Chapter

Stem Cell Therapy and Regenerative Medicine in Autoimmune Diseases

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Abstract

The role of immune system in our body is to defense against the foreign bodies. However, if the immune system fails to recognize self and non-self-cells in our body leads to autoimmune diseases. Widespread autoimmune diseases are rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, and more yet to be added to the list. This chapter discusses about how stem cell-based therapies and advancement of regenerative medicine endow with novel treatment for autoimmune diseases. Furthermore, in detail, specific types of stem cells and their therapeutic approach for each autoimmune condition along with their efficiency to obtain desired results are discussed. Ultimately, this chapter describes the recent trends in treating autoimmune diseases effectively using advanced stem cell research.

Keywords: autoimmune disease, stem cell therapy, regenerative medicine, hematopoietic stem cell lines, mesenchymal stem cells, rheumatoid arthritis

1. Introduction

Autoimmune disease [AID also called as autoimmune disorder] is a result of immunological imbalance and intolerance. In such a condition, an immune response is produced against the healthy tissues or substances present in our own body [1]. Though, there were roughly 67 autoimmune diseases known as per the reporting of American Autoimmune Related Disease Association [AARDA] in 1992 with 40 in suspicion, the number has grown to be in a range of 150 AID in 2016. With such a rapid incidence, AID has an impact on the social status and economy of the country too. With a mean age of onset at 65, AID targets the age group of 20–29 [2]. Gender-based studies continue to be a conundrum due to biased data reports and sexual dimorphism [3]. A series of events trigger AID, but the trigger that causes such a holocaust still remains unknown. Environmental factors, misregulation of immune system, and heredities are few common factors that influence AID out of the humungous list. Smoking, alcohol, industrial pollution, oral contraceptives, birth weight, breastfeeding, protein intake, geography, and socioeconomic status are some of the possible environmental triggers associated with AID. In case of misregulation of genes, the association of human leucocyte antigen (HLA) class II encoded HLA-DRB1-DQA1-DQB1 haplotype has been detected with several AIDs, including type 1 diabetes, Graves' disease, and rheumatoid arthritis.

2. Classification and types

AID is broadly classified into two types; systemic and organ specific. In systemic autoimmune disease, autoimmune response targets self-antigens that are distributed in various organs resulting in widespread tissue damage. Most affected areas include joints, skin, kidneys, heart, lungs, and red blood cells. On the other hand, antigens present over a particular organ are targeted in organ-specific autoimmune response [4]. Body parts that are affected by AID are represented in **Figure 1**. Prominent examples under both categories are considered and discussed in the following sections.

Systemic	Local disorders
Rheumatoid arthritis	Endocrinology: diabetes mellitus
Systemic lupus erythematosus (SLE)	Gastrointestinal: Crohn's disease
Scleroderma	Neurological: multiple sclerosis

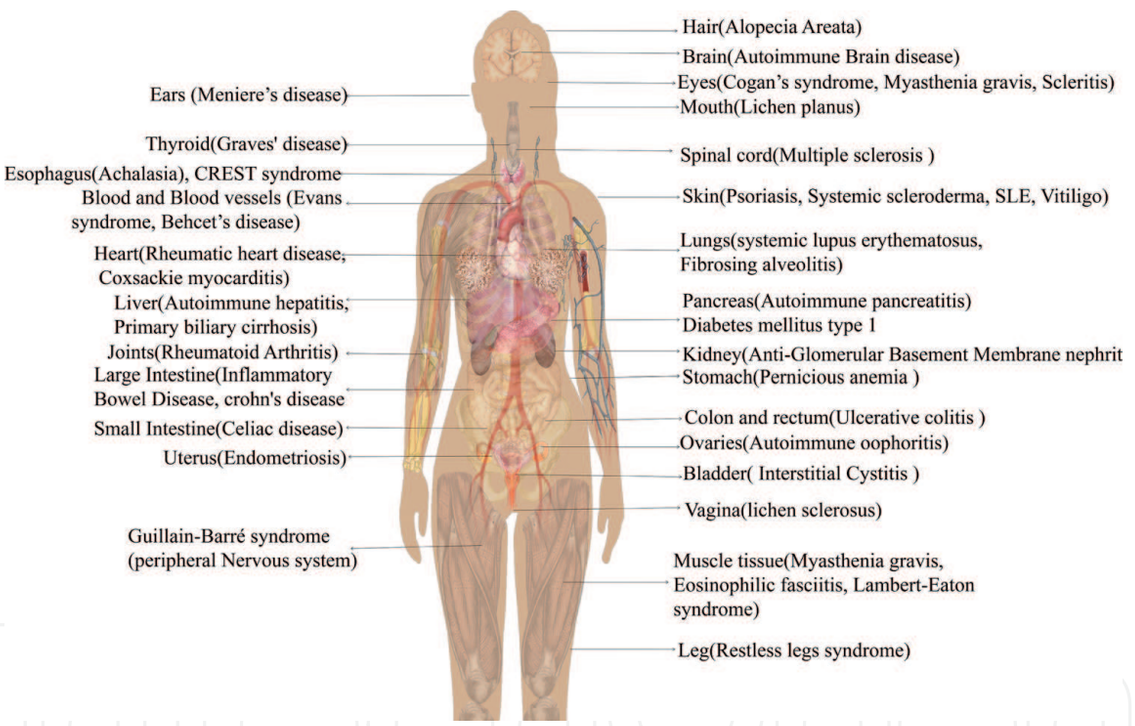

Figure 1.
Body parts affected by autoimmune disease condition.

Current therapies lead to symptoms alleviation concomitant with side effects. Hence, stem cells can be a potential answer to the proposed conundrum by bridging the gap between the problem and the solution. The following section condenses on the therapeutic potential of stem cells.

3. Stem cells

With a lead role to play, stem cells have been superheroes in regenerative medicine. Possessing the ability to self-renew, multilineage differentiation, mobility and homing, stem cells can treat many diseases by turning out to be any kind of cell through differentiation [5–8]. Stem cells can be classified into two major groups,

which include embryonic stem cells (ESC) and adult stem cells (ASC). Other type of stem cell is induced pluripotent stem cells [iPSCs] that can be produced in the laboratory by reprogramming adult cells to express embryonic stem cell characteristics.

3.1 Embryonic stem cells (ESCs)

ESCs are derived from an embryo approximately 3 days after fertilization with totipotency to give rise to more than 220 cell types in the future. ESCs face a critical reception due to complications such as rejection, directed differentiation, and source of ESCs. Method of obtaining ESCs involves the destruction of blastocysts and those who believe that life begins at the blastocyst is a human life, and to destroy that is unacceptable and immoral, this procedure is equally risk to female donors being consented [8].

3.2 Adult stem cells (ASCs)

ASCs are derived from the adult human body, precursor cells that can efficiently mend the body to help promoting homeostasis. Major accessible sources of ASCs include bone marrow, adipose tissues, and blood. Hematopoietic stem cells (HSCs) can differentiate into immune stem cells (multipotent) and all kinds of blood cells including white blood cells, red blood cells, and platelets [9].

3.3 Induced pluripotent stem cells (iPSCs)

iPSCs can be generated in the laboratory by introducing reprogramming factor in the somatic cells that express the defining properties of embryonic stem cells. This provides an opportunity to generate pluripotent patient-specific cell lines, to generate model for human disease, and also used as a tool for drug development. Moreover, the tissues derived from iPSCs are almost identical with the donor cells; thus, it avoids the major rejection issue arose by the immune system [10].

3.4 Stem cells and their timeline

Once the Second World War came to an end, the world turned its concentration from research in destructive and nuclear weapons toward welfare of the human race after NATO. When such a scenario occurred and scientists started working on the betterment of human race, a path was paved for research on stem cells. The following table is a timeline containing significant events pertaining to stem cells [11, 12].

Year	Significant endeavors
1963	Self-renewing property of transplanted mouse bone marrow cells were first documented by Canadian researchers Ernest A McCulloch and James E Till
1968	First bone transplant was performed for leukemia
1978	Discovery of stem cell in human cord blood
1981	Embryonic stem cells were isolated from mice
1988	Embryonic stem cell lines generated from a hamster
1995	First embryonic stem cell line was derived from a primate
1996	First British and European stem cell company (ReNeuron) emerged
1997	Cloned lamb from stem cells

Year	Significant endeavors
1997	Leukemia origin was found as hematopoietic stem cell, thus indicated a possible proof of cancer stem cells
1998	James Alexander Thomson and his team cultivated the first human embryonic stem cells in a laboratory dish
1999–2000	Scientists discovered that manipulating adult mouse tissues could produce different cell types indicates bone marrow cells could produce different type of other cells
2001	For the first-time Christine Mummery and her team used stem cells to create beating heart cells outside the body
2002	Chunhui Xu and team found that heart muscle cells can be made from human embryonic stem cells
2003	Antonio Beltrami described a small population of stem cells in the heart that help in repair itself after damage
2004	Valérie Planat-Bénard and colleagues found that heart-like cells could be heart-like cells could be cultivated from adipose tissue
2004	First UK Stem Cell Bank (UKSCB) accredited
2006	Shinya Yamanaka of Japan reprogrammed adult cells and formed "induced pluripotent stem cells"
2007	Anthony Atala claimed that a new type of stem cell had been isolated in amniotic fluid
2007	Direct transformation of Human skin cells to iPS cells found by Shinya Yamanaka has become the revolutionary breakthrough in stem-cell biology
2009	Cardio 3 bioscience company performed lineage guided Stem cell transplant for heart failure and heart attack
2010	Geron company conducted first clinical trial for spinal cord injury and two successful human embryonic stem cell trials were conducted by Advanced Cell Technology for macular degeneration
2011	Geron terminated hESC trials and first hESC cell lines were generated
2012	Human embryonic stem cells show promising treatment for blindness
2013	-Advanced cell technology and Cardio 3 bioscience published clinical results -Brainstorm demonstrates positive results in phase 1 and phase 2 clinical trials -Aastrom-terminated phase 3 clinical study conducted for critical limb ischemia -Patient-specific human embryonic stem cells were produced
2013	Shoukhrat Mitalipov produce hESCs from fetal cells
2014	Masayo Takahashi performed the world's first trial for iPSC derived transplant to treat a form of age-related blindness
2014	Charles Vacanti Haruko Obokata at the Riken Center for Developmental Biology announced a breakthrough discovery of the concept pre-embryonic state. Dieter Egli of the New York Stem Cell Foundation and Young Gie Chung from CHA University independently produce hESCs from adult cells, using therapeutic cloning
2016	Jo Mountford and the University of Glasgow, culturing red blood cells from stem cells to make a limitless supply of clean blood for transfusion
2019	Xuefei Gao et al. for the first time derived the Expanded Potential Stem Cell lines (EPSCs) of pig and human cells which has the important implications for developmental biology, regenerative medicine, organ transplantation, disease modeling, and screening for drugs

4. Action of stem cells on AID

Hematopoietic stem cells (HSCs) were first employed to serve as a solution to leukemia and lymphoma. Eventually, after conducting trials over animal model experiments, hematopoietic stem cells found its application in destruction of self-reactive memory cells and in regeneration of self-tolerant immune cells; hence

constructing a new functional immune system from hematopoietic precursors. HSC transplantation has been used to treat several types of AID over the past 15 years with a 30% decline in the progress of the AID [13–15].

Mesenchymal stem cells (MSCs) were another kind of multipotent stromal cells that were almost omnipotent, discovered by Frienden Stein et al. Being immunosuppressive, MSCs were found to suppress inflammation and downregulate pathogenic immune response triggered in Graft versus Host Disease (GVHD) and in AID such as multiple sclerosis, autoimmune diabetes, and rheumatoid arthritis [16, 17].

4.1 Hematopoietic stem cell transplantation

HSC transplantation to treat AID has been in progress since 1970s. HSCs are typically obtained from bone marrow, peripheral blood, or umbilical cord blood. Source of HSC may be autologous or allogeneic. Differentiation of hematopoietic stem cells into all kinds of blood and immune stem cells is represented in **Figure 2.**

4.1.1 Isolation of HSCs

Stem cells are mobilized from the bone marrow to peripheral blood, which will facilitate the collection of HSCs without general anesthesia or bone marrow harvest. The method of mobilization can be done by a variety of protocols. Majorly protocols make use of granulocyte colony stimulating factor or cyclophosphamide. Cyclophosphamide leads to rebound mobilization of stem cells as it is both immunosuppressive and myelosuppressive. Leukapheresis is used to collect the HSCs and purification is done by identifying stem cell containing $CD34^+$ markers or lineage-specific surface markers by negative selection of T or B cells. Negative selection process leads to T cell depletion in the auto graft [18, 19].

While isolation was first performed in murine model, efforts have been made to develop human models. Fluorescence-activated cell sorting (FACS) has been employed

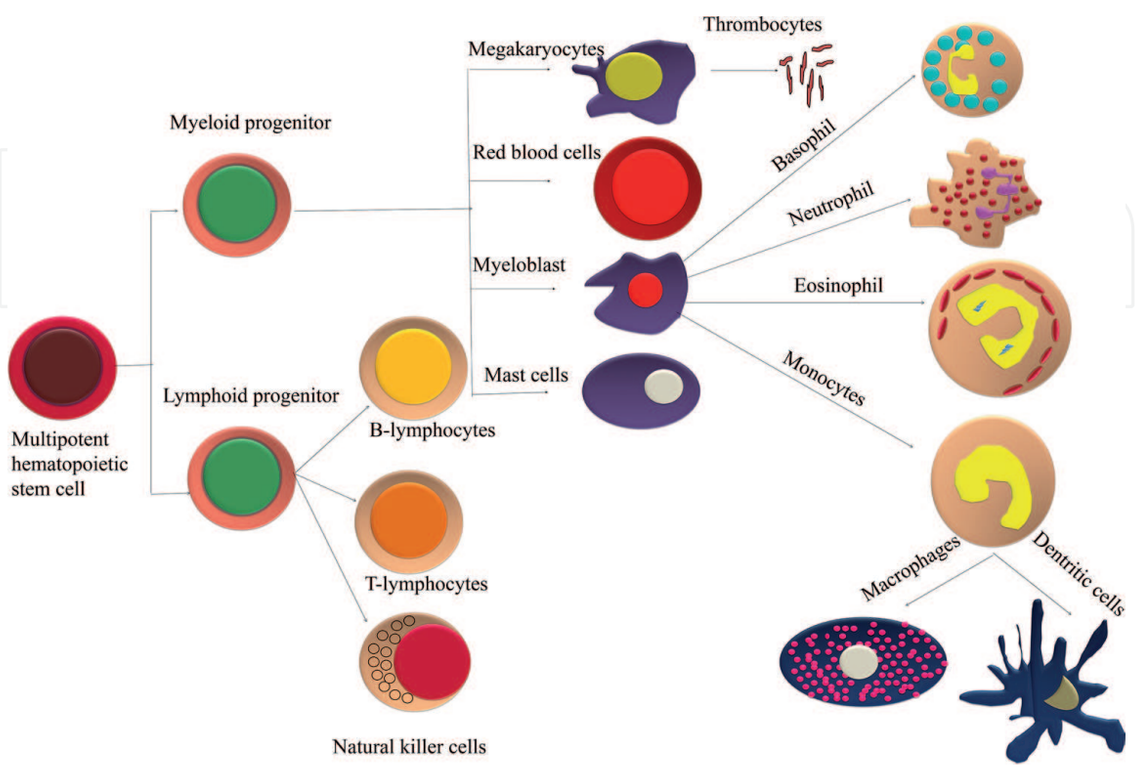

Figure 2.
Differentiation of multipotent hematopoietic stem cells.

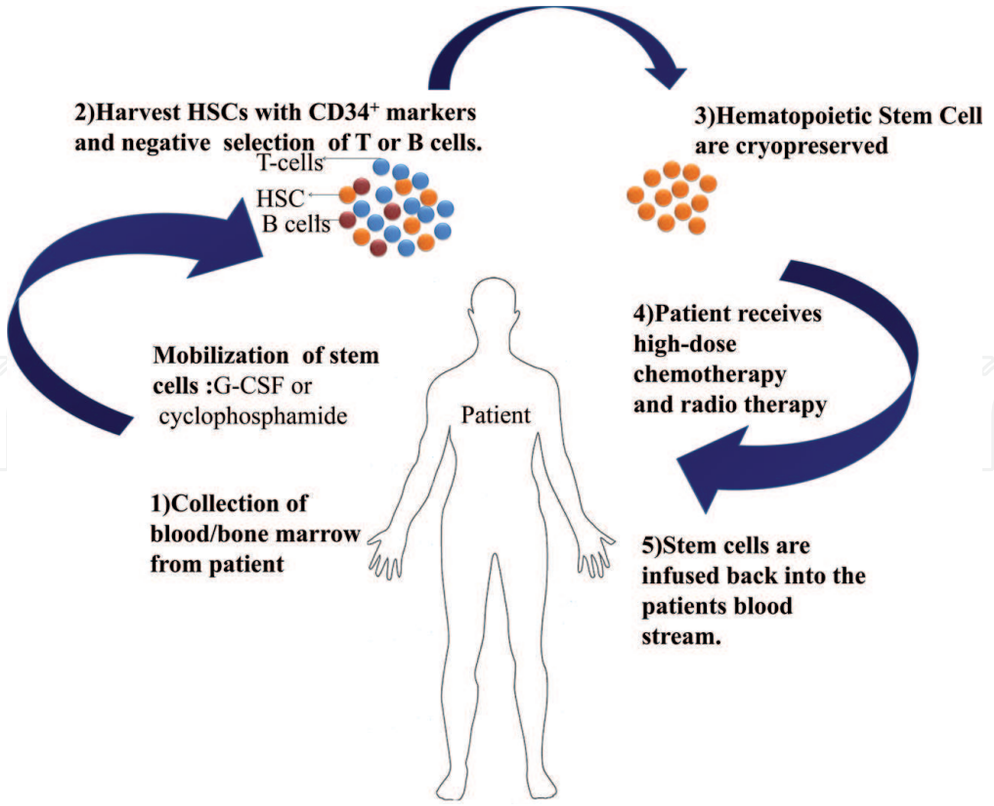

Figure 3.
Autologous stem cell transplantation.

for isolation, recognition, and quantification of smaller number of cells in a huge population. The technique is so accurate that there is a cent percent probability in purity [20].

4.1.2 Autologous HSC transplantation

Autologous HSC transplantation has been used to treat several AIDs such as rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, and systemic lupus erythematosus. As the name suggests, autologous HSC transplantation uses the subject's own stem cell avoiding tissue rejection. This kind of transplantation eradicates autoreactive immunologic memory through conditioning with highly active cytotoxic agents. Then, B and T cells can be introduced to auto antigens and undergo self-tolerance; in contrast, environmental factors that trigger autoimmunity might not occur again throughout the subject's lifetime [21–24]. The step wise protocol for autologous stem cell transplantation is depicted in **Figure 3.**

4.1.3 Allogenic HSC transplantation

Allogenic transplantation is done between two subjects whose human leucocyte antigen (HLA) match. Even though the HLA gene matches, the recipient will undergo immunosuppressive medications to tone down graft-versus-host disease. In this type, the donor may be closely related, syngeneic (identical twin of the patient) or may be unrelated but with HLA match. In allogeneic HSCTs process, the healthy stem cells are transferred to the recipient's bloodstream to reform a healthy immune system and this method appears to improve chances for cure and in long-term remission. However, there were also cases of rheumatoid arthritis subjects affected by drug-induced aplastic anemia, where relapse occurred since all the immune competent cells were from the donor [25–28]. Autoimmunity is treated using HSC transplantation and the following are the action of HSCs:

1. Developing tolerance by T regulatory cells.

2. Developing tolerance of autoreactive and alloreactive B cells.

3. Deleting alloreactive and autoreactive T cells in thymus.

4. Deleting peripheral autoreactive and alloreactive T cells.

5. Destruction of autoreactive B cells and T cells mediated by the immune system.

6. Immunosuppressive conditioning and autogenic HSC transplantation leading to immunomodulation.

The step wise protocol in allogeneic stem cell transplantation is represented in **Figure 4.**

4.2 Mesenchymal stem cell transplantation

MSCs possess the ability to differentiate both *in-vivo* and *in-vitro* into different lineages, which include adipose, bone, cartilage, muscle, and myelosupportive stroma (**Figure 5**) [29]**.** Isolation of MSCs can be done from bone marrow, skeletal muscle, adipose tissue synovial membranes, connective tissues in adults, cord blood, and products of placenta; each of which is defined by using phenotypic markers and their functional properties [12, 30–32]. Allogeneic MSCs can be transplanted into a patient without preconditioning and still have positive clinical effects on the subject without acute toxicity [33, 34]. MSCs possess the following abilities that make them a clinical success [35].

1. Homes to inflammation site when delivered intravenously following tissue injury.

2. Differentiates into a variety of cells.

3. Secretes multiple bioactive molecules that facilitate recovery of injured cells and inhibition of inflammation in return.

4. Lacks immunogenicity and possess immunomodulatory functions.

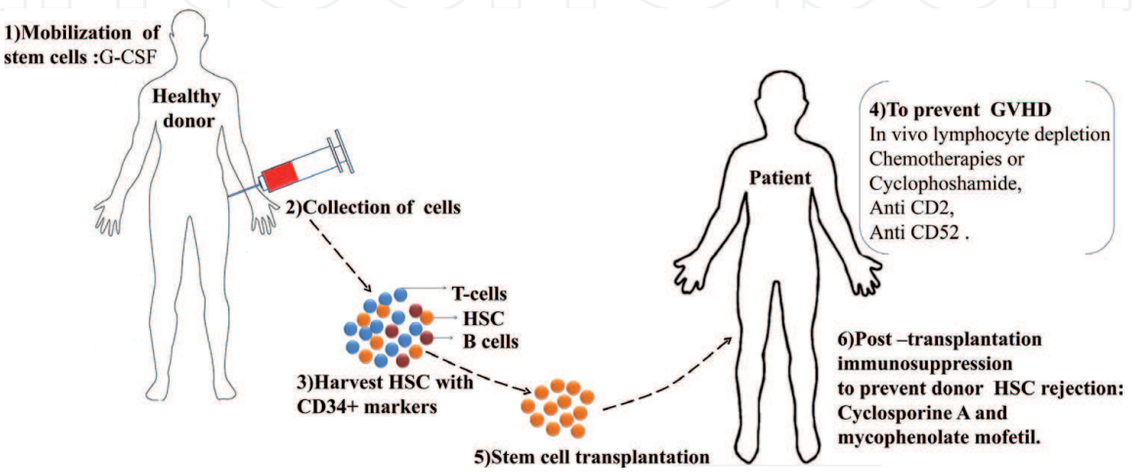

Figure 4.
Allogeneic stem cell transplantation.

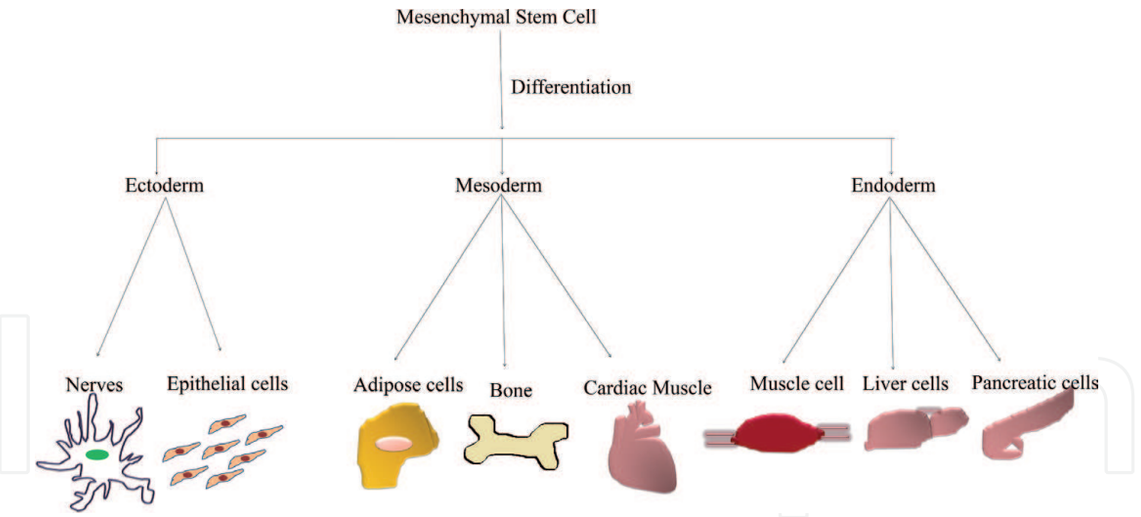

Figure 5.
Mesenchymal stem cell differentiation.

MSCs can also migrate and engraft at the inflammation site, when administered locally or systemically [36, 37]. Various cases of such an ability is discussed in the below paragraph.

Ortiz et al. found that murine MSCs could respond during a lung injury, ameliorating inflammation while adopting epithelium-like phenotype; when mice were injected with bleomycin [38]. Liu et al. found that MSCs could migrate to the site of injury in muscle tissues [39]. Yagi et al. found that the migration of MSCs was influenced by a variety of tyrosine kinase growth factor receptors such as platelet derived growth factor (PDGF) and IGF-1 and chemokines such as CCR2, CCR3, CCR4, or CCL5. Chemokines were found to lessen migration of MSCs in *in vitro* migration assays. MSCs are more privileged as they express low levels of HLA class I and HLA class II, CD40, CD80, and CD86 cannot be detected on the cell surface. Class I and class II molecules were found to increase when stimulated with interferon; thus, facilitating an increased efficiency of MSCs by being immuno-suppressive and possessing immunological friendly phenotype [40, 41].
Animal models of experimental autoimmune encephalomyelitis were found to be successfully treated with MSCs, while the case was hazardous in collagen-induced arthritis (CIA). Autologous bone marrow-derived MSCs were found to be anti-proliferative toward stimulated T cells derived from normal subjects and AID subjects [42–44].

4.2.1 Isolation of MSC

Markers such as CD44, CD73, CD90, and CD105 for MSCs with the lack of CD14, CD31, CD33, CD34, and CD45 are used for isolating MSCs using cytofluoro-metric analysis. Due to their heterogeneity, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (ICST) published three minimal criteria for MSCs [35]:

- MSCs should adhere to plastic when in standard culture conditions.
- Display of surface antigen expression pattern including $CD73^{+}$, $CD901^{+}$, $CD105^{+}$, $CD34^{-}$, $CD45^{-}$, $CD11b^{-}$, $CD14^{-}$, $CD19^{-}$, $CD79a^{-}$, HLA-DR^{-}.
- MSCs must be multipotent with the ability to differentiate into osteogenic, chondrogenic, and adipogenic lineage.

4.2.2 Autologous and allogeneic MSC therapy

MSC therapy has been widely applied and two different modes of therapy are discussed below. Isolation of cells is done based on the markers stated above and the cells are delivered using two approaches: intravenous and intra-arterial injection. In intravenous injection, the MSCs migrate to the affected site and can stay up to 13 months in the body. Moreover, route of administration is chosen based on the application used to resolve [45]. Autologous MSCT is obtained from self, while allogeneic MSCT is performed between individuals whose HLA expressions match. Both autologous and allogeneic MSC therapies are used to subside inflammation and hence are used to treat disease such as systemic lupus erythematosus, Crohn's disease, multiple system atrophy, multiple sclerosis, amyotrophic lateral sclerosis, and stroke [46].

4.2.3 MSC over HSC

HSCs have been associated with the risk of Graft versus Host Disease (GVHD). On the other hand, conducted preclinical studies prove that MSCs were successful. When MSCs were infused intravenously in leukemia subjects who were grafted with HSCs, the GVHD incidence was found to be loud (4). GVHD is suppressed by secretion of transforming growth factor β (TGF-β), prostaglandin E2, and indoleamine 2,3-dioxygenase, which in turn suppresses T cell proliferation and activation. Hence, MSCs were found to be compatible rather than HSCs.

5. Application of stem cells to treat AID

5.1 Systemic AID

Systemic autoimmune diseases are broad range of related diseases characterized by misregulation of immune system that gives rise to activation of immune cells and attack auto antigens, which result in multi-tissue/organ damages. In the following section, prominent examples of systemic AID and their therapy with stem cells are discussed briefly with proven animal model and clinical studies.

5.1.1 Rheumatoid arthritis (RA)

RA affects approximately 1.5% of the world population, and it is characterized by chronic joint inflammation, production of auto antibodies accompanied with various degrees of bone, and cartilage erosion triggered due to immunological self-intolerance [47–49]. It is a multifactorial disease, results from the combination of misregulation of genetic factor, immune system, and environmental exposure. However, the precise underlying mechanism of RA is not clear. In RA subjects, 80% of them comprise rheumatoid factor, an auto antibody specific to the Fc region of the IgG. There is no clear evidence about the source of inflammatory cytokines in specific stem cells. However, on contrast, RA can be transmitted as well as abolished by allogenic and autologous hematopoietic stem cell transplantation [50].

5.1.2 Current treatment methods

Current treatment methods include drugs, therapies, and surgeries. Drugs such as steroids and nonsteroidal anti-inflammatory drugs (NSAID); and disease-modifying antirheumatic drugs (DMARD) such as methotrexate, leflunomide, and plaquenil to slacken the progression of the disease and biological DMARD. Therapy

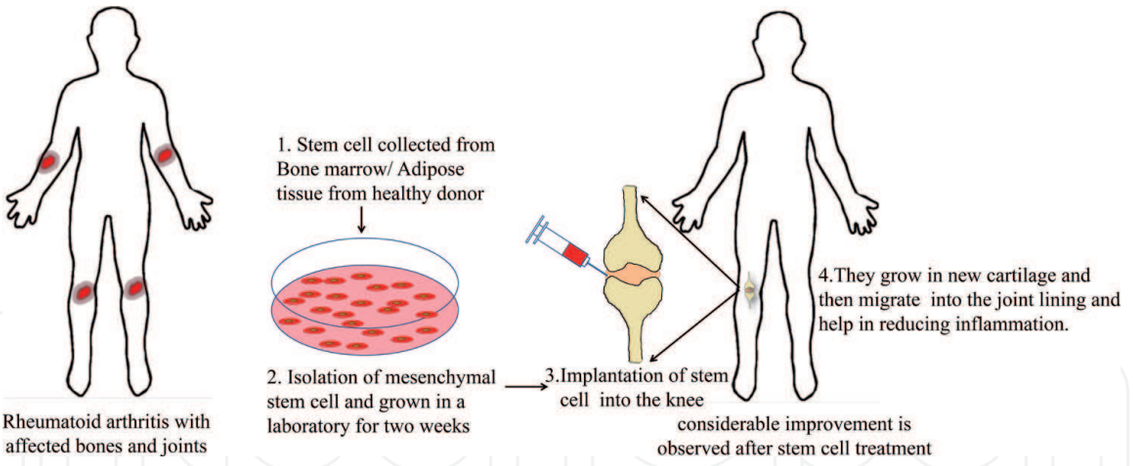

Figure 6.
Treatment method for rheumatoid arthritis using allogeneic mesenchymal stem cell transplantation.

includes cryotherapy, short wave or microwave diathermy, and physiotherapy. Heat and cold treatment can soothe pain. Surgery such as total knee replacement, tendon repair, or joint infusion is done according to the magnitude and site of damage.

Current therapy includes the use of hematopoietic stem cell transplant and mesenchymal stem cell transplant. However, recurrence was found to occur in majority of the cases irrespective of $CD34^+$ graft selection. Preclinical studies were performed and the trial consisted of three phases. The first two phases were found to establish potential characterization of the technique with high dose chemotherapy within safety limits. Improved response was noted with increased doses in the conditioning regimen and with post SCT therapy was studied but the graft manipulation was not taken into consideration. Phase three was attempted with widespread use of biological anti-rheumatic agents. Autologous SCT is considered in rare subjects, who resist both conventional and biological treatments [51, 52]. **Figure 6** represents the treatment method for rheumatoid arthritis using allogeneic mesenchymal stem cell transplantation.

5.1.2.1 Animal model study

Gonzalez et al. performed the study over a mice model. Injection of adipose-derived MSCs was followed by the decrease in inflammatory cytokines and chemokines with an expansion of Th1/Th17 cells and increase in IL-10. Together, it was found to induce peripheral tolerance by controlling self-antigen reactive T cells. Further, an increase in $CD4^+$, $CD25^+$, Fox $P3^+$, T-reg led to the suppression of self-reactive response. Other studies described the differences between *in vivo* and *in vitro* studies. In *in vitro* studies show that MSCs inhibit T cell proliferation by regulating IFN-γ levels while *in vivo* studies show that the transplantation did not have an effect on the progression of the disease. The real complication lies in the MSCs reaching the lymph and spleen nodes when injected [53]. Bouffi et al. demonstrated that the MSCs had an immunosuppressive effect involving a pathway regulated by prostaglandin 2. There were also evidences showing that T-reg cell induction was not influenced by the MSCs and hence choosing a different age group for the mice used in the study could have been a factor for the complications listed previously [43].

5.1.2.2 Intra-bone marrow-bone marrow transplantation (IBM-BMT)

SKG/Jcl mouse with T cell-mediated AD that mimics RA. BM cells of C57BL/6 J mice were transplanted to SKG/Jcl mice and there was no incidence of arthritis for

12 months with replacement of hematolymphoid cells with the donors' cells. IBM-BMT is a viable method and lends further credit to be tested in humans [54, 55].

5.1.2.3 Autologous stem cell transplantation (ASCT)

Elimination of mature autoreactive lymphocytes is done by manipulation of the graft by antithymocyte globulin (ATG) combined or with $CD34^+$ by itself. The method basically depends on G-CSF and throughout the process, immunosuppression is done to introduce the SCs into the subject [56].

5.1.2.4 Clinical trial studies

Moore et al. conducted a study over 33 subjects and the subjects were randomly incident to autologous transplantation of non-manipulated cells or selected $CD34^+$ cells. Non-manipulated stem cells were found to produce a better effect. Syngeneic transplantation of HSCs between twin brothers could control recurrence for at least 24 months. Healthy lymphocytes in a syngeneic transplantation could modify immunoregulation disorder. EBMT with 76 subjects out of which majority of the subjects responded well, but relapse rate was high [57, 58].

5.1.3 Systemic lupus erythematosus (SLE)

SLE is a rare chronic AD, which is characterized by upregulation of IFN-regulated gene transcripts. In SLE, antibodies are generated against nuclear and cytoplasmic antigen. Autoreactive plasma cells play a major role in inducing SLE and hence short-lived plasma blasts are found in positive subjects. Reduced stem cell proliferation, BM dysfunction, and decline in $CD34^+$ cells are associated with SLE. Hematopoietic system of SLE subjects had several defects due to the unbalanced expression of cytokines and growth factors. Transplantation of hematopoietic stem cells in MRL/lpr mice was found to reduce the occurrence. MSC transplantation was found to ameliorate the progression by inhibiting T lymphocytes and Th2 proliferation [59, 60].

5.1.3.1 Current treatment methods

Current treatment techniques include medication. The medication prescribed depends on the purpose served by the drug; disease modifying antirheumatic drugs, immunosuppressive drugs for immunomodulation, analgesics for analgesia, and intravenous immunoglobulins. In terminally ill cases, kidney transplant is an option while lesser silica, pesticides, and mercury levels can also have an impact on the subject. In recent years, hematopoietic stem cells and mesenchymal stem cells have been used for the drug-resistant SLE.

5.1.3.2 Animal model study

SLE animal model of W/BF1 mouse had a resultant decline in platelet count due to the production of anti-DNA antibodies and anti-platelet antibodies. These mice were found to possess lupus nephritis along with myocardial infarction, high WBC count, and hypertension. Transplantation of BM cells from normal mice was found to cure lupus nephritis, thrombocytopenia, and anti-phospholipid antibody syndrome. Normalization of platelet count was accompanied along with reduction

in antiplatelet antibody levels and anti-phospholipid levels. BMT along with thymus transplantation in MRL/Lpr mouse could treat AID as the allogeneic T cells were naïve T cells that were resistant to apoptosis with lesser Fas expression [61, 62].

5.1.3.3 Clinical studies

The first autologous hematopoietic stem cell transplantation for SLE was performed by Marmont et al. [62]. In this approach, peripheral $CD34^+$ stem cell source was used after mobilization with CYC and granulocyte colony stimulating factor. According to European Group for Blood and Marrow Transplantation (EBMT), registry for HSCT in SLE patients showed around 80% of overall survival and 29% of disease-free survival and with a mortality rate of 15% suggests a goof efficacy and safety of autologous HSCT. In case of allogeneic HSCT, EBMT data showed that out of two patients, one patient died of infection and other had progressed disease after 3 years and thus clinical use of allogenic HSCT for SLE is limited. Mesenchymal stem cell transplantation was developed after 10 years of HSCT, and this approach showed a better efficacy with low cost compared to HSCT. Overall in the past 5 years, the advantage of stem cell therapies for SLE patients has increased tremendously with an initial development in high dose immunosuppression maintained by HSCT being followed by MSCT approach [63, 64].

5.1.4 Systemic scleroderma

Systemic sclerosis (SSc) is characterized by expansion of dysregulated fibroblast clones, which are uncontrollable and over expression of genes that constitute the extra cellular matrix, collagen type I in particular. SSc is characterized by high case-specific mortality as a result of internal organ disease and is also accompanied by other burdensome outcomes.

5.1.4.1 Classification

5.1.4.1.1 Limited (CREST syndrome)

Symptoms associated with limited syndrome are listed as follows.

- Raynaud's phenomenon (vasoconstriction with less blood supply in the hands resulting with a color transition from red, white to blue in cold conditions).
- Calcinosis (calcium deposition occurs in the nodules).
- Dysfunctional esophagus promoting difficulty in swallowing.
- Clerodactyly (fingers have thickened skin).
- Telangiectasias (features such as dilated capillaries in hand, face and mucous membrane).

5.1.4.1.2 Diffuse (systemic sclerosis)

Diffuse scleroderma shows up mostly in organs such as kidney, esophagus, heart, and lungs. It is either combinational or occurs separately. It is more fatal when it occurs in the lungs. Symptoms mostly include changes in the skin within a year, frictional rubs of tendons, lung, and GIT-associated complications, respectively [65, 66].

5.1.4.2 Current treatment methods

Current treatment method only focuses on treating some of the symptoms that softens the skin and to lessen the inflammation condition, but is not completely curative and still remains as a puzzle. Some patients may get benefit by exposure to heat but non-lethal manifestations such as fatigue, calcinosis, and anorectal dysfunction still remains as a challenge.

5.1.4.3 Clinical trials with autologous stem cell transplant for early diffuse SSc

In the first trail, American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST), 10 patients who received autologous HSCT compared with 9 patients who received 1.0 g/m^2 intravenous CYC. Adverse events were poorly documented in this study, but seven of nine were worsened. In the second trail, Autologous Stem Cell Transplantation International Scleroderma (ASTIS) 79 patients who received autologous HSCT compared with 77 patients who received 750 mg/m^2 IV CYC monthly for 12 months. This study results in higher mortality rate in the first year but had better long-term survival rate than those treated with CYC alone. The third trail scleroderma cyclophosphamide or transplantation (SCOT), 36 patients who received autologous HSCT compared with 39 patients given monthly IV CYC over 12 months. Despite the low numbers included in this study, the data demonstrated the efficacy of HSCT over CYC. Overall, the data provided by ASTIS and SCOT supports the HSCT over IV CYC [67, 68].

5.1.4.4 Clinical trial studies

A 16 year-old subject with localized scleroderma was selected. The subject possessed multiple plaque lesions along the trunk on 2008. By 2010, the subject had a progress in the condition involving the right half of the body further resulting in face asymmetry. Autologous HSCT was performed in 2011 by injecting fludarabine, cyclophosphamide and equine anti-thymocyte globulin along with GCSF and acyclovir till engraftment. Supplemental dose of co-trimoxazole was given for prophylaxis, irradiated single donor platelets, and red blood cells for supportive care, respectively. No post transplantation complication was found and the subject was found to be stable with no progress in lesions after 41 months. The subject had no progress in the disease condition and no immunosuppression was done once the transplantation came to an end [69].

6. Organ-specific AID

The following section discusses prominent examples in Organ specific AID and their association with stem cells.

6.1 Type 1 diabetes (T1D)

T1D is an autoimmune disease with a strong genetic component that tends to occur in childhood. As of 2014, an estimated 387 million people have diabetes worldwide, out of which T1D accounts for 5–10% worldwide. Characterized by the destruction of insulin-producing β cells by the auto antibody directed against it. Hence, introduction of insulin or islet replacement is necessary for homeostasis by regulating sugar levels [70].

Autoreactive $CD4^+$ and $CD8^+$ T cells target against islet cells. SCs could differentiate into insulin producing β cells. Sources of stem cells for diabetes therapy include embryonic stem cells (MSC), hematopoietic stem cells (HSC), and induced pluripotent stem cells (iPSCs). Following stem cells therapy, C-peptide secretion, HbA1c level, and insulin levels are monitored for better intervention of the efficiency of the technique. Monitoring response of T cells to HLA-A2-retsricted insulin B10, pre-pro-insulin, islet antigen, GAD65 and pre-pro islet amyloid polypeptide might hint the efficiency of SCT [71, 72].

6.1.1 Current treatment methods

Current treatment methods focus on producing insulin to regulate the blood sugar level. Insulin is injected into the subject and the blood sugar level is monitored at various time points. Islets cells are transplanted in certain cases along with immune suppression.

6.1.2 Animal model study

Soria et al. used mice model to study type 1 diabetes. In the study, mice derived ESCs were allowed to differentiate into insulin producing cells and were injected into a diabetic mouse. Secreted insulin could reverse glycaemia. Further SCT was also successful in streptozotocin induced diabetic mice. iPSCs obtained from mouse ESCs could synthesize insulin by cleaving pro-insulin into C-peptide and insulin. It is also evidential that ESC derived cells consisted of all β cell features except for production of insulin at high glucose levels [73].

Oh et al. chose BM-derived cells for their mice model. The experimenters found that when the medium was supplemented with DMSO and high glucose concentration, the cells transformed into insulin producing cells (IPC). Moreover, the cells could aggregate mimicking the islet cells. Blood sugar level regulation could be done up to 3 months successfully [74].

Xie et al. found that hBM-MSC were able to give rise to IPC with addition of Activin A. Differentiated cells could produce insulin in glucose-dependent manner and could regulate blood sugar level until a month in diabetes induced mice [75].

6.1.3 Clinical trial study

Hu et al. performed Type 1 diabetes over three human subjects during the year 2011. Selection criteria used for the study was that the onset period should be less than 60 days staying within a healthy BMI of 22. Two subjects were treated with BM-derived SCs delivered by liver puncture. Before the therapy, the subjects were positive for insulin cells Ab (ICA) and glutamic acid decarboxylase (GAD). After a 12-month follow up, the subject was found to be negative on ICA, GAD, and insulin antibody. Subject's serum also had increase in C peptide and a decline in blood glucose and HbA1C and glycosylated Hb.

Dr. Chen et al. studied the long-term effects of implanting Wharton's jelly-derived MSC (WJ-MSC) from umbilical cord. Twenty-nine subjects were used to participate in the study by dividing into two groups. Group 1 comprises of people injected with WJ-MSC and group 2 had people treated with insulin once in 3 months for a period of 21 months. The HbA1C and C-peptide levels were found to decline in group 1 subjects documenting the success of WJ-MSCs [76, 77].

6.2 Multiple sclerosis

Multiple sclerosis (MS) is a neurological disability in which the myelin sheath around the axons of the brain and the spinal cord are demyelinated. In MS, T and B cells initiate the inflammatory attack. Such damage cannot be reversed and hence causes many complications. No current therapy has found a solution to arrest the progress of the disease. SCT for MS subjects was found to replace neural precursors such as oligodendrocytes and myelin with attenuation in the autoimmune process locally [78, 79].

6.2.1 Current treatment methods

Current treatment methods include administering corticosteroids such as oral prednisone and intravenous methylprednisolone, oral treatments such as fingolimod, dimethyl fumarate, teriflunomide, siponimod and infusion treatments include ocrelizumab, natalizumab, alemtuzumab, and mitoxantrone. Beta interferons, glatiramer acetate, dimethyl fumarate, fingolimod, and teriflunomide are prescribed to reduce nerve inflammation. Plasma exchange (plasmapheresis) is another technique in which blood plasma is removed from blood cells and then mixed with albumin and put it back to the body. Other treatments such as physiotherapy, muscle relaxants (Zanaflex and Lioresal), and medications to reduce fatigue (amantadine and methylphenidate) are also applied when the magnitude of symptoms increase. Currently, stem cell therapy using MSCs or iPSCs shows great potential as treatment for MS. **Figure 7** shows iPSC-based therapeutics for multiple sclerosis.

6.2.2 Animal model study

Deng et al. performed a murine model study in mice affected by experimental autoimmune encephalomyelitis (EAE). EAE shared common features with human model of MS. During the study, it was evidential that the injection of MSCs could pacify myelin oligodendrocyte glycoprotein (MOG) induced EAE. There was a

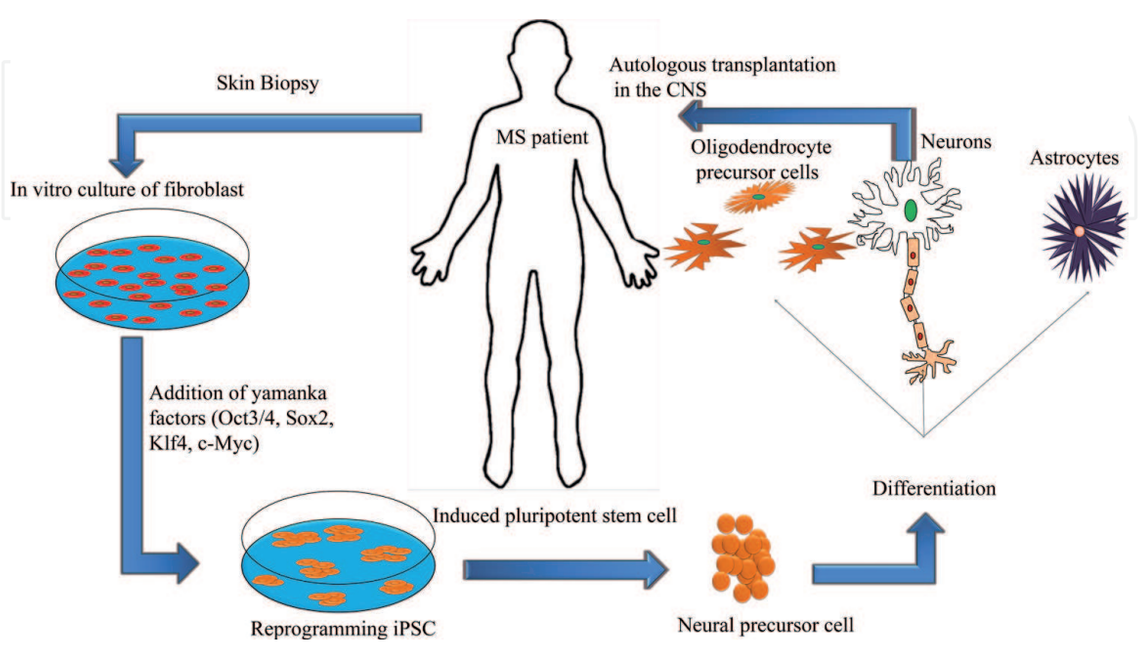

Figure 7.
Human iPSC-based therapeutics for multiple sclerosis.

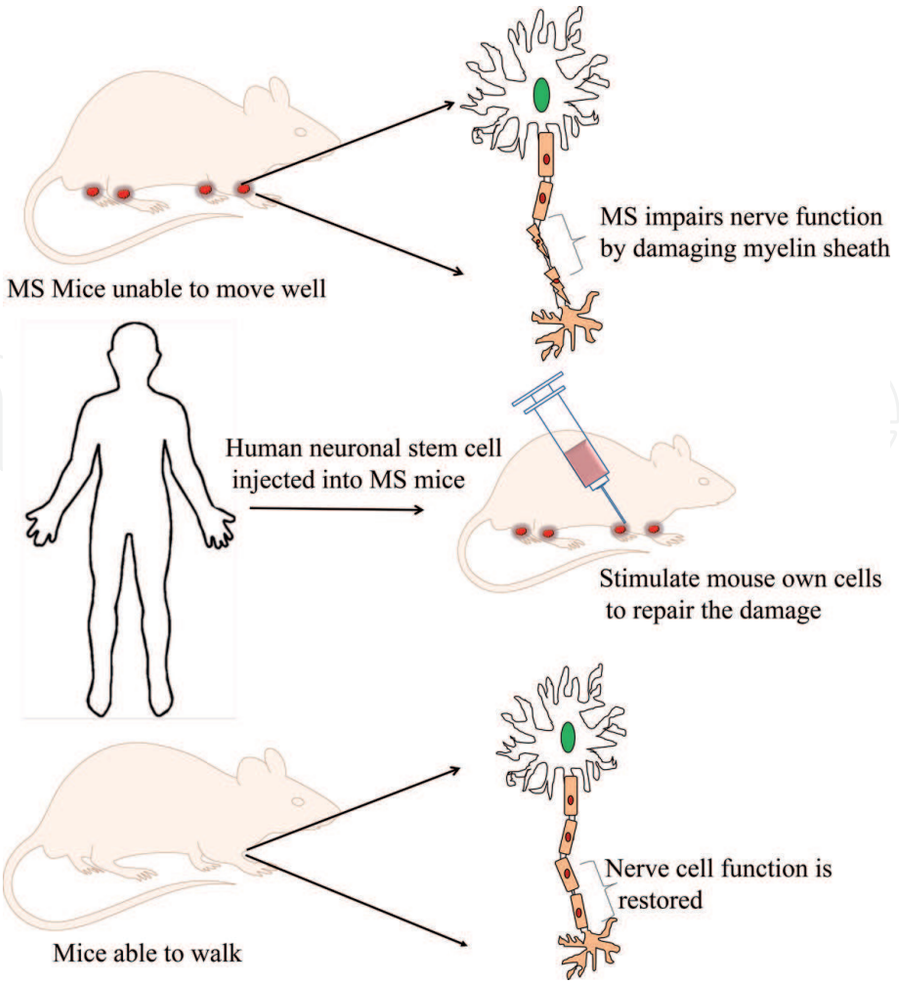

Figure 8.
Stem cell treatment for mice affected with multiple sclerosis.

decline in the infiltration of T cells, B cells, and macrophages into the brain and spinal cord. MSCs were found to migrate to the spleen and inflamed CNS to thereby have a neuroprotective effect on the CNS **Figure 8**. Further, such a therapy was also found to help in oligodendrogenesis and also increased the magnitude of symptoms. As a result, $CD8^+$ cells were more in the brain Deng et al. Carmen Marin-Bariasco et al. derived MCSs from SJL/JCrl mice. During the study, it was evidential that there was a modulation in the progress of the disease [80, 81].

6.2.3 Clinical trial study

The first reported AHSCT was performed on MS subjects in 1995 and re-myelinization occurred in the damaged sites. In 2002, HSCT was performed over 200 subjects affected with MS and there was reduction in inflammation at the CNS. However, complications such as infection and high T cell associated mortality and morbidity rates occurred during the study. Bonab et al. found that MSCs when injected intrathecally produced no adverse effects in 10 patients with non-responsive disease. Karusis et al. proceeded with phase one and two with 10–15 subjects. They found that there was no adverse effect produced during the follow up period of up to 28 months. Outcomes such as increment in $CD4^+$, $CD25^+$ regulatory T cells, decline in proliferative response of lymphocytes, and activation markers on dendritic cells. Connick et al. transplanted autologous MSCs in 10 subjects. The team found that such a therapy was found to reduce progress of general disability and improve visual function of subjects [82].

Riccardo et al. performed an autologous HSCT for severe progressive multiple sclerosis in a multicenter trial on 19 subjects with rapidly progressive MS with a score up to 7 on the scale for expanded disability status. After stem cell mobilization with CY and filgrastim, patients were conditioned with 1,3-bis[2-chloroethyl]-1-nitrosourea, etoposide, aracytin, melphalan, and followed by horse ATG. All patients showed clinical stabilization or improvement and three patients experienced deteriorate as a result of transplant related complication and 1 beyond the baseline. Among 19 patients, no death was reported after the change of conditioning to CY plus ATG. These studies indicate that HSCT is able to induce a prolonged clinical stabilization in severe progressive MS patients, resulting in both sustained treatment-free periods and improved quality of life [83].

6.3 Crohn's disease

Crohn's disease is characterized by recurring episodes of inflammation in the GI tract. The exact cause for Crohn's disease is unknown. Sources can be genetical, immunological, environmental, or even microbial. Hereditary transfer of Crohn's disease ends up with a higher probability and the incidence is 30 times higher in siblings. Crohn's disease is associated with the auto activation of T cells, especially Th1and Th17. Environmental factors such as dietary constituents and smoking also play a role in acquiring crohn's disease. High level of interleukins such as IL-21/IL-22, MMP 9 and fecal calprotectin are associated with the disease [84, 85].

6.3.1 Current treatment methods

On a major scale, drugs and techniques are employed to allay symptoms and consequences of the disease. Anti-inflammatory drugs such as corticosteroids are administered. Immune system suppressors are administered and drugs vary a wide range from cyclosporine to azathioprine. Antibiotics are and other medications such as anti-diarrheal, pain relievers, calcium and vitamin D supplements, vitamin B-12 shots and iron supplement. Surgery is done in certain cases and nutrition therapy is also recommended in certain cases.

6.3.2 Animal model study

Both canine and mice model were used to study Crohn's study. Cavazza et al. induced CD in 8-week year old mice by injecting Dextran sulfate sodium. The outcome obtained by the experimenters was a positive outcome, adipose-derived MSC could achieve the therapeutic effect and human cord derived blood platelets (hCBPL) were found to reduce colitis score [86].

Hoffman et al. used a dog affected with canine anal furunculosis as it had the same features as a human fistulizing Crohn's disease. Human ESCs derived MSCs were injected into six dogs used in the study. As a result, the interleukins associated with Crohn's disease (IL-2 and IL-6) were reduced after 2 months of post injection. After 3 months, the dogs were found completely free and after 6 months two dogs had relapse [87].

6.3.3 Clinical trial study

Molendijk et al. performed allogeneic bone marrow-derived mesenchymal stromal cells transplant to promote healing of refractory perianal fistulas in patients with Crohn's Disease. About 21 patients were randomly grouped and given injections of MSCs into the wall of curettage fistula in three different cell concentration

and control (1×10^7 (n = 5), 3×10^7 (n = 5), and 9×10^7 (n = 5), and n = 6 of placebo cells). Fistula healing was observed and observed that there was nil association between local administration of allogenic MSCs and the adverse events in subjects affected by perianal fistulizing Crohn's disease [88]. Garcia-Olmo et al. performed clinical trials over 10 subjects (8 males and 2 females). In six subjects, there was complete cessation of suppuration of the fistula. Partial response was seen in three subjects with decline in suppuration. A year later there was a nil score on six cases with two cases where the incontinence score improved from the range 12-8 to 5. Nil adverse effects were observed throughout the experiment [89].

Ciccocioppo et al. studied the long-term effects of MSC therapy on eight subjects during a period of 7 years from 2007 to 2014. Disease remission was noted for up to 12 months with a gradual decline in between followed by remission again. The probability of a disease-free state declined from 88% in the first year to 37% in the last 4 years [90].

7. Trial results of stem cell therapy

Though stem cell therapy is found to be a promising solution, in the long run several complications follow. But there are also cases where the technique was found to be ineffective over certain subjects. Hence, impact of the technique as a whole is discussed in the following section.

A retrospective analysis of subjects affected by AID was taken into account. Nine hundred subjects were taken into consideration with a lead count of 345 on MS, followed by other AIDs such as the systemic sclerosis (175), SLE (85), RA (89), juvenile idiopathic arthritis (65), and idiopathic cytopenic purpura (37).

One third of the subjects responded completely while two third of the remaining had no response. There were 85% five-year survivals and 43% progress free survival during the whole period of study. On the better side, transplant related mortality was 1% for RA subjects while it came up to 11% for SLE and JIA. On the worse side, HSCT could cause acute toxicity and end up subjects with infection and bleeding. In Systematic Sclerosis subjects, HSCT was found to induce rapid fluid and electrolyte shifts. In juvenile idiopathic arthritis (JIA), fatal macrophage activation was found to occur as a result of immunosuppression. Though subjects were affected by fungal and other infections, there were also lethal outcomes due to second autoimmunity. Worst case scenario also included re-expression and relapse with a reduction in magnitude of the disease [91, 92].

8. Conclusion

Overall, this chapter highlighted the advances in the clinical use of stem cells in the treatment of an array of systemic and organ-specific autoimmune disorders. The treatment of many types of autoimmune diseases was conducted through the administration of autologous/allogenic HSCs and MSCs transplantation. Although the progress in clinical trials using stem cells in AID modification, immunomodulation, and regenerative purposes are certainly encouraging, still most of the treatment methods are still in the early stages. This is due to the clinical results reported are not clear about therapeutic efficacy and only a significant number of studies were conducted in humans, while most of them are conducted in animal models of immune-related diseases. This indicates the need for the conduction of randomized clinical trials in relevant immune-related diseases for the potential application of stem cell treatment. Due to the substantial variation among studies, comparing

results from one stem cell-based medicinal product to another is very challenging. Therefore, uniform regulation of the clinical application of stem cells is highly indispensable for minimally invasive, customizable and individualized therapeutic method for a safe and successful treatment alternative. It is also important to determine the most appropriate source of stem cells that should be applied for the treatment of each autoimmune disease. In conclusion, despite the need for further studies, the treatment of immune-related diseases through the administration of stem cell is progressively ceasing due to many questions regarding the risks of stem cell application and its potential side effects that need better answers.

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Conflict of interest

The author declares no financial or commercial conflict of interest.

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