Journal of Cell and Tissue Research Vol. 20(2): 6915-6918 (2020)
(Available online at www.tcrjournals.com)
ISSN: 0973-0028; E-ISSN: 0974-0910

Review Article

RECENT ADVANCES IN STEM CELL THERAPEUTICS: A REVIEW

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Raceived: August 12, 2020; Accepted: August 30. 2020

Abstract: In most general terms, stem cells can be called as unspecialized cells that can undergo self-replication and differentiation. The discovery stem cells from various sources, their isolation, in vitro characterization and differentiation potential have significantly advanced our knowledge on human development and disease. During the normal course of life time of an organism, stem cells are involved in the regeneration and repair of degenerating or diseased cells. Stem cells are emerging as therapeutic agents to treat many unmet medical needs in the recent years. In many instances where conventional drugs are not efficacious, scientists and clinicians are counting on the immense potential of stem cells for therapeutic product development.

Key words: Stem cells therapy

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Dedication: *During his tenure as Adjunct Professor Dr. P.D. Gupta brought laurels to Manipal University, by conducting summer course, published books and guiding research in Pharmaceutics and Mechanical engineering. We are happy to dedicate this research work to him on his 81st Birthday.*

INTRODUCTION

There has been a debate for a few years as to whether stem cells should be considered as a 'practice of medicine' or 'drug'. US FDA allows the use of stem cells without 'drug approval' only under *Title 21* of the electronic Code of Federal Regulations (CFR) Part 1271.10(a) [1], minimal manipulation criterion and the 21 CFR 1271.10(a) [2] homologous use criterion [1]. This falls under the scope of practice of medicine, not under drug. In contrary, if the stem cell are more than minimally manipulated (e.g., cultured in the lab), then it is considered as a drug by most regulatory agencies in the world including USFDA. During cell or non-structural tissue processing, if the relevant biological attributes of cells or tissues are not altered, then it falls under minimal manipulation. In short, homologous use means usage of a recipient's cells or tissues with donor's cells, tissues, or product derived from them that has the same basic functionality in the recipient as in the donor. For example, the use of cells, tissues, or product derived from adipose tissue for the purpose of repair, reconstruction of lost part, or complete replacement, or possible supplementation of adipose tissue qualifies to be considered a homologous use.

Autologous and allogeneic therapies: There are two modalities of stem cell transplantations, autologous or allogeneic, depending on the origin and destination of the cells involved in the procedure. In autologous stem cell transplants, the donor and recipient are always same person, whereas in allogenic stem cell transplants, donors are different from recipients. Autologous transplants may be relatively safer but are much expensive compared to the allogeneic transplants. Because of this, majority of stem cell companies involved in product development are focussing on allogeneic product development.

Major sources of stem cells and their clinical development: Stem cells are broadly categorized into embryonic, adult or induced pluripotent stem cells.

Embryonic stem cells (ESCs): First human ESCs were derived in 1998 by James Alexander Thomson [2]. ESCs are immortal, being pluripotent they care capable of forming all types of cells that makes up an adult body. As ESCs are hyper proliferative, they also pose the threat of transforming into cancer cells. Mainly because of this reason and also due to some ethical concerns, the product development using ESCs did not gain much importance. Geron Corporation, the United States Company developing ESC therapy abandoned the clinical trial in the early phase. Astellas Institute of Regenerative Medicine, USA, is developing stem cell therapy for macular degeneration using human ESC derived Retinal Pigment Epithelium transplants [3]. As of now ECS derived products have not entered commercial phase.

Adult stem cells: Adult stem cells are present in many locations of human body to support the repair, maintenance and regeneration of the cells and tissues. Adult stem cells can be sourced from the bone marrow, peripheral blood, adipose tissue, umbilical cord, etc. and these multipotent cells are not as versatile or proliferative as embryonic stem cells. It is generally regarded that adult stem cells are safe for therapeutic development but due to their limited potential, they do not produce all specialized cell types present in the human body. Majority of the clinical trials employ adult stem cell products and several products are already being marketed. Two noteworthy products were approved in the year 2012, one is Prochymal®from Mesoblast Ltd (Australia) for paediatric acute graft-versus host disease (approved product in Canada and New Zealand) and the other is Cartistem® a product from Medipost Co. Ltd. (South Korea) for the treatment of articular cartilage defects appearing in knee osteoarthritis (approved in South Korea). Although United States doesn't have prominent approved products, several products are accessible to the patients with Regenerative Medicine Advanced Therapy (RMAT) Designation. Table 1 lists some prominent stem cell products that have secured marketing approval in the last five years.

Induced pluripotent stem cells (iPSCs): iPSCs are generated by reprogramming somatic cells by the introduction of genes important for maintaining the essential properties of embryonic stem cells (ESCs). There are risks associated with retroviruses used in the generation of iPSCs as they could potentially trigger the expression of cancer-causing genes by inserting DNA anywhere in the genome. Although ethical issues related to the embryos are not there, ethical issues related to the use of donors, potential risks of tumour development may restrict the growth of this field in the future.

Table 1: Name and description of the prominent products, companies holding their approval in the specified territories and the year of approval

Product Name (company)	Product Description (Allogeneic/Autologous)	Country of Marketing Approval (MA) or conditional MA (year approved)
Ortho-ACI® (Orthocell Ltd.)	Autologous *Chondrocyte* Implantation treatment for the symptomatic defects of articular *cartilage* of the joints (Autologous)	Australia (2018)
ALOFISEL (Takeda Pharma)	Adipose stem cells suspension as injection for the treatment of complex perianal fistulas in patients suffering from Crohn's disease (Allogeneic)	European Union (2018)
SPHEROX (CO.DON AG)	Spheroids of human matrix associated chondrocytes for repairing cartilage defects in the knee (Autologous)	European Union (2017)
HOLOCLAR® (Chiesi Farmaceutici)	Ex vivo cultured human corneal epithelial cells with stem cells for moderate to severe limbal stem cell deficiency (Autologous)	European Union (2015)
Stempeucel® (Stempeutics Research Pvt Ltd)	Ex-vivo cultured human mesenchymal stromal cells (MSCs) for treatment of Critical Limb Ischemia due to Buerger's disease (Allogeneic)	India (2017)
Stempeucel® (Stempeutics Research Pvt Ltd)	Ex-vivo cultured human mesenchymal stromal cells (MSCs) for treatment of Critical Limb Ischemia due to Peripheral Arterial Disease (Allogeneic)	India (2020)
Temcell HS (JCR Pharmaceuticals Co. Ltd.)	Mesenchymal stromal cells for treatment of acute graft versus host disease (aGVHD) (Allogeneic)	Japan (2015)
Stemirac (Nipro Corp.)	Expanded autologous mesenchymal stromal cells (MSCs) for the treatment of spinal cord injury (Autologous)	Japan (2018)
KeraHeal - Allo™ (Biosolution Co., Ltd.)	Composite cell product (a hydrogel type, skin-derived keratinocytes therapy product) for deep 2rd degree burns (Allogeneic)	South Korea (2015)
HPC, Cord Blood (MD Anderson Cord Blood Bank)	Cord-blood derived hematopoietic stem cell therapy product indicated for use in unrelated donor hematopoietic progenitor cell transplant procedures in conjunction with the relevant preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders that are affecting the hematopoietic system that may be inherited, acquired, or result from myeloablative treatment (Allogeneic)	United States of America (2018)

However, recent research findings on iPSCs are encouraging and several scientists all over the world are involved in developing new cell-based therapies. Japan is the first country to initiate clinical trials using iPSCs, now other countries have joined the race. Clinicaltrials.gov shows more than 50 on-going clinical trials using iPSCs worldwide, although products are yet to enter commercial phase. Some of the major companies involved in iPSC research are Cyanata Therapeutics (Australia), ReproCELL (USA), Ncardia (Netherlands), Astellas Pharma Inc (Japan), Applied Stem Cell (USA), Fate Therapeutics (USA), Fujifilm Cellular Dynamics Inc (USA), ViaCyte (USA), Sumitomo Dainippon Pharma (Japan).

Stem cells in COVID-19 treatment: In Coronavirus disease 2019 (COVID-19), the virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) trapped in the aerosols infect healthy individuals causing respiratory illness of varying degrees. COVID-19 outbreak has affected more than 200 countries and the World Health Organization (WHO) had declared it as global pandemic on 11 March 2020. To date, there is no consensus on specific antiviral treatment efficacious in COVID-19 patients and there are no approved drugs for treating this disease. Infected patients are offered supportive care mainly for the symptomatic relief. In an effort to combat this disease, several groups are working on small molecules, vaccines, convalescent plasma therapy, cell therapy, etc. It is important to note that MSCs offer significant hope to combat this disease as evidenced by several ongoing studies.

Mesenchymal stromal cells (MSCs) belong to a type of adult stem cells which are non-haematopoietic and do not require Human Leucocyte Antigen (HLA) matching before transfusion. They are known to be anti-inflammatory, anti-apoptotic and hypo-immunogenic in nature [4]. As per several published articles, MSCs exert therapeutic action on Acute Respiratory Distress Syndrome (ARDS) by promoting restoration of epithelial and endothelial permeability, increasing alveolar fluid clearance, and facilitating lung tissue recovery. Several clinical trials using MSCs on COVID-19 patients are registered in Clinicaltrials.gov. Early results using allogeneic MSCs in severe COVID-19 patients have shown promising results in reversing the severity of infection

in critically ill patients. Thus, it is expected that allogeneic MSCs offer hope for critically ill COVID-19 patients by slowing or halting the disease progression which will in turn lead to significant recovery rate.

CONCLUSIONS

Selection of stem cells for therapeutic development mainly depends on their safety profile. Adult stem cells are preferred source for therapeutic development because of their safety and efficacy. Stem cell therapeutics offer hope for several debilitating diseases and also diseases like COVID-19. Globally, several companies are involved in stem cell product development and India is not far behind. Infrastructure development for the manufacturing of raw materials and end products, technology development for large scale manufacturing, fast track regulatory approval pathway are some of the challenges the stem cell industry faces today. Future looks promising with several new stem cell products in the advanced stages of clinical trials and a few of them already in the commercial market.

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