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REVIEWS

A Comparison of Mesenchymal Stem Cell Lineages for Treatment of Diabetes Mellitus

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Diabetes Mellitus (DM) is a disease with increasing incidence rates and global awareness. Both type 1 (T1D) and type 2 (T2D) diabetes are classifications that require lifetime management. The dysfunction of β islet cells is a primary complication that requires treatment and may lead to several life-threatening complications including blindness, heart disease, and kidney failure. Mesenchymal stem cells (MSCs) are well known for their tissue regenerative action and have shown promising results for restoring β islet cell function as well as ameliorating sequelae of DM. There are several subtypes of MSCs, and each subtype is accompanied by a unique array of pros and cons. This review highlights 3 lineages of MSCs—bone marrow MSCs, adipose-derived (ADSCs), and umbilical cord (UBC-MSCs) - and summarizes the current feasibility and efficacy of each. On evaluation, current primary literature sources suggest that umbilical cord MSCs appear to have the most potential, with particular future implications for exosome research.

INTRODUCTION

Diabetes Mellitus (DM) is a disease with an increasing incidence rate that affects all age groups.[1] According to the Centers for Disease Control and Prevention's National Diabetes Statistics Report for 2020, 10.5% of the US population has been diagnosed with diabetes.[1] Apart from the direct effects to human health, the most common serious complications of diabetes include blindness, heart disease, lowerlimb amputation, and kidney failure.[2] Type 1 diabetes (T1D) is an autoimmune disease characterized by accrued damage to pancreatic islet β cells, while type 2 diabetes (T2D) is characterized primarily by insulin resistance. T1D accounts for 5.2% of all diabetes cases, with T2D making up the rest.[1] The need for adequate and cost-effective treatment is becoming increasingly important.

The treatment for a multifaceted disease such as diabetes must be considered in the context of prevention. Ideal treatments must restore proper functionality and sensitization of pancreatic β cells, while also creating a surmountable response to the underlying autoimmune dysfunction. Living a healthy lifestyle by increasing physical activity and considering weight management can help in mitigating the incidence and severity of complications. Pharmacological treatment of T2D can be added to lifestyle modifications and involves treating insulin resistance, typically with metformin. Metformin is a widely accepted, effective, well-tolerated, and cost-effective drug for the treatment of T2D.[2,3] Additional treatment regimens may include daily insulin injections, which are largely used for both T1D and T2D.

As early as the turn of the 21st century, research on diabetes has shifted toward incorporating stem cell technology to improve understanding of the disease's pathophysiology and therapy options.[3] Stem cell treatment can simultaneously tackle the underlying autoimmune problem, while providing avenues for insulin regulation, both in the context of T1D and T2D.[4,5] Furthermore, effective stem cell treatments would eliminate the need for daily management of diabetes.

Stem cells vary in their utility, functionality, and ease of obtaining; thus, the choice to use a specific site of stem cell origin must be considered. Mesenchymal stem cells (MSCs) are considered the most attractive cell source for regenerative medicine.[6] The feasibility of culturing MSCs is not limited to a specific stage of life. MSCs can become functional in different types of human tissues. Further, because MSCs are derived directly from human tissue, they have low antigenicity and thus have the potential to be an ideal treatment option for diabetes.[6] Use of adult MSCs as an instrument for regenerative medicine has been argued to be more prospective than embryonic stem cells, because they eliminate ethical controversies related to stem cell harvesting while maintaining multipotency.

However, the efficacy of MSCs has not been fully explored in the context of diabetes, and there is potential for research breakthroughs to mitigate diabetes sequelae and reduce health care expenditure. The purpose of this review is to provide an overview of 3 types of MSCs (bone marrow–derived MSCs [BM-MSCs], adipose-derived stem cells [ADSCs], and umbilical cord–derived MSCs [UBC-MSCs]) and evaluate their efficacy in the treatment of diabetes, as well as implications for future research.

BONE MARROW–DERIVED MSCs

The first tissue source from which MSCs were originally isolated from was bone marrow, and bone marrow remains the main source of MSCs compared with other tissues.[7] Research using bone marrow–derived stem cells has maintained interest because of the cells' plasticity and ability to differentiate into not only mesenchymal lineage cells, but also endoderm tissue and endothelium.[8] Despite the depth of research this lineage of stem cells has, it remains an ongoing area of research. Overall, the potential role of BM-MSCs in the treatment of diabetes focuses on 3 pillars: as a source of stem cells for β islet cells, a facilitator of β islet cell regeneration, and as an immune modulator.[9]

There is a plethora of research that addresses whether BM-MSCs can effectively act as a source for new islet β cells. Ianus et al[8] found in animal models that BM-MSCs that populated pancreatic islets exhibited markers and physiological behavior characteristic of β cells on their own: these cells expressed insulin and were positive for GLUT2 and relevant transcription factors. Importantly, the new cells also secreted insulin when stimulated with glucose and responded appropriately to glucagon-like conditions.[8] The ability of BM-MSCs to

properly function in the context of restoring insulin sensitivity and regulation in vivo has been expanded in subsequent literature. Animal models demonstrating pancreatic damage, once transplanted with BM-MSCs expressing *c-kit*, were found to initiate pancreatic regeneration and reduce hyperglycemia via adequate insulin production.[10] Importantly, most of the transplanted cells were restricted to pancreatic islet and ductal tissue and did not proliferate in negative capacities.

Evidence has also suggested a role for BM-MSCs in the regeneration of endogenous β cells. Research has shown that BM-MSCs from mice can differentiate in vitro into insulin-producing cells (IPCs) and that the differentiated cells express pancreas-specific marker genes.[6] Human BM-MSCs transfected with *PDX-1*, *Neuro D*, *and Ngn-3* (genes that are involved in inducing IPCs and programming of insulin-producing β islet cells) differentiate into cells that produce insulin but lack the ability to express insulin in response to glucose. However, transplantation of mouse BM-MSCs decreased levels of blood glucose in diabetic mice.[6] The capacity of these cells to initiate endogenous pancreatic regeneration shed light on a potential means by which these cells could contribute to restoration of organ function.

BM-MSCs can also provide positive outcomes in the autoimmune context of diabetes. Solis et al[6] demonstrated that in animal models, BM-MSCs can inhibit antigen-presenting cell activity and suppression of Th1 and Th17 cell development (cells involved in β-islet cell destruction and the pathogenesis of autoimmune diabetes), therefore preventing the onset of T1D. This research cited other studies that reported the immunomodulatory properties of BM-MSCs in islet transplantation from one species to another, which was demonstrated by their ability to reduce inflammation markers (such as tumor necrosis factor-α and interleukin 1β) while increasing markers of immune tolerance. This strategy could possibly help circumvent the issue of immune-related graft rejection in transplantation.

While the literature so far on BM-MSCs has revealed promising findings, some studies offer conflicting results. After an infusion of autologous bone marrow was reported to restore insulin secretion in T1D, data from Esmatjes et al[9] aimed to reproduce these results. Specifically, their aim was to evaluate the effect of an intrapancreatic infusion of autologous bone marrow blood on production of insulin in patients with T1D. However, follow-up tests revealed that C-peptide levels remained undetectable and that there was no change in the insulin dose or metabolic control, suggesting the therapy was not effective in regenerating β-islet cell function.[9] In fact, the study was stopped early when deemed unethical due to the negative results. The study suggested, based on its findings and the inconsistency of previous studies, that intrapancreatic autologous bone marrow infusion has no effect on β islet cell function or insulin secretion in patients with T1D.[9] It is important to consider this inconsistency in findings in a larger context: there are possibilities that suggest

shortcomings of BM-MSC diabetes treatment, but this may also illuminate publication bias within the field. In other words, much of the results surrounding BM-MSCs as treatment for diabetes remains inconclusive.

Similarly, Choi et al[11] encountered issues while investigating the ability of BM-MSCs to differentiate into pancreatic β islet cells for replacement therapy. Bone marrow transplantation successfully occurred with hematogenous cells populating the pancreas after bone marrow transplantation. Despite an increase of cell proliferation in islet cells and a few insulin-positive cells surrounding pancreatic ducts, there were no cells that expressed insulin (or glucagon for that matter). Under their specific experimental conditions, the data collected suggested that differentiation from bone marrow–derived cells to β islet cells does not always occur, resulting in cell populations that are dissimilar in morphology and function.[11]

BM-MSCs have also been used as a potential treatment of complications of diabetes, specifically dementia and diabetic retinopathy.[12] While the incidence of dementia is higher in patients with diabetes, no effective treatments have been developed.[12] Animal model studies have demonstrated that BM-MSCs can improve diabetes-induced cognitive impairment by repairing damaged neurons and astrocytes through exosome transfer.[12] An exosome is an extracellular vesicle that is produced from endosomes of a cell that contains certain proteins, amino acids, and nucleic acids from the origin cell. Specifically, this research found that treatment was successful in normalizing atrophy of neurons and astrocytes in addition to synaptic loss within the hippocampus. The study hypothesized that humoral factors, such as exosomes released from BM-MSCs, were the main therapeutic factors and might be a promising mechanism for improving diabetes-induced cognitive deficit.[12]

Diabetic retinopathy is another complication of diabetes and is a leading cause of blindness in a high percentage of adults with diabetes. It is believed that hyperglycemia and hypertension have causative impact on diabetic retinopathy; thus, ameliorating these causes can influence this serious complication.[13] BM-MSCs have shown promising results in the regeneration of damaged retina and have been demonstrated to have a neuroprotective effect in rats with ocular hypertension. It is believed that these stem cells should be studied for use in retinal regeneration in patients with diabetes due to their plastic nature and role in repairing vasculature.[13] Gaddam et al[13] investigated this using CD14+ cells (a type of bone marrow–derived angiogenic cell), which impact vascular repair and could possibly be used for cell therapy of diabetic retinopathy. BM-MSCs that were injected into the eye were observed to integrate into the inner retina and transform into glial cells, improving the ERG amplitude (a measure of retinal function) and preserving vision. Despite these promising results, the effectiveness and long-term safety of BM-MSC therapy are questionable after Gaddam et al[13] found that some of the human bone marrow cells migrated into nontarget tissue.

Despite research of BM-MSCs appearing the most well-established, concerns involving the pain and invasive nature of bone marrow aspiration have led to the exploration of different MSC sources.[7]

ADIPOSE-DERIVED STEM CELLS

Adipose-derived stem cells (ADSCs) are a branch of MSCs that has attracted attention in recent years for 2 primary reasons. First, they are autologous cells that can be collected repeatedly from 1 individual through minimally invasive methods, such as lipoaspiration, to subcutaneous tissue. Second, since their discovery at the beginning of the 21st century, ADSCs have proven to be self-renewable.[14] Studies have also shown that ADSCs have the potential to differentiate into IPCs, allowing them to be used in autologous transplantation in the treatment of diabetes.[15,16]

Adipose tissue is abundant in all people, regardless of weight. ADSCs can be sufficiently harvested from just 1 g of fat and, therefore, are easily obtainable in potential recipients of stem cell therapy. Adipose tissue is also inherently efficient in regulating glucose homeostasis via hormone production such as leptin and adiponectin.[15] In several recent studies, human ADSCs were induced to differentiate into IPCs using several genetic modifications, such as by overexpressing micro-RNA (*miR-375*) that target pancreas development, suppressing the Sonic hedgehog pathway, or transducing pancreatic developmental transcription factors such as Pdx1.[16–18] These cultured human ADSCs then formed functional β islet-like cellular aggregates (ICAs) and once engrafted into the pancreas of animal models, portrayed functional β islet phenotype. In a study by Kajiyama et al,[16] diabetic mice became normoglycemic, with glucose levels within normal range maintained for the remaining follow-up period of the study (up to 15 weeks) without becoming tumorigenic. ADSCs have direct beneficial outcomes in diabetic glucose regulation, and the breadth of research with these stem cells suggests their safety, sustainability, and promise for positive outcomes.

The regenerative characteristics of ADSCs affords these stem cells the ability to be used as treatment for conditions that occur secondary to diabetes that are due to insufficiency in angiogenesis. In these instances, the stem cells are administered via injection, as opposed to transplantation, and noticeably ameliorate the consequential conditions.

Diabetic peripheral neuropathy is a painful complication of chronic diabetes, involving up to 66% of patients with T1D and 59% of patients with T2D.[19] Currently, there seems to be an insufficiency in treating diabetic neuropathy with analgesics due to decreased efficacy and an abundance of adverse effects. Neuropathic pain can be traced to pro- and anti-inflammatory cytokines, damaging the structure and function of peripheral nerves.[19] This opens an exploration into using ADSCs for their inflammatory modulation rather than masking the symptoms with pharmacological management. ADSCs have been

shown to secrete immunomodulatory factors such as TGF-β, IL-10, and leukemia inhibitory factor (LIF).[19] Consequently, an injection treatment of ADSCs showed a reduction in neuroinflammation and peripheral immune activation, as well as restoration of skin innervation for up to 12 weeks after treatments, indicating the potential of ADSCs as a promising treatment option for diabetic neuropathy.[19]

Erectile dysfunction is another common complication that 20% to 70% of male patients with diabetes experience. Liu et al[20] showed that ADSCs improve vascular endothelial function in erectile dysfunction, which is particularly useful because patients with diabetes have a lower efficacy of first-line oral medications for erectile dysfunction. With injection of cultured ADSCs expressing vascular endothelial growth factor into the corpus cavernosum, Liu et al[20] found an increase in endothelial function and increased smooth muscle mass, which translated to an ability to achieve and maintain an erection starting on day 7 after treatment and continued through the end of the study, which concluded at 28 days.

Another complication of diabetes is diminished wound healing due to a reduction in angiogenic ability. Along with neuropathy, patients with diabetes may experience serious tissue loss due to deficient epithelization. Furthermore, serious injuries or foot ulcers could lead to whole limb amputations. Treatment with ADSCs in combination with Exendin-4, a glucagon-like peptide-1 receptor agonist, showed an enhancement in angiogenic effects in endothelial cells and keratinocytes, significantly improving diabetic wound healing within 14 days.[21]

Although there are promising data in favor of using ADSCs for diabetic treatment, certain questions remain unaddressed. Although Liu et al[20] found an increase in endothelial function and increased smooth muscle mass when ADSCs were injected into the corpus cavernosum, very few ADSCs could be successfully tracked 28 days following implantation, posing a difficulty in future long-term studies of ADSCs. It is also unclear whether the beneficial effects of Exendin-4 and ADSCs on diabetic wound healing are additive or synergistic.[21] In addition, while the self-renewing capability of ADSCs are beneficial in therapy, this can quickly become a repercussion by secreting factors that can accelerate the production and growth of tumors. Wei et al[22] showed that ADSCs promoted tumor-initiating capacity and tumor growth ability of breast and colon cancer cells through an IL-6 related pathway. Specifically, this IL-6 pathway can promote tumor development by promoting the initiation, proliferation, and metastasis of cancer cells, as well as the inhibition of apoptosis.[22] Further, research regarding the optimization of ADSCs to play the role of insulin-producing β islet cells continues to be conducted as studies search for the optimum area of adipocyte harvesting, as well as comparing and contrasting ADSCs from individuals with vs without diabetes.[17]

UMBILICAL CORD–DERIVED MESENCHYMAL STEM CELLS

There are many sources for MSCs, but one of the simplest sources is the umbilical cord. Umbilical cords have traditionally been discarded after birth; thus, obtaining umbilical cord MSCs (UBC-MSCs) is not only minimally invasive, but also has less ethical implications compared with the other MSCs, because they are harvested from typically discarded tissue after birth, rather than extracted directly from human tissue. MSCs of the umbilical cord can be subdivided into 2 subtypes. The first is human UCB-MSCs, which as the name suggests originate from the primitive blood cells of the umbilical cord. The second is Wharton's Jelly MSCs (WJ-MSCs), which come from the umbilical cord tissue that surrounds umbilical cord blood vessels. In this subsection, both subtypes of UBC-MSCs will be evaluated.

As a newer type of therapy for diabetes, stem cell treatments have adopted and improved on existing knowledge and discoveries. The apelin peptide has already been suggested in the treatment of T2D due to its role in glucose uptake and reversing insulin resistance.[23] However, its short half-life limits its usefulness as a drug therapy. This limited therapeutic utility was addressed by expressing apelin in stem cells, specifically in WJ-MSCs, recombined with the *APLN* gene and using a well-documented diabetes rat model.[24] Compared with control, the WJ-MSCs with apelin lead to several important and primary markers of diabetes: improved insulin sensitivity, pancreatic β cell proliferation, increased insulin levels, and reduced inflammatory markers.[24] Using the same animal model, WJ-MSCs have also been found to effectively be induced into IPCs and improve glucose regulation in vivo.[25] This cell population, when injected in vivo (into the portal vein), properly migrated to the pancreas where they sporadically differentiated into IPCs. These 2 studies demonstrated that WJ-MSCs have direct benefit to important biological measures of diabetes management through conventional stem cell induction but can also provide benefit for treatment using peptides that have otherwise low half-lives. It is imperative that for any stem cell therapy to be an effective treatment in human health, these cells must survive in vivo and perform their primary functions as intended. One important aim of this study is to evaluate stem cell results in human populations for treating diabetes. There is some evidence that long-term treatment with WJ-MSCs in T1D can reduce plasma glucose directly after a meal.[4] Important to note, however, is that fasting blood glucose between the treatment and control groups in this study did not differ. Fasting blood glucose is one that is regularly used to assess the efficacy of diabetes treatment.[23,25] Despite this apparent limitation, long-term effects were at least sustained 6 months after treatment when the final data points of the study were taken. Those who received WJ-MSCs showed reduced hemoglobin A_{1c} (HbA1c) levels (a widely accepted marker for diabetes). Additionally, the treatment group required reduced daily insulin requirements, which the

authors speculated was because of the enhanced pancreatic β cell function (which was corroborated by the higher serum levels of C-peptide, an endogenous marker for insulin production).[4]

Parallel results to the outcomes illustrated above by Hu et al[4] were found using WJ-MSCs for T2D treatment: there were decreased glucose levels after a meal, decreased HbA1c, decreased insulin requirements, and enhanced β cell function. In addition, there was a significant decrease in diabetic complications, including diabetic nephropathy, peripheral neuropathy, and retinopathy, following WJ-MSC therapy over 3 years.[5] The combination of these 2 studies showed promising results that WJ-MSCs can be an effective treatment for both T1D and T2D.[4,5] Additionally, both studies demonstrated that the WJ-MSCs were unlikely to spontaneously differentiate into cells that were harmful in the context of diabetes.[4,5]

UBC-MSC treatment for diabetes is not limited to WJ-MSCs. UCB-MSCs are a different type of MSC that originate from primitive blood vessels of the umbilical cord, rather than the tissue that surrounds umbilical cord blood vessels (WJ-MSCs) but can still be induced to become IPCs. Research on the utility of UBC-MSCs encompasses many similar pillars seen with WJ-MSCs. UCB-MSCs have been shown to have successful transplantation into animal models and that these cells produced and secreted insulin as IPCs as well.[26]

The utility of UBC-MSCs in the context of the autoimmune fundamentals of diabetes has also been explored. El-Sherbiny et al[27]and Yin et al[26] showed that infusion of these cells demonstrated 2 mechanisms of anti-inflammatory effects. The first effect was through downregulation of IL-6 cytokines, which are a mediator for the acute phase response. IL-6 has been previously shown to play a key role in the pathogenesis of both T1D and T2D, perhaps due to inflammation that inevitably destroys the endogenous pancreatic β cells. The second method suppressed inflammation by inducing macrophages from an inflammatory to anti-inflammatory state. These findings were demonstrated both in vitro (using mouse bone–derived macrophages)[26] and in vivo (pancreatic β cell function).[27]

Another interesting avenue relating to the utility of USB-MSCs is their application beyond the cells themselves and into their functionality as exosomes. The injection of UCB-MSC exosomes in vivo found similar findings in the reversal of insulin resistance and preventing inhibition of β islet cell destruction.[28] An area of future potential with UCB-MSC exosomes arises from additional findings from Sun et al.[28] Specifically, this study found additional inflammatory effects (decreased TNF-alpha) as well as increased receptor sensitivity (expression of GLUT4 on muscle and GLUT2 on hepatocytes).[28] If the use of exosomes can repeatedly demonstrate promising results, this could be an alternative to direct injection of MSCs. Of relevance,

the use of exosomes could provide a cheaper and more feasible approach to treat diabetes because manufacturers will likely be able to mass-produce these exosomes.

There is substantial evidence that using UCB-MSCs in the treatment of diabetes (T1D and T2D) is promising. These cells have the capability to differentiate into β islet cells, whether by purposeful induction or spontaneously.[25] Additionally, these cells have been shown to be receptive to gene recombination, which could have implications for targeted therapies within diabetes treatment.[24] Importantly, UCB-MSCs mediate the autoimmune conditions of diabetes with their ability to prevent destruction of β islet cells via macrophages. This is particularly relevant in T1D, in which there is evidence to indicate that the autoimmune dysfunction stems from macrophage destruction of pancreatic β-islet cells.[27]

UC-MSCs show a broad spectrum of utility, but there is still much more to learn about the specific functions, long-term benefits and consequences, and feasibility within the realm of diabetes. One limitation of its therapeutic benefit may be that native apelin is rapidly degraded by endogenous enzymes with a half life of less than 5 min in humans.[29] Additionally, insignificant improvements in blood glucose levels and glucose metabolism have been shown in rats transplanted with UBC-MSCs.[25] Overall, there is a lack of data and research in the use of UBC-MSCs as a treatment option. However, it seems plausible that after multitudes of human-based trials, UBC-MSCs have the potential to be a viable option for both T1D and T2D in the future.

CONCLUSIONS

MSCs have great potential in the treatment of diabetes for several reasons, including the accuracy of differentiation, low antigenicity, and ease of obtainment from various stages of life and cells of the body.[6] Three subtypes of MSCs have been highlighted in this article: BM-MSCs, ADSCs, and UBC-MSCs.

BM-MSCs remain a common source of MSCs because they exhibit plasticity and are able to fulfill several roles in diabetes treatment: a source of β islet cells, a facilitator of β islet cell regeneration, and an immune modulator.[9] Some studies have shown these stem cells can act effectively as a source for new β islet cells by restoring function, insulin sensitivity, and regulation.[6,10] However, acquisition of BM-MSCs involves invasive and painful bone marrow aspiration procedures. Furthermore, several studies posed contradictory findings that BM-MSCs lack the ability to differentiate into properly functioning β islet cells,[11] and are not able to express insulin in response to glucose.[9] These inconsistencies indicate BM-MSCs may not be the most reliable source of treatment for patients with diabetes.

ADSCs are multipotent stem cells that are safe to harvest with minimally invasive procedures. Being autologous, ADSCs are self-renewable with minimum immune rejection[15] and are appropriate for transplantation as well as treatment for sequelae of diabetes.[16] However, due to this same reason, ADSCs raise the issue of reabsorption into the body, potentially minimizing the effects of stem cell treatment or transplantation and requiring subsequent therapy.[14] Furthermore, there is room for more research in the aspect of the location of optimal adipose tissue harvesting and whether adipose tissue from people with and without diabetes are more efficacious.[17] Ultimately, a universal protocol is necessary if ADSCs are to be accepted as the standard of care for diabetes treatment.

Of the 3 types of MSCs discussed in this article, UBC-MSCs have shown the most promise for the treatment of diabetes. Evidence on UBC-MSCs provides data that can potentially supplement the shortcomings of BM-MSCs and ADSCs. Importantly, however, it should be mentioned that UBC-MSC research is relatively new, and lack of conflicting research may be due to a combination of publication bias, random chance, and lack of exploration.

Immunomodulation was a feature present for all 3 types of MSCs for diabetes treatment. However, these studies cannot be directly compared against one another, because they include different methods and immunogenic markers. For example, BM-derived stem cells lead to the inhibition of Th1 and Th17,[6] while research on ADSCs focused on TGF-β, IL-10, and LIF.[19] In comparison, the role of immunomodulation for UBC-MSCs focused on macrophage activity and IL-6.[27] Importantly, the exact mechanisms of these immunomodulatory factors, as well the interaction between them, are not fully understood.

Aside from the aforementioned limitations, harvesting for both ADSCs and BM-MSCs is invasive, while UC-MSCs are harvested from the umbilical cord, which is generally discarded anyway. Last, there are promising recent discoveries with UBC-MSC exosomes, which have been shown to have similar results as UBC-MSCs themselves. Furthermore, the lipid component of exosomes give them a slow clearance in circulation and show a lack of both toxicity and immune reactivity.[28] There is potential feasibility to graduate exosome UBC-MSCs as a diabetes treatment in large scale, indicating fewer legal and ethical concerns due to not transplanting any stem cells. While the future for diabetes treatment using stem cells is moving in the right direction, more work must be conducted to understand the long-term consequences, economic feasibility, and optimal culturing strategies.

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