

# Regenerative medicine: an analysis of origins, trends and potential therapeutic applications, with a focus on hematopoietic stem cells

## 1. Origins of regenerative medicine

Regenerative medicine, or the concept of creating fully functioning tissues to repair or replace tissue or organ function (NIH Fact Sheets 2018), has drawn the attention of scientists for the better part of a century. However, a specific definition is difficult to isolate. The realm of regenerative medicine includes conceptions such as tissue engineering and cell therapy, all the while employing a bench-to-bedside approach that is characteristic of translational medicine. Essentially any treatment that involves stem cells will be considered a sect of regenerative medicine, and although there are different types of stem cells, the idea behind infusing these cells is essentially the same between the distinct types—to replenish the levels of cells that are either depleted or to replace cells that are not functioning properly. The term “regenerative medicine” was ostensibly coined by Leland Kaiser, in his 1992 article over hospital administration (Kaiser 1992). Although the term itself is in its relative infancy, the concept of tissue regeneration is nothing new. In the 18<sup>th</sup> century, Lazzaro Spallanzini and Charles Bonnet observed regeneration of limbs in salamanders (Towle 1901). After substantial research on the phenomenon of animal regeneration, the possibility of constructing artificial organs was mentioned as early as the 1930s, in the book The culture of organs (Carrel 1938). However, the technology required for these kinds of procedures was not in the scientific community’s arsenal at the time. There were many obstacles these scientists had to overcome.

When discussing regenerative medicine, quite possibly the most developed and widely implemented procedure in this realm is the infusion of stem cells. Regarding stem cell transplants, it is important to note that the two most common types of transplants are autologous and allogeneic. Autologous transplants involve the transfer of stem cells from within the patient's own body, whereas allogeneic transplants involve the transfer of stem cells from one individual to another. As one could imagine, allogeneic transplants present more of a challenge. More specifically, the most pervasive hurdle in allogeneic stem cell transplants is the body's innate immunological response to the introduction of these foreign cells. The body, in many cases, views these newly introduced cells as harmful pathogens, resulting in an immunological onslaught on the transplanted stem cells. Throughout the history of regenerative medicine, many bright researchers have made tremendous strides in overcoming the difficulties of allogeneic stem cell transplants.

In 1939, the first human bone marrow transfusion was given, performed in an attempt to treat a patient with aplastic anemia (a condition in which there are not enough new blood cells in the body) (Osgood, Riddle, and Mathews 1939). Although unsuccessful, this experiment was a milestone in the study and development of regenerative medicine. Four years later, P.B. Medawar and T. Gibson observed the human body's reaction to sets of autografts and homografts (tissue grafts taken from same species of recipient). Throughout the study, they demonstrated that the homografts began to degenerate within days, in stark contrast to the autografts (which were extremely successful) (Medawar and Gibson 1943). This experiment marked the advent of the study of immunological responses to foreign, regenerative cells. At the culmination of scientists' endeavors to conceive solutions to this problem, a group of researchers discovered the benefits of inoculating animal fetuses with allogeneic spleen cells. Once the

fetuses were exposed to these foreign cells, they acquired a tolerance to cells originating from the same donor. This discovery allowed the researchers to successfully perform allografts when the animals were adults (Billingham, Brent and Medawar 1953). In addition to allogeneic and autologous stem cell transplants, there also exists syngeneic transplants. Syngeneic transplants involve the transfer of cells that are genetically similar/identical (the transplant of cells from one identical twin to another).

In 1956, Dr. E. Donnall Thomas accomplished the first successful syngeneic bone marrow transplant between two humans, implementing stem cell infusion in order to treat leukemia. The patient's tissues utilized the donated bone marrow to make new, functioning blood and immune cells (Encyclopaedia Britannica). Just one year later, Dr. Thomas performed the first allogeneic hematopoietic stem cell transplantation (Thomas et al. 1957). In this particular study, six patients received radiation and chemotherapy before receiving an intravenous infusion of bone marrow from a normal donor. However, within 100 days of the infusion, all six of the patients had died. At the time of this procedure, little was known about histocompatibility, and the concept of matching a donor to a recipient had not yet taken root.

In 1968, decades after The culture of organs was published, the first successful allogeneic bone marrow transplantation was performed in humans (Starzl 2000). The procedure implemented human leukocyte antigen (HLA) matching and was completed by Dr. Robert Good. The transplant, performed to treat a 5-month-old boy with an immune deficiency disease, used bone marrow donated from the patient's 8-year-old sister (Wright 2003). In the latter half of the 20<sup>th</sup> century, medical breakthroughs such as blood banks and bone marrow registries began to completely revolutionize blood/tissue typing and matching. The introduction of these organizations marked the beginning of a sharp increase in accessibility to bone marrow and

blood cell donations. In 1973, the first unrelated donor bone marrow transplant was carried out in New York at Memorial Sloan-Kettering Cancer Center on a 5-year-old boy with severe combined immunodeficiency syndrome. The bone marrow donor was found through the blood bank at Rigshospitalet in Copenhagen, Denmark (Thomas 1999). The patient received seven infusions of bone marrow, and engraftment eventually occurred, returning blood cell function to normal (ASBMT and CBMTG 2018).

However, in the past few decades, new routes of obtaining hematopoietic stem cells have been discovered and implemented. One widely-used alternative to bone marrow transplantation is peripheral blood stem cell transplantation (PBSCT). In this method, the stem cells come directly from the bloodstream via a process called apheresis, in which the stem cells are isolated and collected for storage. In the 1950s, dividing, nonleukemic DNA-synthesizing cells were discovered in peripheral blood. Implicit in this discovery was the possibility of the existence of circulating multipotent cells (Bond et al. 1958). Decades later, the first blood stem cell infusion was attempted in 1981 at Hammersmith Hospital in London (Goldman et al. 1981). That very year, a similar operation was conducted at Johns Hopkins Hospital in Baltimore, Maryland. However, long-term engraftment was not achieved (Körbling et al. 1981). The procedure of autologous peripheral blood stem cell transplantation was first successfully utilized in 1986, when a patient with Burkitt lymphoma underwent myeloablative radio- and chemotherapy, followed by PBSCT at Heidelberg University Hospital in Germany (Körbling and Freireich 2011). As of 2011, the patient was alive without any evidence of disease. Until the last decade of the 20<sup>th</sup> century, allogeneic PBSCT was not considered a viable option because of the high possibility for severe graft-versus-host disease (GVHD), due to the much higher donor T cell content contained in peripheral blood allografts. In 1989, physicians at the University of

Nebraska Medical Center attempted the first allogeneic, HLA-matched donor PBSCT. However, long-term engraftment was not achieved, because the patient died of an infection 32 days after the procedure (Kessinger et al. 1989). In 1995, however, the first successful allogeneic PBSCTs were performed at M.D. Anderson Cancer Center (Körbling et al. 1995), Fred Hutchinson Cancer Research Center (Bensinger et al. 1996), and Kiel University Hospital in Germany (Schmitz et al. 1995). The prevalence of acute GVHD resulting from these trials was relatively comparable to that of allogeneic bone marrow transplantation. In the years since its conception, PBSCT has overtaken bone marrow transplantation as the preferred method of hematopoietic stem cell transplantation, due in no small part to its ease of the procedure.

Another newer method of harvesting hematopoietic stem cells is that of umbilical cord transplantation. The utilization of cord blood in stem cell transplantation has become much more commonplace for a variety of clinical reasons. Umbilical cord blood is extremely rich in HSCs, containing a higher concentration of these stem cells than is normally found in adult blood. In addition to the high concentration of HSCs in cord blood, another substantial advantage that cord blood offers as an alternative source of HSCs is that of lower rates of graft-versus-host disease than those of bone marrow transplants (Kurtzberg 2017). Also, with the emergence of cord blood banks, umbilical cord blood transplantation (UCBT) offers relatively quick accessibility to stem cell transplants (Gluckman 2009). UCBT was first implemented in 1988 at Hôpital Saint-Louis in Paris (Gluckman et al. 1989). In the years to come, the concept of UCBT would rapidly evolve and develop. A multitude of new studies began to expand the potential offered by the use of cord blood in regenerative medicine. In the 1990s, the feasibility and possible efficacy of HLA-matched unrelated-donor transplants was demonstrated (Rubinstein et al. 1995). This discovery was a defining point in the development of cord blood transplantation, because it exhibited the

possibilities of UCBT availability throughout the world, made realistic partially because of cord blood banks. More recently, Claudio Brunstein and others carried out a study indicating that the patient outcomes from UCBT between groups of varying levels of HLA-matching were similar, denoting the vast possibility of mismatched UCBTs (Brunstein et al. 2016). In light of discoveries such as this, umbilical cord blood has started to become a more widely-implemented technique, especially due to the fact that it is a commonly discarded substance—further cementing its importance in the treatment of many life-threatening afflictions.

## **2. Stem cells—what they are**

For an organism with the complexity of a human, there is a stringent necessity for cells that serve a variety of different functions—for example, neurons to coordinate sensation and motor function, red blood cells to facilitate the transport of oxygen, and for lymphocytes to conduct the adaptive immune response. As a human matures, cells begin to differentiate into particular lineages, thereby reducing the potential functions of these cells. If this process does not result in sufficient reservoirs of every individual type of cell, serious, potentially deleterious effects can take place. Herein lies the importance of stem cells, or unspecialized cells that become any one of a number of different cell types. Stem cells have immense possibilities in the realm of medicine, because of their capacity for differentiation. This differentiation can replenish reserves of specific cell classes that have been depleted. This is essentially the mechanism behind stem cell transplantation—the replacement of lost cell types.

In addition to the concept of differentiation into many distinct cell types, another important element of stem cells is that of self-renewal. Self-renewal is the division of stem cells to create more stem cells. This event bolsters the pool of stem cells within the body throughout life. The key aspect of this concept is that it ends in stem cells that still have not differentiated

into a specific cell type (He, Nakada, and Morrison 2009). The process of self-renewal is tantamount to differentiation in its importance regarding survival, because it is vital to retain ample numbers of stem cells in the body (Seita and Weissman 2011). Within the concept of self-renewal, there are two distinct mechanisms: that of obligatory asymmetric replication and that of symmetric differentiation (Shahriyari and Komarova 2013). In asymmetric replication, the division of the stem cell results in one derivative stem cell and one differentiated cell. In symmetric replication, the stem cell divides into either two derivative stem cells or two new differentiated cells. Both symmetric and asymmetric replication are thought to function in maintaining adult homeostasis, and when these processes are disrupted, there can be cancerous growth of undifferentiated cells (Shahriyari and Komarova 2013).

Within the concept of stem cells, there is a variety of different subclasses—most notably

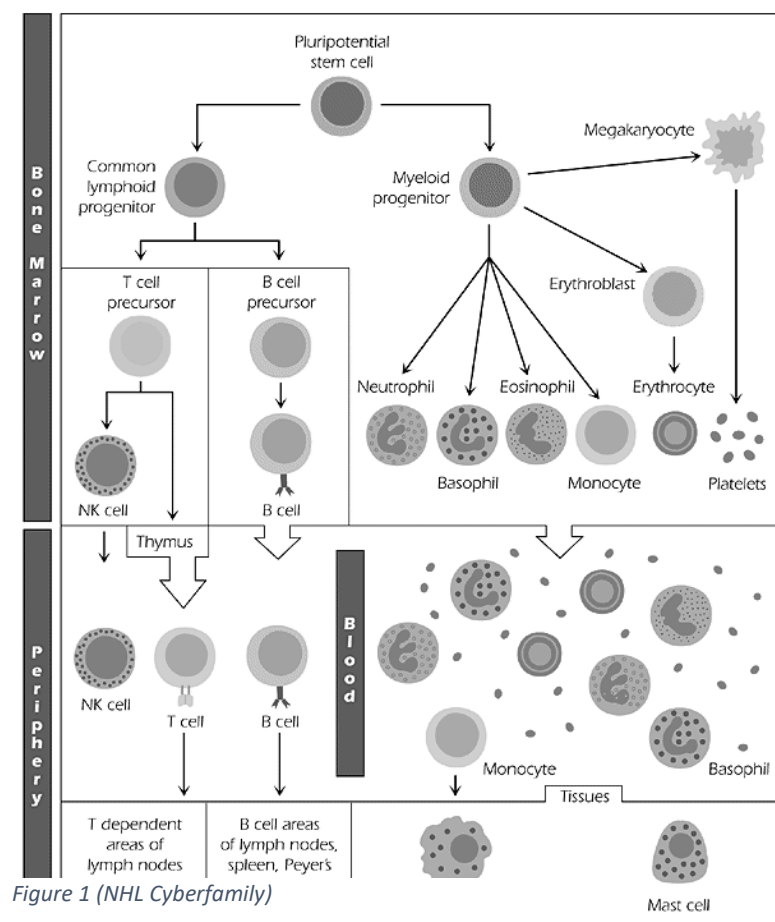


Figure 1 (NHL Cyberfamily)

embryonic, fetal and adult (also called somatic) stem cells (NIH Stem Cell Basics 2018). These different divisions of stem cells are unique in their inherent potency, meaning these distinct types have contrasting levels of capacity for differentiation. The three predominant potency categories of stem cells are totipotent, pluripotent and multipotent (Schöler 2007). In essence,

totipotent cells can differentiate into any cell within the organism itself or the placenta, whereas pluripotent cells can differentiate into any of the cells found within the organism, and multipotent cells differentiate into any cell types within a particular lineage (Binder et al. 2009). There are interesting possibilities with embryonic and fetal stem cells, but there are tremendous ethical concerns about the manner in which these cells are obtained. In human embryonic stem cell research, a moral dilemma arises, because hESC research involves the destruction of an embryo, which has the potential to be a fully-formed human being. Another potential problem that comes to light with hESC research is the possibility of human embryos being created for the sole purpose of stem cell donation. When stem cells are harvested from fetal tissue, they are done so in the aftermath of an abortion, which also raises significant ethical questions (Lo and Parham 2009). In addition to these concerns, there is also a significant safety component in hESC research, because there are risks of bleeding, infection and/or complications of anesthesia as a result of the oocyte retrieval procedures (Giudice, Santa, and Pool 2007). However, the controversy surrounding embryonic stem cell research is not completely at the forefront of scientific debate. This is mainly due to the immense number of lives that have already been saved by utilizing adult stem cells, and the promising future in the realm of ASCs, which has ameliorated the ethical discourse over hESC transplantation methods.

The aforementioned hematopoietic stem cell treatments primarily utilize multipotent cells, because HSCs can differentiate into all of the distinct types of cells found within the blood, through the process of hematopoiesis (Birbrair and Frenette 2016). This category subsumes cells from both myeloid lineages (including macrophages, neutrophils, eosinophils, basophils, erythrocytes and platelets) and lymphoid lineages (including T cells, B cells and natural killer cells). Hematopoiesis is what allows this sect of regenerative medicine to work—bone marrow,

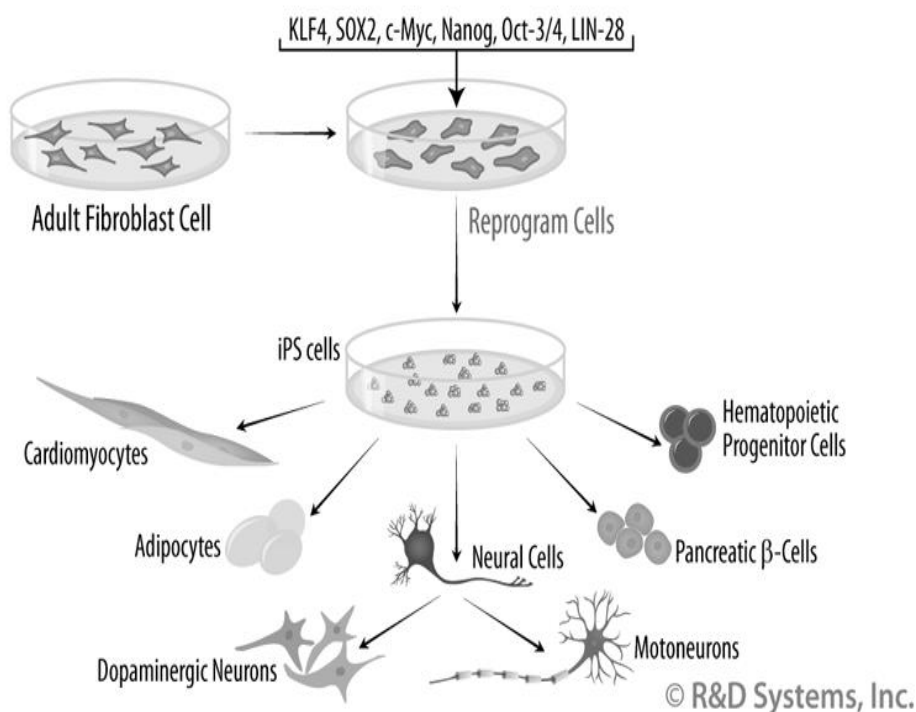


Figure 2 (R&D Systems)

peripheral blood and umbilical cord blood stem cell transplants replenish the depleted levels of specific blood cells in the recipient. For example, when a patient with leukemia is experiencing the harmful consequences

of low functional leukocyte numbers, the rationale for stem cell infusions is the restoration of these leukocytes as a direct result of hematopoietic stem cell differentiation. However, one key component of human stem cell research that has not been mentioned is the concept of inducing adult cells to become pluripotent cells, thereby broadening the possibilities offered by regenerative medicine. These induced pluripotent stem cells (iPSCs) can be generated by the reprogramming of adult cells (through the introduction of certain transcription factors), and are similar to embryonic stem cells in morphology, proliferation, surface antigens and a variety of other factors (Takahashi et al. 2007). These newly discovered iPSCs present a possible method of producing patient- and disease-specific stem cells, presumably increasing the efficacy of future stem cell treatments, while decreasing the prevalence of graft-versus-host disease. In addition to these possibilities, the further development of iPSCs would circumvent the moral and ethical controversy that is ubiquitous in the concept of embryonic stem cell therapy.

Although it was initially suspected that all hematopoietic stem cells were extremely similar in their differentiation capabilities, there is fairly recent evidence that suggests this is not the case. In the 21<sup>st</sup> century, researchers have confirmed that the behavior of HSCs found in adult bone marrow are largely predetermined, implying that HSCs are preprogrammed to function in a certain manner (differentiate into more specific lineages) and that self-renewal unequivocally does not cause stem cells to become more heterogeneous (Müller-Sieburg et al. 2002). In this study, it was discovered that certain HSCs would be skewed in their differentiation toward either lymphoid or myeloid progenitor cell lineages, indicating that different hematopoietic stem cells within the body function in different ways. In other words, HSCs that tend to differentiate into lymphoid progenitor cells should be more useful if one's innate immune system is compromised, whereas HSCs that tend to differentiate into myeloid progenitor cells should be more useful if one has a certain type of anemia or dysfunction in the clotting of blood.

### **3. Disorders managed with hematopoietic stem cells and mechanisms of treatment**

As one can imagine, multipotent hematopoietic stem cells have an extremely diverse range of possibilities regarding treatment due to the fact that they can differentiate into anything from red blood cells to T cells. HSCs can be incredibly useful in treating malignancies such as different types of leukemia and lymphoma (broad cancers which both involve dysfunction in leukocytes), while also presenting options for the treatment of aplastic anemia (decreased production of all blood cells in the body due to bone marrow damage), metabolic disorders, and even human immunodeficiency virus (Hütter et al. 2009) and types of solid tumor cancers such as neuroblastoma (a cancer formed in nerve tissue). It is quite remarkable that the range of conditions and diseases treated by HSCs expands to those that occur outside of the blood, and the full potential of hematopoietic stem cell transplantation has not even been realized yet.

Researchers have only recently begun to investigate the therapeutic possibilities of stem cells for disorders occurring outside the blood (Chagastelles and Nardi 2011). In the past couple decades, for example, over 600 studies have been conducted on stem cell therapy for individuals living with multiple sclerosis (MS), an autoimmune disease that causes nerve cells to be damaged (which can cause muscle weakness and impaired coordination) (Atkins and Freedman 2013). One mechanism behind the treatment of MS with stem cell therapy is that of the recipient's faulty T cells being essentially wiped out by the conditioning and the new stem cell graft. Another vital component in MS research in addition to stem cell therapy is that of induced remyelination, a concept which has been demonstrated in very recent studies dealing with mice (Saha et al. 2015). It is important to note that the cells used to cause remyelination, although isolated from umbilical cord blood, are not stem cells, but rather derived from monocytes. Overall, HSC transplantation is usually exclusively reserved to treat life-threatening conditions, because of the risks associated with the procedure. Although the stem cell treatment regimens differ across distinct hematological (and even some non-hematological) disorders, it is necessary to realize that these diseases can all be treated with the same type of stem cells (HSCs). When malignancies such as leukemia and lymphoma are mentioned, the notion that these diseases can be treated with more blood cells being introduced into the body may sound counterintuitive, but the replacement of these dysfunctional blood cells helps to equilibrate the immune system and the blood. However, it is imperative to delineate that in these treatment regimens, other therapies are administered in conjunction with stem cell transplants to address the over-proliferation of blood cells.

With pre-transplantation procedures, there are essentially two main approaches for the treatment: myeloablative and non-myeloablative conditioning. These conditioning regimens that

are given before the administration of a stem cell transplant involve chemotherapy and/or irradiation. In either autologous or allogeneic transplants, a major function of this conditioning regimen is to eradicate the disease in the body. With allogeneic transplants, an additional component of this pre-transplant process is that it serves the purpose of immunosuppression. As discussed earlier, a patient's immunological response to foreign cells (GVHD) is a significant obstacle that must be overcome in order for any allogeneic stem cell transplant to be successful, and the chemotherapy given beforehand takes steps to prevent this negative reaction to the transplant. The two categories of conditioning, myeloablative and non-myeloablative, differ in the intensity of the treatment. Myeloablative (MA) conditioning essentially involves the destruction of all the existing cells in the bone marrow, while non-myeloablative (NMA) conditioning uses lower dose chemotherapy/radiation that does not wipe out all of these cells. This lower-intensity approach can be beneficial in the sense that it has been associated with lower regimen-related toxicity levels and lower risk of infection post-procedure (Alyea et al. 2006). However, there is an associated higher risk of relapse in cancer that has been treated with reduced intensity (non-myeloablative) conditioning than that of cancer treated with MA conditioning (Wahid and Aqilah 2012). Reduced-intensity conditioning relies almost exclusively on the graft-versus-malignancy (GVM) effect to prevent relapse, because donor T cells help to eliminate the rest of the recipient's hematopoietic stem cells, whereas MA conditioning's high dose chemotherapy and/or radiation functions to help prevent cancer relapse. In essence, the two effects (regarding toxicity levels and risk of relapse) are similar in magnitude, meaning they have negligible impact overall. This results in similarities in overall survival rates between MA conditioning transplants and NMA conditioning transplants (Wahid et al. 2014). For these

specific reasons, non-myeloablative treatment regimens have gained popularity since their inception in the last decade of the 20<sup>th</sup> century.

As new discoveries are made about successful HSC transplantation and procedures improve, there is a greater emphasis placed on reserves of bone marrow, peripheral blood and umbilical cord blood. The presence of banks for these commodities represent a significant constituent of the realm of stem cell treatment. In 1992, the first public cord blood bank was established at New York Blood Center, just a few years after the first successful cord blood transplantation took place (Harvath 2012). Since this cord blood bank was established, dozens of new public cord blood banks have been created (Petersdorf 2010). If mismatched cord blood units are accounted for in estimates of UCB availability, there are more than 700,000 units in public banks worldwide—meaning that over 95% of patients will have access to stem cell treatment (Kurtzberg 2016). Factoring in private banks, there are more than 5 million units worldwide (Kurtzberg 2017). With resources such as these stem cell source banks, the future of hematopoietic stem cell therapy is extremely bright.

#### **4. The future of regenerative medicine**

Although the diseases previously mentioned have impacted countless numbers of people across the globe, HSC therapy has several other tremendous capabilities that are only now being discovered. Now that scientists know that HSCs can treat conditions that are not hematological in nature, they are beginning to test the limits of stem cell transplantation. One example of stem cell therapy possibilities on the horizon lies in the realm of dermatological treatment.

Mesenchymal stem cells, or stem cells capable of differentiating into bone, muscle, cartilage or fat cells, have shown promise in wound healing (partially due to their differentiation into fibroblasts) (Sasaki et al. 2008), and in immunological responses such as graft-versus-host

disease and rheumatoid arthritis (Farini et al. 2014). Now, stem cell transplantation as a means of treating neurological conditions such as stroke, Parkinson's disease or autism is on the horizon. In one recent study, the use of cord blood stem cell transplantation (CBSCT) with rehabilitation therapy was compared to rehabilitation therapy alone, and the results suggested a correlation (albeit a weak one) between the addition of CBSCT to rehab therapy and lower scores on tests for autism (Lv et al. 2013). A lot of this may be due to the ability of the stem cells to promote angiogenesis (the growth of new blood vessels), which helps to counteract the hypoxia in people living with autism (Wilcox et al. 2002). This would alleviate some of the neural dysfunction in these patients, and stem cells also would help with some of the immune dysfunction that is strongly correlated with autism. However, there is much more to learn about autism, and more comprehensive studies must be conducted to further develop stem cell transplantation as a method of treatment for autism spectrum disorders.

Because stem cells can have a significant impact on replacing faulty immune cells and reestablishing healthy immunological function, there has been a substantial amount of research done with many autoimmune disorders (including HIV, mentioned earlier), but one specific point of emphasis with stem cell therapy lies in the treatment of rheumatoid arthritis (RA). RA is a degenerative chronic disease that most commonly affects one's joints, leading to severe inflammation and swelling. The stem cell research on RA involves the use of adipose-derived mesenchymal stem cells (ADSCs) to aid in chondrogenesis (the formation of cartilage from mesenchyme tissue), which holds serious promise in alleviating the symptoms of RA, specifically the swelling and diminished amount of cartilage in the joints. In one particular study, ADSCs were taken from adipose tissue in human subjects with RA and the chondrogenic potential of the ADSCs was studied in vitro (Skalska et al. 2012). However, there is not a

sufficient amount of evidence to conclude that mesenchymal stem cells repair cartilage in areas that are severely inflamed. This is why more studies must be conducted regarding RA in order to discover a feasible and effective method of using stem cells to combat the progression and symptoms of the disease.

Parkinson's disease, a severe long-term degenerative disorder of the central nervous system, currently has no cure, but patients with the disease are usually fairly receptive to treatment. That said, the average patient life expectancy is between 7 and 14 years after diagnosis (Sveinbjornsdottir 2016). Furthermore, levodopa, the main route of treatment of Parkinson's disease, has serious side effects that can markedly reduce quality of life for patients. Stem cells provide a possible alternative with significant potential to be more efficacious than any present remedies. The idea behind the treatment of Parkinson's disease with stem cells is the possibility that these stem cells may replenish the nerve cells in the brain that produce dopamine, thereby alleviating some of the significant symptoms of the disease, such as involuntary motor movements. Studies conducted on rodents and monkeys have already demonstrated that stem cells transplanted can survive and even mitigate behavioral abnormalities (Obeso et al. 2010). Research such as this has brought many important discussions to light about the future of regenerative medicine (and more specifically, stem cell transplantation). For example, it has caused us to realize that diseases previously regarded as a life-shattering are firmly included in the range of possibilities of stem cell transplantation. Also, research on stem cell therapy emboldens researchers from across the world to try novel approaches to old diseases.

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