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# What are the limitations of stem cell therapy?

Stem cells are characterised by perpetual self-renewal through mitotic cell division and the ability to differentiate into a specialised adult cell type (Biehl, J. & Russell, B., 2009). They can be divided into two groups based on their source of origin: embryonic and adult. Embryonic stem cells (ESCs), derived during early development at the blastocyst stage, are pluripotent, meaning they can differentiate into any adult cell types. In contrast, the differentiation of adult stem cells (ASCs) is limited as they can be either multipotent or unipotent (Prochazkova, M., et al., 2015).

A stem cell therapy is defined as any treatment for a disease or a medical condition that fundamentally involves using stem cells or their derivatives to promote the repair of diseased tissues (Aly, R., 2020). It is considered as the frontiers of regenerative medicine because they are critical for the growth, development, maintenance and repair of organs, such as brains, bones, muscles and nerves. However, despite the fact that stem cell therapies show significant promises to treat, or potentially cure, the diseases that have been ineffective with conventional medicines, there are several limitations that need to be addressed before its clinical application.

Although pluripotency is one of the main advantages of using ESCs, there is a risk of uncontrolled differentiation which may induce the formation of tumours or teratomas. Studies carried out by Prokhorova et al. have revealed the formation of teratoma in 33-100% of hESC-transplanted immunodeficient mice, depending on the implantation site, cell maturation, purity and implantation techniques (Volarevic, V., et al., 2018). In addition, another study revealed the risk of abnormal immune response associated with ESCs, which could lead to rejection (Liu, X., et al., 2020). These clearly impose a safety concern and defeat the ‘non-maleficence’ principle of medical ethics. Further ethical concern arises from the fact that ESCs are derived from the pluripotent inner cell mass of the pre-implantation embryos, meaning their production requires the destruction of human embryos (Volarevic, V). Due to the ethical dilemma, all human ESC-based research is prohibited in Italy under the law and the development of hESC-based clinical therapies has been delayed considerably.

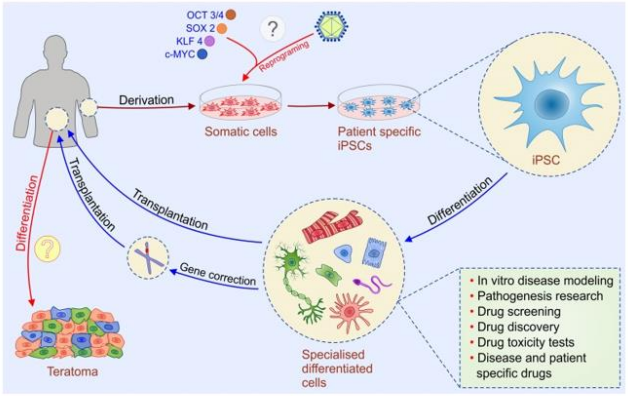


*Fig 1: Steps in producing iPSCs and their potential uses. (Volarevic, V., et al., 2018)*

Induced pluripotent stem cells (iPSCs) (Fig 1) provide a way to overcome this problem as they allow scientists to obtain pluripotent stem cells without the controversy around the use of embryos. In 2006, Yamanaka and Takahashi discovered that it is possible to re-program multipotent somatic cells to the pluripotent state by the exogenous expression of four transcription factors, Oct-3/4, Sox2, KLF4, and c-Myc, which are mainly expressed in ESCs

(Zakrzewski, W., et al., 2019). Generated iPSCs are indistinguishable from ESCs for their transcriptome profiling, epigenetic markings and functional competence, making it an attractive alternative to ESCs (Mahla, R., 2016). Nevertheless, the main safety issue regarding iPSC-based therapy is the risk of teratoma formation; this can occur after the implantation of undifferentiated iPSCs where they may undergo uncontrolled proliferation and undesired differentiation. Although a technique was discovered to remove oncogenes after a cell achieved pluripotency in 2008, it takes a longer amount of time and the process remains inefficient (Sun, Q., et al., 2014).

Another type of stem cell therapy that has been extensively researched is the use of stem cells for treating cardiovascular diseases; despite the numerous pharmacological drugs available cardiovascular diseases are the number one cause of death globally, taking an estimated 17.9 million lives each year (World Health Organisation., n.d.). Further research in the utilisation of stem cells for tissue repair and functional restoration has allowed scientists to be closer to finding a cure for cardiovascular diseases without an effective treatment available, such as myocardial infarction (Roger, V., et al., 2012). The final goal of cardiac stem cell therapy is to restore or regenerate myocardium. In 2001, the human embryonic stem cells (hESCs) were differentiated into cardiomyocytes for the first time by Kehat et al. (2014), and further studies discovered that over-expression of transcriptional factors such as GATA4, Nkx2-5, or MEF2C could induce differentiation of hESCs into cardiomyocytes.

However, the progress of cardiac stem cell therapy has been hindered by the risk of eliciting an immune response in the recipient due to the mismatch in major histocompatibility complex (MHC) class I antigens, which could lead to rejection after transplantation (Lin, H., Otsu, M., Nakauchi, H., 2013). Furthermore, the success of the treatment depends on the number of ESCs that have differentiated into cardiomyocytes to repair the cardiac tissue and only a minor population of cardiomyocytes grafted in mice produced cardiomyocytes. Unfortunately, this proportion was even less in the human model (Sun, Q., et al.).

Moreover, there are limitations associated with specific type of stem cell therapies. For example, multipotent Haematopoietic Stem Cell transplantation (HSC), also known as bone marrow transplant, is the most popular stem cell therapy. HSCs (Fig 2) are the stem cells that can differentiate into any blood cells by haematopoiesis, including erythrocytes, leukocytes, and platelets[12], and they help to address the inappropriate functioning of the haematopoietic system related to diseases such as leukaemia and anaemia (Sun, Q., et al.). Nevertheless, there are several critical disadvantages with HSC transplantation, including the reliance on donors and the risk of infection under immunosuppressive drugs. Also, there are a limited number of

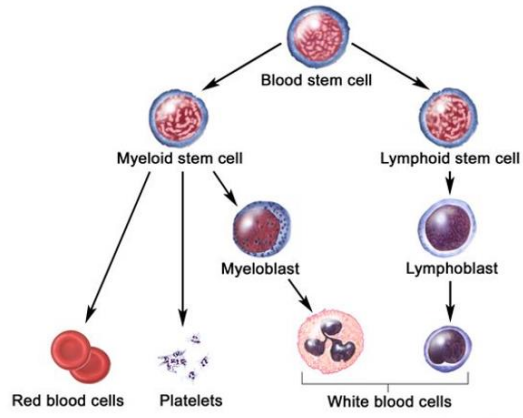


*Fig 2: Haematopoietic stem cell and its differentiation. (National Cancer Institute., n.d.)*

transplantable cells with no efficient ways of collecting them as immunological compatibility greatly limits the number of donor-recipient pairs (Leukaemia & Lymphoma Society., n.d.). Immunological compatibility depends on the degree of "donor-recipient matching", which is determined as the percentage of identity shared between the Human Leukocyte Antigen Loci (HLA) complex of two individuals (Li, M., et al., 2017). Graft versus host disease (GVHD) could develop in patients who received allogeneic HSC transplantation, when successfully grafted donor T lymphocytes recognise the host antigens as foreign, triggering an excess immune response inflammation (Leukaemia & Lymphoma Society). The use of a patient's own unspecialised somatic cells provides the greatest immunological compatibility and researches have been carried out to use iPSCs to generate hematopoietic cells, but the low efficiency and robustness have been the major barriers for use in wider industry (Li, M., et al.).

Other limitations of stem cell therapies are seen in Alzheimer's Disease treatment. Alzheimer's Disease (AD), a more prominent disease in countries with an ageing population, is a progressive neurodegenerative disease characterised by memory loss and cognitive impairment (National Institute on Aging., n.d.). The 2018 World Alzheimer's Disease Report shows that around 50 million people worldwide have dementia caused by AD (Alzheimer's Disease International., n.d.). Although stem cell therapy suggested a new hope for AD treatment with a replacement or regeneration strategy, recent researches looking at using mesenchyma stem cells (MSCs) and brain-derived neural stem cells (NSCs) for treatments showed little evidence to support its clinical application. There was limited evidence for functional or synaptic maturation of MSC-derived neurons in vivo for MSCs and neuro replacement by NSCs also remains limited due to the low rates of neuronal differentiation and a propensity for glial cell formation in vivo (Duncan, T., Valenzuela, M., 2017).

Stem cell therapies can be used for treatment of osteoarthritis, a degenerative condition of the joints caused by the lack of effective repair (Diekman, B., Guilak, F., 2013). Articular cartilage has very little ability for self-repair, resulting in progressive tissue loss and dysfunction following isolated cartilage injuries. Although traditional surgical treatment procedures exist, they are incapable of reversing the damage of articular cartilage, and total joint replacement with artificial components is often required. However, they have a limited lifespan which makes them unsuitable for patients who are physically active, and stem cell therapies may play a role in repairing or replacing the damaged tissues (Fig 3).

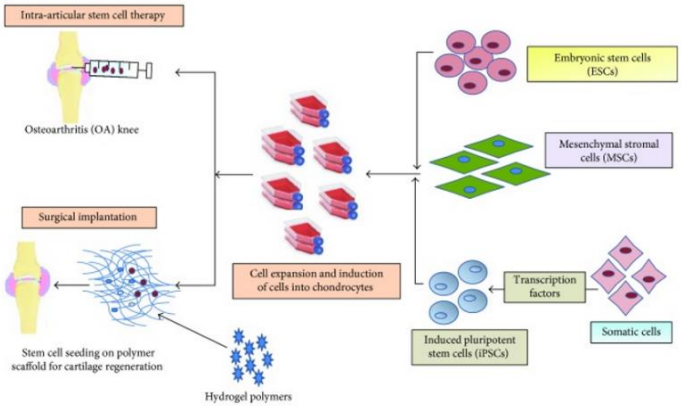


*Fig 3: Schematic of stem cell-based therapy in osteoarthritis (OA). (Dubey, Naveet., et al., 2018)*

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One of the major limitations of stem cell therapies for treating OA is that the chondrogenic potential of stem cells are affected by age. Dexheimer et al. (2011) investigated the effect of age on the characteristics of stem cells by characterising MSCs from 28 patients with an age range of 5-80 years. The study showed that single-cell cloning efficiency and proliferation rate were reduced with age, and the donors who displayed slow proliferation during expansion failed to synthesise type II collagen in pellet culture, highlighting the importance of patient selection since stem cell therapy may not work for all patients. Furthermore, obese patients may not be able to receive stem cell therapy to treat their OA as their stem cells may be compromised by the presence of low-grade systemic inflammation that is associated with obesity (Diekman, B., Guilak, F). This has been supported by other studies which showed that stem cells derived from the visceral fat of obese patients have reduced proliferation rate, greater cell senescence and a reduced differentiation to chondrogenesis, making them unsuitable for use (Roldan, M., et al., 2011).

Moreover, achieving phenotypic stability over long periods of time following implantation is very difficult. Chondrocyte-specific features can be lost by either transition to a fibrocartilage phenotype with increased type I collagen production or transition to the hypertrophic chondrocyte phenotype with increased type X collagen synthesis (Roldan, M., et al.). For example, the experiments by Vinardell et al. (2012) illustrated that stem cells from synovium and adipose tissue tended towards the fibrocartilage pathway whereas, the stem cells from bone marrow were more vulnerable to hypertrophic chondrocyte conversion. These factors limit the number of stem cells available for transplant, making it even more difficult for a wide use of stem cell therapies for OA. Another point to note is that the therapies for cartilage repair employ autologous cells, which means that the development of a universal donor cell is still lacking (Dubey, Naveet., et al., 2018). Currently, reprogrammable methods to induce stem cell differentiation into cartilage tissues are still inefficient.

With the current level of scientific technology, it is difficult to fully understand the mechanism of the function of stem cells in animal models, making it harder to translate the effects to clinical trials successfully (Sun, Q., et al.). Transplantation of new, fully functional organs created by stem cell therapies require millions of working and biologically accurate cells (Zakrzewski, W., et al., 2019); the overall efficiency of stem cell differentiation must be improved to ensure stem cell therapies are reliable, and specific protocols must be developed to advance the large-scale production, survival and integration of transplanted cells as well as to secure the safe application of the therapy all patients. And most importantly researchers must remain morally obligated to ensure that ethical considerations are not undermined by the excitement for progress in clinical translation.

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