoid 199, 201, 242, 250
 Artificial lymphoid tissue 143
 Athymia 141
 Autologous BM-MSCs 238, 240, 241, 242,
 248
 Autologous cell therapy 186, 187
 Autologous cell therapy products 186
 Autologous conditioned serum (ACS) 205
 Autologous stem cells 177
 Autologous stem cell therapy in diabetic
 patients 248

B

Basophils 102, 104, 118, 120
 Beta thalassemia 3, 5, 22, 24
 Bio-engineering hematopoietic cells 136
 Biomaterials 68, 69, 70, 74
 natural 68, 69
 selected 69, 70, 74
 Biomaterial scaffolds 66, 72
 Bioprinting technologies 71, 83, 84, 138
 Blastema formation 5, 10, 11, 14, 16, 25
 Blastocysts 46, 58, 126, 174

- Blood cell development 84, 141, 144
Blood cell generation 103, 114, 136
Blood cells 101, 102, 103, 104, 105, 108, 109, 121, 130, 136, 186, 205
 differentiated 106, 107
 functional red 103
 generating 130
 mature 101, 105, 136
 new healthy 121
 white 104, 186, 205
Blood cell types 102, 103, 104, 105
Blood islands 110
Blood production 52, 108, 110
Blood stream 197
Blood transfusion 120, 129, 207
Blood urea nitrogen (BUN) 207
Blood vessels 12, 37, 50, 52, 68, 116, 117, 139, 213
BM-MSCs and adipose-derived stromal cells 238
Body, embryoid 19, 20
Body condition score (BCS) 202
Bone marrow aspirate 190
Bone marrow cells 101, 106, 113, 170, 188
 adult 113
 primitive 188
 special primitive 188
Bone marrow stem cells 173, 248
Bone marrow transplant (BMT) 23, 101, 120, 121, 122, 123, 124, 125, 188, 209, 237
Bone marrow transplantation 101, 121, 122, 123, 124
Bone marrow transplantation treatment 237
Bone marrow transplants 120, 121, 124, 125, 209
Bone morphogenic protein (BMPs) 59, 73, 76
 functional 76
Building mini-tissue 138
- C**
- Cell culture system 46, 189
Cell differentiation 46, 47, 74
Cell maturation 118
Cell products 171, 176, 182, 187, 192, 211, 212, 213, 215, 218
Cell proliferation 119, 172, 173, 184
 β -cells 3, 5, 50, 51, 132, 249
 adult 249
 derived 51
 differentiated 51
 functional 50, 51
 insulin-producing 51
 maturation of 51
Cells 4, 5, 7, 8, 9, 11, 12, 13, 15, 17, 18, 19, 20, 21, 22, 23, 24, 25, 32, 36, 37, 38, 39, 40, 41, 44, 45, 46, 47, 48, 49, 52, 53, 54, 56, 58, 60, 66, 67, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 82, 101, 102, 103, 104, 105, 106, 107, 108, 109, 111, 112, 113, 114, 115, 116, 117, 118, 120, 121, 122, 123, 126, 127, 128, 129, 130, 132, 134, 135, 136, 139, 140, 142, 143, 170, 171, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 189, 190, 193, 195, 196, 197, 202, 204, 208, 209, 211, 212, 213, 214, 215, 216, 217, 235, 239, 241, 246, 248, 250
 accessory 136
 adipose 38
 allogeneic 123, 177, 186
 allogenic 204
 alveolar cells Clara/club 38
 beta 216
 binucleated 22
 bioprinting 67
 bi-potent progenitor 40
 cardiac 41
 cartilage 179
 centroacinar 38
 common progenitor 134
 connective tissue 36
 entero-endocrine cells chief 38
 enucleated 132
 erythropoietic 136
 exhibited morphological ageing 246
 follicular cells thecal 38
 glial 21
 haematopoietic 7, 52
 hematopoietic lineage 118
 hepatic 53, 113, 235
 inflammatory 9, 202
 mesangial 54, 104
 mesendoderm-derived 37

- migrating epidermal 11
- migratory 18
- modified 134
- mononucleated 13
- mucous 38
- multiple myeloma 140
- myeloid-derived suppressor 104
- neural 20
- neuronal 171
- non-mesenchymal 235
- non-stem 216
- nucleated 190
- osteoblast 75
- osteolineage 116
- osteoprogenitor 73
- parenchymal 9, 75
- parietal 38
- placental 112
- plasma 118, 140, 208
- pluripotent 37, 129, 174
- pluripotent germ 60
- producing synthetic 130
- solid organ 176
- spindle-shaped 235
- stem/progenitor 176
- therapeutic 174
- Cells repair 211, 175
 - adult stem 175
- Cell therapy 177, 187, 188, 189, 218
 - allogeneic 187, 188, 189
 - application of 177, 218
- Cell therapy applications 170, 188, 218
- Cell therapy treatment, successful 177
- Cell tracking 180, 181
- Cell types 3, 5, 26, 36, 37, 40, 41, 43, 46, 47, 48, 49, 50, 52, 54, 58, 71, 72, 74, 82, 102, 104, 105, 106, 108, 126, 128, 131, 138, 171, 172, 173, 174, 175, 177, 179, 182, 188, 197, 212, 214, 215, 216
 - endodermal 48, 58
 - mature 36, 49, 105, 108, 128
 - mature blood 105, 106
 - mesodermal 52, 54
 - multiple 71, 82, 138, 216
 - stem 3, 5, 26, 102, 173
- Cellular adhesion 70
- Chain, beta-globin 23
- Characterising hematopoietic stem cells 107
- Chemokines 25, 46, 104, 115, 119, 181
- Chemotherapy 60, 101, 119, 123, 124, 141, 171
- Chimeric antigen receptors (CARs) 189
- Cholangyocytes 52
- Chromosomes 19, 122, 184
- Chronic gingivostomatitis 192, 198, 208, 216, 218
- Chronic kidney disease (CKD) 192, 195, 198, 206, 207, 208, 217, 218, 239
- Chronic liver diseases 53
- Chronic wounds 210, 238
- Clusters, heterogeneous stem cell 16
- Common lymphoid progenitors (CLPs) 105, 107
- Compensatory regeneration 8, 9
- Computerized tomography (CT) 198
- Conditional deletion of SCF in endothelial cells 7
- Connective tissue 9, 11, 12, 37, 38, 215
 - diseased 215
- Connective tissue fibroblasts 38
- Contact, direct 14, 115, 117
- Contrast 9, 10, 14, 21, 38, 39, 69, 102, 103, 112, 113, 133, 243, 246
- Control mesendoderm formation 39
- Cord blood 113, 124, 131, 132, 182, 188, 189, 192, 246, 247
 - umbilical 113, 124, 188, 189, 192
- Cord blood transplants 124, 125
- Cortico-medullary junction 119
- Corticosteroids 193, 204, 208
- Critical limb ischemia (CLI) 234, 238, 239, 250
- Critical quality attributes (CQAs) 186, 215
- Crohn's disease 234, 235, 243, 244, 250
- Crohn's disease activity index (CDAI) 244
- Cuboidal epithelial cells 38
- Culture conditions, inductive 17, 19
- Cultures 19, 20, 21, 22, 37, 47, 48, 53, 56, 58, 60, 62, 77, 112, 113, 126, 127, 128, 134, 137, 138, 139, 140, 173, 182, 193, 213, 236
 - organoid 56
 - static 137, 140
- Culture systems 138, 141, 182
- Culturing endodermal cells 50

CXCL12 expression on endosteal cells and blood vessels 139

D

Damaged tissues 3, 6, 59, 69, 71, 174, 175, 183, 210, 211
Debilitating diseases 176, 192, 197, 199
Dedifferentiated blastema cells 14
Deficiency, pyruvate kinase 133
Degenerative diseases 26, 170, 198, 211, 212, 217
Degenerative joint disease (DJD) 193, 197, 198, 201
Dendritic cell (DC) 38, 102, 104, 118, 119, 121, 127, 141, 171, 172, 177
 follicular 104, 119
Derived MSCs 185, 187, 194, 195, 247, 248
 adipose 185, 194, 195
Differentiated hepatic-like cells 53
Differentiation 6, 7, 11, 12, 15, 16, 18, 19, 37, 39, 41, 44, 46, 47, 48, 49, 51, 53, 56, 58, 61, 62, 66, 69, 70, 72, 73, 74, 81, 105, 107, 108, 112, 113, 117, 118, 127, 131, 134, 137, 171, 172, 174, 175, 179, 195, 196, 203, 236, 241, 242
 endodermal 49
 human CD34+ cells 18
 mesodermal 48
 organ-restricted stem-cell 175
 sexual 55
 terminal 117, 134
 trilineage 179, 234
Differentiation 50, 71, 74
 of human satellite cells 74
 of Pancreatic β -cells 50
 processes 71
Disease conditions 235, 236, 248
Diseases 5, 23, 53, 54, 57, 71, 76, 84, 103, 125, 136, 140, 173, 176, 177, 178, 184, 185, 196, 198, 199, 203, 204, 205, 207, 208, 209, 210, 212, 213, 217, 218, 237
 chronic 136, 199, 207, 209
 joint 177, 199, 203, 204
 neurodegenerative 178, 217
DNA repair 195, 196
Dorsal aorta 109, 111, 120

Downstream targets 40, 41, 44
Duchenne Muscular Dystrophy (DMD) 83
Ducts 55
 mesonephric 55
 paramesonephric 55

E

Early vascular cells (EVCs) 83
Ectoderm 3, 5, 37, 39, 40, 58, 59
 extra-embryonic 59
Ectopic expression 13, 128
Effects 122, 181, 204, 205, 212, 235, 236, 237
 anti-inflammatory 204, 205
 immunomodulatory 181, 212, 235, 236
 lethal 122
 therapeutic 212, 235, 236, 237
Efficacy trial 214, 215
Embark 3, 15, 16, 24
 constituent cells 3
Embryogenesis 37, 44, 46, 109
Embryonic development 37, 195
Embryonic stem cells 12, 37, 53, 58, 60, 80, 81, 126, 174, 175, 195, 209, 217, 235
Embryonic stem cells (ESCs) 37, 53, 58, 60, 61, 62, 80, 81, 126, 131, 132, 174, 175, 184, 195, 209, 217, 235, 249
Embryonic stem cells autologous MSCs 249
Embryos 36, 39, 40, 45, 46, 43, 44, 45, 102, 103, 109, 127, 174
 early 40, 45, 46, 103
Endoderm 5, 36, 37, 39, 40, 41, 43, 44, 45, 46, 52, 53, 55, 56, 58, 110
 definitive 36, 43, 45, 58
Endodermal derivatives 52, 54
Endodermal precursors 43, 49
Endoderm differentiation 44
Endoderm generation 44, 45
Endosteal cells 139
Endosteum 115, 117
Endothelial cells 7, 9, 38, 41, 50, 52, 53, 83, 110, 111, 113, 114, 117, 119, 138, 171, 241
 activated 171
 expressing 53
 lymphatic 119
 purified 113

vascular 7
Endothelial cells fibroblasts 38
Endothelial progenitor cells (EPCs) 79
Endotoxins 142
End systolic volume (ESV) 241
Engineered 77, 82, 141, 210
 cardiovascular tissues 77
 tissue constructs 210
 tissue width 82
 hematopoietic and lymphoid organs 141
Engineer replacement tissues 210
Engraftment abilities 112, 113
Eomesodermin 40, 41, 43
Eosinophils 102, 104, 118, 120
Epiblast cells 59, 60
 proximal 59
Epimorphic regeneration 3, 4, 5, 10, 11
Epimorphic regeneration and
 retrodifferentiation 4
Epithelial cells 36, 38, 42, 52, 54, 110, 118,
 119, 128, 142, 173
 basal 54
 columnar 38
 pigmented 173
Epithelial progenitor cells form 141
Epithelium 11, 12, 14, 52, 56, 125
 uretic 56
 wound 11, 12
Erythroblasts 107, 117, 130
Erythrocytes 7, 18, 104, 105, 109, 110, 119,
 120, 130, 131, 132, 133, 134
 enucleated 132, 134
 primitive 109, 110
Erythroid 18, 20, 104, 109, 120, 124, 127
 definitive 104, 120
Erythroid cells 112, 113, 117, 127, 131, 133
 definitive 112
 healthy mature 133
 hemoglobin-expressing 129
 immune-matched 133
 primitive 127
Erythroid progenitors 18, 101, 120, 121, 133
Erythropoiesis 117, 119, 130
ES-derived hematopoietic progenitors 127,
 128
Extracellular matrices 70, 171
Extracellular matrix 9, 10, 25, 67, 68, 72, 74,
 75, 137, 138, 213

F

Factors 14, 40, 43, 44, 46, 66, 67, 68, 70, 72,
 73, 81, 114, 116, 118, 124, 132, 134,
 136, 138, 178, 183, 188, 199, 210, 211,
 217, 234
 biological 72, 73
 colony-stimulating 124
 soluble 43, 70, 72, 114, 116, 118, 138
Feedback loops 45
Feeder cells lines 132
Fibroblasts 9, 14, 79, 83, 133, 174, 202, 209
Fibrosis 9, 10, 197, 210
Fibrotic tissue 210
Flow cytometry 18, 20, 107
Fluorescence-activated cell sorting (FACS)
 48, 56, 107
Fluorescent protein, green 47, 48, 180
Foregut endodermal tissues 50
Function 71, 78, 138, 139
 anisotropic 78
 biological 71, 138, 139
Functional 39, 139, 141, 177
 models of cell therapy 177
 thymic tissue 141
 tissue equivalents 39
 tissue units 139
Fused deposition modelling (FDM) 65, 67, 68

G

Gastro-intestinal epithelial tissue 37
Gastrulation 36, 37, 43, 44, 49, 59, 108
GATA4 signalling 58
GATA family 44, 45
Gene expression 25, 43, 44, 138, 185, 196,
 234
Generation of mature erythroid cells 129
Genital tract 57
Germ layers 4, 5, 36, 37, 39, 40, 41, 58
Germ layer specification 37
Germ layer stem cells transition 16
Germline stem cells (GSCs) 213
Glomerular endothelial cells 38
Glomerular filtration rate (GFR) 206, 207
Goblet cells 38
Goosecoid 40, 43, 47

Graft-versus-host-disease (GVHD) 123, 124, 125, 172, 183, 245, 250
Granulocyte-macrophage progenitors (GMPs) 107, 249
Granulocytes 6, 7, 18, 102, 103, 105, 107, 124, 190
 colony-forming unit 18
Green fluorescent protein (GFP) 47, 48, 180

H

Haematopoietic stem cells (HSCs) 5, 6, 7, 101, 102, 103, 105, 106, 107, 108, 109, 111, 112, 113, 114, 115, 116, 117, 120, 121, 123, 126, 130, 134, 140, 174, 242
Heart tissue 82
Heart valve replacement 78
Hematological conditions 7, 22, 23, 135
Hematopoietic 3, 4, 17, 48, 101, 102, 103, 109, 112, 141, 175
Hematopoietic activity 114
Hematopoietic cells 38, 107, 108, 109, 110, 111, 112, 113, 114, 126, 127, 128, 137, 138, 140, 141, 175
 hepatic 113
 mature 107
 source of 112, 113
 transplantable 109
Hematopoietic development 114, 128
Hematopoietic niches 101, 103, 110, 113, 114
 embryonic 114
Hematopoietic progenitor cells 124, 171, 188
Hematopoietic progenitors 112, 113, 120, 127, 137, 139, 141, 142
Hematopoietic stem 107, 109, 114, 124, 125
Hematopoietic stem cells 101, 102, 123, 130, 170
Hematopoietic stem cell transplantation 121, 125
Hematopoietic stem cell transplantation (HSCT) 121, 125, 136
Hematopoietic system 6, 15, 17, 102, 103, 104, 107, 108, 123, 127, 133, 134, 140, 143, 144
Hematopoietic tissues 101, 103, 109
 injecting 122
Hepatitis 53, 54, 130, 240

Hepatoblasts 52
Hepatocytes 4, 22, 36, 52, 53, 54
Hepatogenesis 52, 53
Hierarchical production of mature cells 105
Hip dysplasia (HD) 198, 200
Histogenesis 4, 5, 6, 16
HSC activity 107, 108, 111, 112
HSC generation 111, 112
HSC transplantation 102, 103, 135
Human embryonic and induced pluripotent stem cells 55
Human inferior turbinate-tissue 77
Human leukocyte antigen (HLA) 124, 183
Human leukocytes 3, 4, 5, 15, 17, 19, 20, 24, 26
Human satellite cells 74
Hyaluronan 9, 10, 204
Hydrogels 67, 69, 72, 79, 81, 82, 137
 photosensitive 79
Hydroxyapatite 69, 70
Hydroxyl carbonate apatite (HCA) 73
Hypokalemia 207

I

IL-7-expressing cells 118
Immune cells 104, 140, 143, 171, 181, 235, 236
 activated 181
 basic 171
 innate 104
 specialized 171
Immunohistochemistry 20
Immunotherapy 172, 189, 190
Induced pluripotent stem cells 14, 37, 39, 49, 50, 54, 55, 56, 102, 103, 128, 173, 174, 217, 235
Inflammation, sites of 235, 236
Injury, spinal cord 188, 217
Insulin requirement 243
Insulin secreting cells 51
Integration, positional 4, 5, 6, 12
Intermediate mesoderm 41, 54
Interstitial cells 54, 78
 renal 54
Intervertebral disc disease 199, 201
Intra-articular injections 193, 194, 204, 211

Intravenous infusion 121, 122, 195, 217
IPS and dedifferentiated blastema cells 14
IPS cells 47, 49, 51, 56, 58, 59, 72, 128, 129,
133, 174, 177
corrected 129
human 128
Iron chelation therapy 135

K

Karyotyping 22, 23
Kidney disease 56, 239
Kidney organoids 55, 56
Kupffer cells 38, 104, 121
endothelial cell 38
Kupffer cells and blood vessels 52

L

Labeling, fluorescent 180
Labile tissues 6
Lameness scores 193, 194
Left ventricular ejection fraction (LVEF) 241
Lentiviral vectors 135
Leukaemic cells 24
Leukemia inhibitory factor (LIF) 46, 60
Leukocytes 3, 5, 17, 18, 19, 22, 104, 140, 172
Leydig cells 38
Ligament injuries 198, 205, 206
Lineages mast cells 104
Liver disease 240
Liver regeneration 8
Lymph nodes 104, 121, 143
artificial 143
Lymphocyte cell surface 171
Lymphoid cells 38, 105, 107
innate 105

M

Macrophages 18, 38, 52, 104, 105, 107, 109,
117, 119, 120, 121, 124, 129, 141, 143,
202, 208
central 104, 117
erythroblastic island 120
tissue-resident 143
Magnetic resonance imaging (MRI) 198, 242

Major histocompatibility complex (MHC) 5,
15, 172, 183
Marginal reticular cells 119
Matrix metalloproteinases 13, 25, 202
Matured adipose tissue 248
Mature erythroid cells 129
Mean corpuscular hemoglobin concentration
(MCHC) 24
Mean corpuscular volume (MCV) 23
Megakaryocyte-erythrocyte progenitors
(MEPs) 107
Megakaryocytes 7, 18, 102, 109, 110, 117,
118, 120, 124, 127, 140
proplatelet-producing 140
Memory plasma cells 140
Mesangial cells podocytes 38
Mesenchymal cells 3, 4, 11, 13, 14, 142
committed 3, 14
differentiated 11
Mesenchymal stem cells (MSCs) 7, 21, 79,
112, 116, 124, 171, 176, 178, 179, 180,
181, 182, 183, 184, 185, 187, 189, 190,
191, 192, 193, 197, 203, 204, 205, 209,
211, 215, 217, 218, 234, 235, 236, 237,
238, 239, 240, 241, 242, 243, 244, 245,
246, 247, 248, 249, 250
Mesenchymal stromal cells localizing 116
Mesenchyme 51, 55, 56
metanephric 56
Mesendodermal cells 40, 44, 48
candidate 40
purified 48
Mesendoderm 36, 40, 41, 42, 45, 46, 47, 62,
84
development 40, 41, 45, 46
differentiation 47, 48
formation 36, 41, 42, 45, 84
lineages 40, 47
Mesoderm-derived connective tissue
component 37
Mesoderm-derived lineages 36, 37
Mesoderm development 43
Mesoderm differentiation 43
Methylcellulose 18, 19
Monoclonal antibody 3, 5, 15, 17, 20, 74, 107
Mononuclear cells 13, 15, 18, 23, 107, 140,
190, 215, 246
derived 215

Morphogenesis 4, 12
 Morphological identity 246
 MSC proliferation and chondrogenic differentiation 241
 MSCs 193, 195, 239, 241, 242, 246, 247
 adipose tissue-derived 242
 application of 239, 241, 242
 cultured 193, 195
 foetal 246, 247
 MSCs in tissue repair 250
 Mucositis 125
 Multifunctional cytokine 172, 173
 Multiple sclerosis (MS) 244, 250
 Multipotent stromal cells 70
 Muscle 36, 38, 40, 41, 54, 68, 83
 skeletal 36, 38, 40, 41, 68, 83
 smooth 38, 54
 Muscle-derived stem cells 76
 Myeloid cells 113
 Myeloma patients, multiple 140

N

Nascent stem cell recruitment 178
 Natural Killer (NK) 104, 105, 113, 129
 New tissues, generating 39
 Niche for expansion of blood stem and progenitor cells 112
 Niches 114, 115, 116, 139
 endosteal 115
 perivascular 114, 116, 139

O

Oligodendrocyte 20, 21
 Omphalomesenteric artery hematopoietic progenitors and stem cells 120
 Organ bioengineering 82
 Organ failure 105, 209
 Organogenesis 37, 62
 Organ-on-a-chip technologies 138, 139, 142
 Organ regeneration potentials 184
 Organs 4, 6, 8, 11, 12, 26, 36, 37, 38, 43, 45, 50, 57, 62, 66, 70, 71, 73, 74, 76, 82, 83, 84, 101, 102, 112, 113, 120, 136, 139, 141, 143, 144, 171, 174, 175, 180, 184, 187, 197, 206, 210, 211, 213

 blood-producing 113
 complex 26, 66, 213
 hematopoietic 102, 113, 120
 Organ transplantations 55, 188
 Orthopedics 199, 241
 Osteoarthritis 176, 186, 192, 193, 195, 197, 198, 199, 200, 201, 204, 208, 209, 212, 216, 218, 242, 250
 Osteoblasts 7, 38, 75, 115, 138, 189
 Osteogenesis imperfecta (OI) 234, 237, 250
 Oxidized nanoparticles 180

P

Paediatric tracheobronchomalacia patient 76
 Pancreatic β -cells 50
 Pancreatic cell differentiation 51
 Pancreatic cells 51
 mature 51
 Paracrine effects 238
 Peak vertical force (PVF) 193, 194
 Peripheral arterial disease (PAD) 239
 Peripheral blood 3, 5, 26, 131, 189, 211, 239, 244, 246
 human 3, 5
 Peripheral blood stem cell transplant (PBSCT) 121
 Peripheral blood HSPCs 131
 Peripheral blood mononuclear cells (PBMCs) 247
 Peripheral blood stem cells (PBSCs) 123
 Peripheral blood stem cell transplant (PBSCT) 121
 Peyer's patch inducer cells 104
 Photopolymers 63, 64
 Photosensitive gels 79
 Platelet rich plasma (PRP) 192, 203, 205, 211, 218
 Pluripotent stem cell classes 5
 Pluripotent stem cells 14, 15, 46, 47, 49, 50, 62, 84, 126, 128, 129, 131, 132, 141, 174
 Polycystic kidney disease 57, 207
 Polysulfated glycosaminoglycans (PSGAGs) 202, 205
 Primary biliary cirrhosis (PBC) 240
 Primitive erythroid cells enucleate 110
 Primordial germ cells 55, 59, 61

migrating 55
 Primordial germ cells (PGCs) 55, 59, 60, 61
 Printing 63, 65, 66, 67, 73, 78, 82, 83, 138
 of Biomaterials in Tissue Engineering 66
 processes 63, 66, 67, 73
 techniques 63, 65
 technologies 63, 78, 82, 83, 138
 Progenitor cells 18, 43, 56, 77, 79, 105, 107,
 109, 111, 112, 114, 118, 124, 125, 126,
 131, 170, 175, 184, 188, 211, 212
 circulating 175
 endogenous 211
 endothelial 79
 human cardiac-derived cardiomyocyte 77
 lymphoid 118
 multipotent 107
 primitive haematopoietic 18
 renal 56
 Progenitor populations 36, 101, 143
 Progenitors 50, 51, 53, 101, 102, 103, 107,
 118, 120
 hepatic 53
 mature pro-B-cells 118
 multilineage 120
 pancreatic 50, 51
 Proliferation and differentiation of cells 66, 74
 Prostate 38, 54, 57
 Protocols 51, 70, 82, 125, 131, 132, 134
 tissue decellularisation 70
 Purified cells transcribe 20

Q

Quiescent tissue 8

R

Recapitulate hematopoietic tissue function 140
 Reconstitution assays 108
 Regenerative capabilities 209
 Regenerative medical intervention during liver
 disease 52
 Re-morphogenesis 4, 5, 17
 Reticular cells 117, 119
 Retinoic acid 51, 56, 58
 Retinoic acid receptors (RARs) 13

Retrodifferentiated haematopoietic stem cells
 (RHSC) 5, 23
 Retrodifferentiated stem cell state 17
 Retrodifferentiation 5, 17, 18, 21, 22, 25
 all-time points post 21
 hematopoietic 18
 human leukocyte 5, 17, 21, 22
 inducing 18, 25
 Retrodifferentiation of human leukocytes 15
 Retrodifferentiation process 4
 Reversion process 15, 16

S

Scaffolds 66, 70, 71, 72, 73, 74, 75, 76, 78,
 143
 3D-printed 69, 73, 74
 biocompatible 75, 143
 fabrication of 74, 75
 printed 71, 72, 73, 74, 76, 78
 sacrificial 76
 tissue-engineered 66, 70, 72, 73, 74
 Schirmer tear test (STT) 193
 Schwann cells 7, 117, 244
 nonmyelinating 117
 Secretory cells 14
 luminal 14
 specialized 14
 Septum transversum mesenchyme (STM) 52
 Sertoli cells 38

Sickle cell patients 130, 136
 Single cells, labelled 40
 Single secretory cells 14
 Sinusoidal obstruction syndrome 125
 Smooth muscle cells (SMCs) 9, 41, 78, 79
 Solid organ transplant (SOT) 245
 Somatic cells 60, 133, 134, 174, 185, 196
 human 133
 Source for *ex vivo* erythroid cell generation
 131, 132
 Source of therapeutic stem cell populations
 124
 Sources, fresh tissue 171
 Sources of hematopoietic stem Cells 123
 Specialized cells 6, 14, 15, 16, 24

- committed 16
 - Specialized tissue macrophages and dendritic cells 102
 - Stage organ failure 197, 210
 - Staining, producing cells 17
 - Stellate cells 9, 52
 - activated hepatic 9
 - Stem 46, 49, 126, 128
 - embryonic 46, 49, 126
 - induced pluripotent 49, 126, 128
 - Stem cell 14, 51, 113, 177
 - best characterized somatic 113
 - derived mesenchymal 177
 - single basal 14
 - transplanted glucose-responsive 51
 - Stem cell activity 107, 124
 - rich 124
 - Stem cell antigens 3, 14
 - embryonic 14
 - Stem cell 5, 6, 7, 15, 22, 37, 66, 73, 77, 79, 105, 107, 115, 117, 120, 124, 133, 144, 173, 188, 210
 - biology 144, 173, 183, 188, 210
 - bioprinting 77, 79
 - compartments 6, 22
 - differentiation 37, 66, 73
 - division 105
 - factor (SCF) 7, 107, 115, 117, 120, 133
 - infusate 5
 - lineages 183
 - marker 15
 - mobilization 124
 - Stem cell niche 117, 248
 - diabetes influence 248
 - Stem cell production 5, 177, 196
 - intensive 177
 - Stem cells release 178
 - Stem cell therapy applications 206
 - Stem cell transplantation 125
 - Stem cell treatments 176, 214, 215
 - Stereolithography 63, 64, 138
 - Stress erythropoiesis 119, 120
 - Stromal cells 7, 25, 52, 72, 77, 115, 116, 117, 118, 137, 138, 143, 234
 - derived mesenchymal 77
 - epithelial 118
 - mesenchymal 72, 117, 234
 - mesodermal-derived 52
 - perivascular 7
 - Stromal vascular fraction (SVF) 192, 193, 204
 - Structures 12, 25, 37, 39, 50, 66, 67, 68, 71, 72, 74, 75, 76, 77, 79, 81, 138, 143
 - generating histologically-organized mesodermal 25
 - Suppression, immune 218
 - Surface, luminal 57, 58
 - Synthetic matrix 83
 - Systemic lupus erythematosus (SLE) 243
 - Systems 6, 7, 37, 39
 - central nervous 37, 39
 - haematopoietic 6, 7
- ## T
- T-cell development 118, 119
 - T-cell receptor (TCR) 24, 118
 - T-cell receptors revert 24
 - T-cells 171, 172, 177, 178, 179, 183, 189, 190, 243, 246
 - activated 243
 - immature 171
 - memory CD8 246
 - naïve 172
 - regulatory 171, 172
 - T-cells proliferate 189
 - Telomerase 184, 195
 - Telomere shortening 184
 - Tendon repair 176, 192, 216, 242
 - Tf helper cells 104
 - β -thalassemia 130, 135, 136
 - Therapeutic applications 171, 173, 177, 178, 190, 213, 237
 - Therapeutic debut 237
 - Therapeutic products 213, 214, 215
 - Therapeutic stem cell populations 124
 - Therapies 49, 101, 109, 123, 128, 134, 136, 170, 174, 176, 178, 182, 183, 189, 190, 191, 192, 202, 203, 204, 205, 208, 209, 210, 211, 218, 244, 250
 - cellular 203, 205
 - gene 134, 189
 - immunosuppressive 244
 - medical 204, 208, 211, 218
 - regenerative 49, 101, 192, 250
 - Thymic cortex 118

- Thymic medulla 118
Thymic microenvironment 119, 127, 141, 142
Thymic nurse cells 118, 119
Thymopoiesis 118, 119
Tiludronate 205
Tissue architecture 36, 39, 141
 complex 36
Tissue bioengineering 82
Tissue breakdown 196
Tissue components 10
Tissue damage 178, 212
 immune mediated 212
Tissue decellularisation 70
Tissue degradation 209
Tissue-engineered intestinal structures 143
Tissue-engineered spleen 142
Tissue engineering 62, 66, 82
Tissue growth 210
Tissue injury 6, 9, 175
Tissue integrity 4, 249
Tissue interactions 52, 234
 orchestrate host 234
Tissue maintenance 196
Tissue oxygenation 109
Tissue reconstruction 4
Tissue regeneration 12, 73, 196, 208, 210,
 211, 213
Tissue rejection 82
Tissue repair 4, 170, 172, 176, 210, 234, 237,
 248, 250
Tissue repair and organ rescue 239
Tissues 15, 37, 50, 56, 57, 62, 68, 71, 74, 75,
 77, 82, 83, 101, 103, 106, 108, 109, 111,
 112, 125, 142, 175, 195, 212, 213, 215,
 244, 246
 birth-associated 246
 blood-producing 101
 cardiac 68
 ectopic 244
 embryonic 108, 109
 endoderm-derived 37, 50
 epithelial 37
 extra-embryonic 112
 mammalian 175
 mesendodermal 71, 75
 mesendodermal-derived 74
 mesendoderm-derived 62
 peripheral 50, 106
 revolutionized 213
 splenic 142
 stomach 57
 target 215
 tracheal 71, 74
 transplanted 125
 urogenital 56
Tissue scaring, reduced 187
Tissue sources 236
Tissue stem cell function 196
Tissue transplantation 187
Tooth extractions 208
Trachea, tissue-engineered 76
Tract 36, 37, 39, 43, 54, 57
 genitourinary 37, 43, 54, 57
 reproductive 36, 54
Transcription factors 14, 40, 43, 62, 105, 115,
 174, 234
Transcripts 25
Transdifferentiation 4, 5, 6, 16, 17, 20, 21, 22,
 24, 26, 133, 176
Transdifferentiation processes 26
Transformation 54, 234, 236
Transient retrodifferentiation of human
 leukocytes 19
Transplantation 50, 51, 53, 56, 57, 60, 62, 66,
 72, 82, 84, 101, 102, 103, 108, 112, 113,
 121, 123, 124, 125, 128, 133, 178, 180,
 183, 188, 208, 211, 216, 217
 intravenous 211
 secondary 108
Transplantation of β -cells 51
Transplants 101, 121, 125, 186, 245
 peripheral blood stem cell 121
 umbilical cord stem cell 121
Treatment regimen, standard 177
Tubular epithelial cells 38
- ## U
- Umbilical cord 124, 125, 197, 235, 246, 247,
 248
Urogenital 41, 55, 56, 58, 59, 61
 ridges 55
 sinus 41, 55, 56, 58, 61
Urothelial cells 58, 59
Urothelium 38, 57, 58, 59

V

Vascular bed tissue 82
Vascularity, increased 202
Ventral tissues 111, 114
 adjacent 114
Visceral endoderm 43, 45, 59, 110
Vitelline artery hematopoietic progenitors and
 stem cells 120

W

Wharton's jelly 189, 234, 235, 248
Wound healing 9, 10, 13, 178, 186, 234, 237,
 238
 non-scar 9

Y

YS hematopoietic cells 111



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