Review Article:

The Prospect of Stem Cells for HIV and Cancer Treatment: A Review

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ABSTRACT

Background: The news regarding the successful treatment of uncured diseases is extremely exciting. Recently, the study of stem cells has been widely considered.

Objectives: The stem cells have the potential to be converted to all specialized functional cells.

Methods: Advances in cell engineering and genetic reprogramming of the stem cells have contributed to novel approaches that may bring hope to HIV and cancer patients.

Results: In this regard, HIV patients recently received a stem-cell transplant that replaced their white blood cells with HIV-resistant versions (obtained from stem cells). However, only a few clinically successful approaches are available on new stem cells.

Conclusion: This review includes two parts; in the first section, the reader can obtain a basic idea about stem cells, whereas the second part emphasizes new opportunities and directions in translating stem cells basic research to the clinical applications.

Introduction

Stem cells are specialized human cells that can maintain themselves by auto-renewal and transformation into specific mature cells through differentiation. Each cell inside the body possesses a set of particular functions. In contrast, stem cells are the cells with no specific role; however, they can be transformed into almost all kinds of cells needed for the biological system. Studying stem cells has been recently widely considered as they can help clarify the sophisticated mechanism of action of the cells. Therefore, the research on stem cells is regarded as remarkably promising in the treatment of diseases that are currently incurable [1, 2, 3].

The stem cells are rare in most tissues. Prospective identification and isolation of the stem cells are mandatory components in research on stem cells. Although all tissues can be generated from stem cells, it is still challenging to purify and identify the stem cells. However, using Somatic Stem Cells (SSCs), as a successful approach, has developed a few years ago. Moreover, the Hematopoietic Stem Cells (HSCs) have considered as potential candidates for the generation and regeneration of the blood-forming system using in bone-marrow

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transplantation. A recent study showed that the differentiation potential of HSCs is more than previously expected to allow reconstruction of non-hematopoietic tissues. Further studies on differentiation will open a new scope of the therapeutic use of stem cells in immune (hemato-lymphoid) systems and cancer therapy [2, 3].

In this review, we described the current knowledge about stem cells, including their differentiation, classification, and therapeutic applications. We also considered the potential of stem cells for genetic reprogramming-based approaches to treat HIV and cancer.

Origin of Stem Cells

The stem cells are found in four main primary sources [4]: (i) adult body tissues (adult stem cells), (ii) embryos (embryonic stem cells), (iii) connective tissue or stroma (mesenchymal stem cells), and (iv) skin cells or tissue-specific cells (induced pluripotent stem [iPS] cells) [5, 6]. Moreover, scientists are engaged in finding methods to develop stem cells from various cells using genetic "reprogramming" techniques (Figure 1) [7].

Adult stem cells

Typically, stem cells are present in the body throughout life and are used by the body, if needed. Adult stem cells are also known as tissue-specific or somatic stem cells and appear after the development of the embryo. However, unlike embryonic stem cells, they can be abundant in juveniles as well as in adults. Although these cells are retained in a non-specific state, they are more specialized and unique than embryonic stem cells. These types of cells remain unchanged and maintain their original state until the body requires them for a particular purpose, such as the specific skin or muscle cells re-growth.

Throughout one's lifetime, the living body undergoes constant repair and regeneration processes for the maintenance of tissues as a natural healing method. In some organs, like the gut and the bone marrow, stem cells are often found to be differentiated to provide new body tissues for maintenance, repair, and cell renewal purposes. Stem cells in the biological system are mostly found in bone marrow, brain, blood and blood vessels, skeletal muscles, skin, and the liver [8].

Moreover, adult stem cells can differentiate and are subjected to self-renewal processes indefinitely or non-specifically. It means that they might be able to generate many cells or even a complete redevelopment of the original organ. Division and regeneration of stem cells can heal a skin wound or even an injured organ like the liver.

Embryonic stem cells

The embryonic stem cells are developing in the earliest stage of pregnancy when the egg is fertilized by a sperm cell, and 3-5 days later, the embryo is ball-shaped or seems like a blastodermic vesicle. The resulting blastodermic vesicle contains stem cells and is later implanted within the womb. In general, the embryonic stem cells generated from a blastodermic vesicle are four to five days old. The stem cells generated from embryos are typically obtained from in vitro fertilization (IVF) of the embryo.

In IVF clinics, numerous egg cells are artificially fertilized in a test tube to ensure the survival of at least one of them as a healthy embryo. Afterward, the surviving embryo is implanted in the uterus to make the case pregnant. When a sperm cell fertilizes an egg, these cells are combined to create a cell known as a zygote. This non-cellular fertilized ovum then begins to divide, forming 2, 4, 8, 16, and more cells. The final mass resulted from the consecutive division of cells is termed as an embryo. As the embryonic mass increases its cell number to around 150-200, the aggregation of those cells is collectively known as a blastodermic vesicle.

The blastodermic vesicle typically consists of two parts: an outer cell mass that becomes a part of the placenta and an inner cell mass, which will further form a physical structure. In the presence of the proper stimulants, the embryonic stem cells will convert into blood cells, skin cells, and other cells needed to one's body. Furthermore, in early pregnancy, the blastodermic vesicle stage

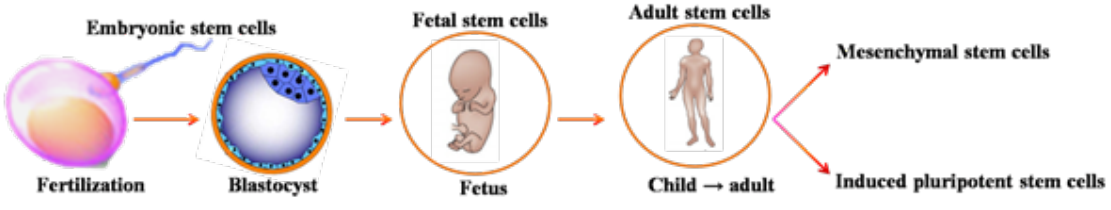

Figure 1. Normal generation of different stem cells

Table 1. Classification of stem cells

No.	Stem Cells	Properties
1	Totipotent	These stem cells can differentiate into all possible cell types. Cells produced by the first few divisions of the fertilized egg are called totipotent. At the same time, the embryonic stem cells are deliberated as pluripotent instead of totipotent because they cannot become a part of the extra-embryonic membranes or the placenta [9].
2	Pluripotent	These cells are derived from an early-stage pre-implantation embryo. The pluripotent cells can differentiate into almost all cells [10].
3	Multipotent	These cells can differentiate into all cells in a closely related family of cells. For example, mature hematopoietic stem cells can become red blood cells, white blood cells, or platelets [11].
4	Oligopotent	These can convert into a few different cell types. Mature lymphoid or myeloid stem cells can differentiate in this way [12].
5	Unipotent	They can only generate the cells of their own type. However, they are stem cells because they can renew themselves. An example is adult muscle stem cells [13].

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lasts five days before the embryo is implanted within the uterus or womb. At this stage, stem cells begin to differentiate. Embryonic stem cells, compared with adult stem cells, can differentiate into several cell types [8].

Mesenchymal Stem Cells (MSCs)

The mesenchymal stem cells (MSCs) originate from the connective tissue or stroma that surrounds the body's organs and tissues. Scientists typically use MSCs to make new body tissues, like bone, cartilage, and fat cells. As a result, the MSCs have considered as a promising option to solve a vast range of health issues [5].

Induced Pluripotent Stem Cells (iPS)

The iPS cells can be generated in a research lab using skin cells and different tissue-specific cells. These cells behave like embryonic stem cells. Therefore, iPS cells can be potential candidates for developing several therapeutic methods [5].

Classification of stem cells

The stem cells are classified based on their potential to differentiate into different types of cells, including, totipotent, pluripotent, multipotent, oligopotent, and unipotent stem cells (Table 1) [9-12].

Typical uses of stem cells

Stem cells are vital for living organisms for many reasons and can play several important roles. For example, several stem cells can tackle the role of all cell types, and also they can regenerate damaged tissue under the right stimulants. This potential may save lives or repair the wounds and tissue injury in individuals. Several types of stem cells can be used for different purposes, such as tissue regeneration, cardiovascular disease treatment, brain disease treatment, cell deficiency therapy, blood disorders treatments, and donating or harvesting stem cells.

Tissue Regeneration

Stem cells are mostly used for tissue regeneration. For example, doctors have already used stem cells from a lower place of the skin's surface to create new skin tissue. They can repair a severe burn or another injury by graft this tissue onto the broken skin, and new skin can grow back.

People who need a kidney transplant should wait on the transplant list to get a kidney. Also, the organ donor shortage is a concern. On the other hand, the instructing stem cells can be differentiated under proper conditions to a healthy kidney. Accordingly, researchers studying stem cells are trying to use them to grow a particular tissue or organ (Figure 2) [14].

Cardiovascular illness treatment

In 2013, a team of scientists from the Massachusetts General Hospital reported that they could construct blood vessels in laboratory mice using human stem cells [15]. After two weeks of inserting the stem cells, the matrix of blood-perfused vessels had formed perfectly. The new blood vessels were almost identical to the natural ones. They hoped that this kind of technique might eventually facilitate to treat individuals with cardiovascular and vascular diseases [15].

Brain disease treatment

It is expected that stem cells may become a renewable source of replacement cells and tissues to treat brain conditions, like Parkinson and Alzheimer. In Parkinson dis-

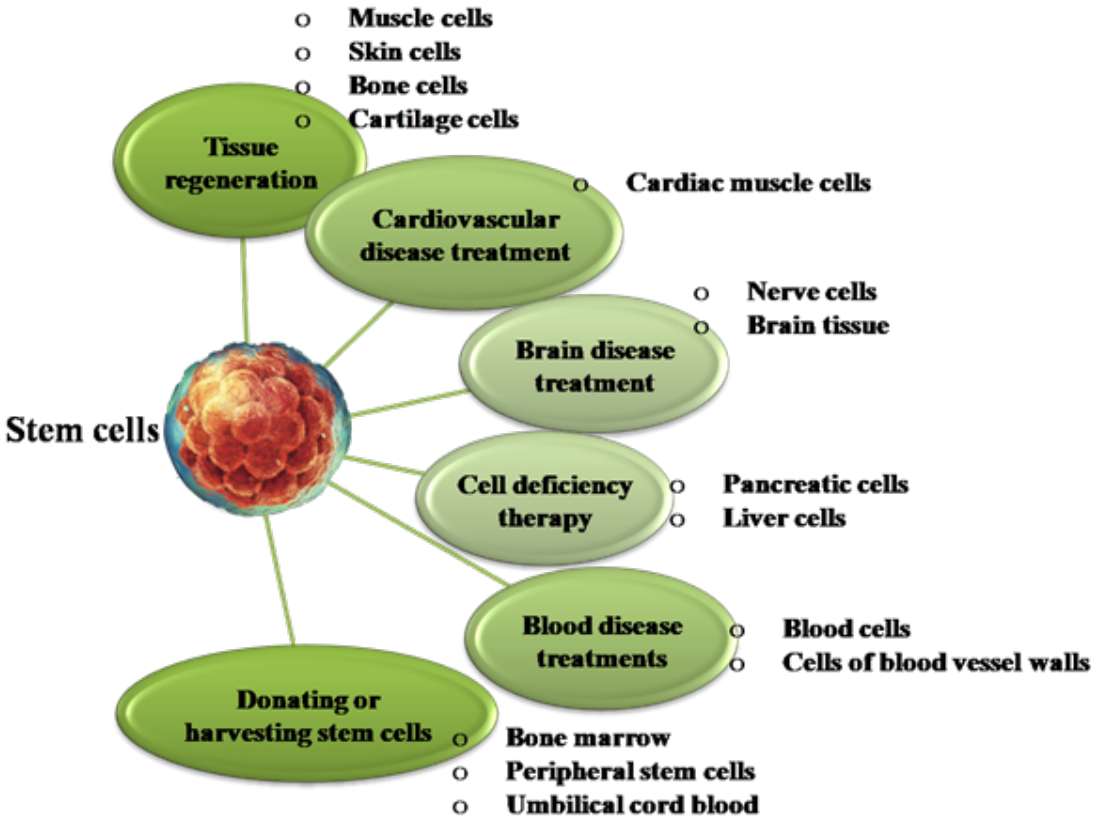

Figure 2. Potential applications of different stem cells

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ease, injury of brain cells ends up in uncontrolled muscle movements. Researchers may use stem cells to fill the damaged brain tissue. This might recover the specialized brain cells that stopped the uncontrolled muscle movements. The researchers have tried to differentiate embryonic stem cells into these cells. Therefore, the treatment of such disorders seems very promising [16].

Cell deficiency therapy

Researchers have envisioned developing healthy cardiac cells in the laboratory so that these modified and fabricated cells can be transplanted into patients with severe cardiovascular disease. These new cells may repair heart injury by replacing the heart muscle with healthy tissue. Similarly, the individuals with type I diabetes may receive pancreatic cells to switch the insulin-producing cells that have lost or been destroyed. The only current therapy may be a pancreas transplant, and there are very few pancreases available for pancreas transplant [17].

Blood disease treatments

Adult Hematopoietic Stem Cells (HPCs) are currently used to treat blood disorders, like leukemia, sickle cell anemia, and different immunological disorders. Normally, the HPCs found in blood and bone marrow may produce all blood cell types. Also, the mature blood cells, like red blood cells, can carry oxygen and White Blood Cells (WBCs) are responsible for fighting disease [18].

Liver diseases

The liver transplantation is considered the first treatment option of many end-stage liver diseases. However, the lack of donor and the complications of immune responses (rejection) are often the challenges of liver transplantation. At the same time, it is reported that MSCs can differentiate into functional hepatic cells in vitro under fixed experimental conditions. The bone marrow-derived MSCs transplanted intravenously into the mice with liver failure showed the regeneration of hepatic cells and improvement of the experimental liver failure [19].

In stroke and neurological injury

Brain injuries, like stroke, are the leading causes of disability worldwide. The neurological injuries are difficult to recovery by the currently available drugs in the market. The MSC treatment and RNA cargo in exosomes

Table 2. Representative examples of different stem cells in clinical trials in phase IV

Conditions	Treatments	Year
Asherman's syndrome	Bone marrow CD133+stem cell transplantation	2015
Wounds	Amniotic stem cells	2015
Congestive heart failure	Stem cells infusion	2016
Waldenström macroglobulinemia	Autologous stem cell transplantation	2016
Lymphoma	Hematopoietic stem cell transplantation	2016
Androgenetic alopecia	Adipose-derived stem cells suspension	2018
Myopathy	Mesenchymal stem cell transplantation	2018
Multiple myeloma	Autologous peripheral blood stem cell transplant	2019

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and microvesicles exosomes and extracellular vesicles have demonstrated positive effects in the healing of neurological injuries. This approach replaces the dead neurons by functionalized grafted MSCs using exosomes. Such cell-based therapies are a potential candidate for brain repair and promote recovery after stroke, traumatic brain injury, and other neurological diseases [20].

Donating or harvesting stem cells

People can donate stem cells to assist a loved one, or they can use them in the future if needed. Bone marrow, peripheral stem cells, and umbilical cord blood are the main sources of HSCs.

Bone marrow

These types of cells are taken from the hip or pelvic bone. Afterward, the physicians separate the bone marrow to collect the stem cells, followed by storing or donating them when needed [5].

Peripheral stem cells

In this method, an individual can receive many precursor injections that cause the bone marrow to release stem cells into the blood. Next, the blood is drained out from the body, a machine separates the stem cells, and the blood is transferred to the body [21].

Umbilical cord blood

Some individuals donate the cord blood, and others store it [22]. In this application, the stem cells are harvested from the umbilical cord without causing damage.

Prospect of stem cells in the treatment of HIV and other incurable diseases

Stem cell transplantation can be used to treat different disorders that currently incurable. They are also useful to develop a new therapeutic strategy against infection and also can be applied to better treatment of autoimmune diseases, like HIV or type I diabetes [23, 24]. Treatment of such diseases has not been the first reason to use stem cells as their application has been considered for several years [25] (Table 2) [adapted from the https://clinicaltrials.gov].

HIV treatment

The Human Immunodeficiency Viruses (HIV) are two species of lentivirus (a subgroup of retrovirus) that infect humans who, over time, develop Acquired Immunodeficiency Syndrome (AIDS) (Figure 3) [25]. HIV attacks cells in the immune system. The virus destroys WBCs in the immune system called a T-helper cell (T-cell) and makes copies inside of these cells. The T-cells also called CD4 cells. As HIV pulverizes more CD4 cells and makes more duplicates of itself, it gradually weakens a person's immune system. More importantly, if the person is unable to take anti-retroviral treatment, he will increasingly fail to control the infection and diseases.

Genetic engineering of stem cells is the basis for HIV treatment, where patient-derived stem cells have genetically engineered to combat HIV infection. Several clinical trials and in vitro and in vivo studies have been conducted in this regard (Table 3) that are promising for AIDS patients [26-37].

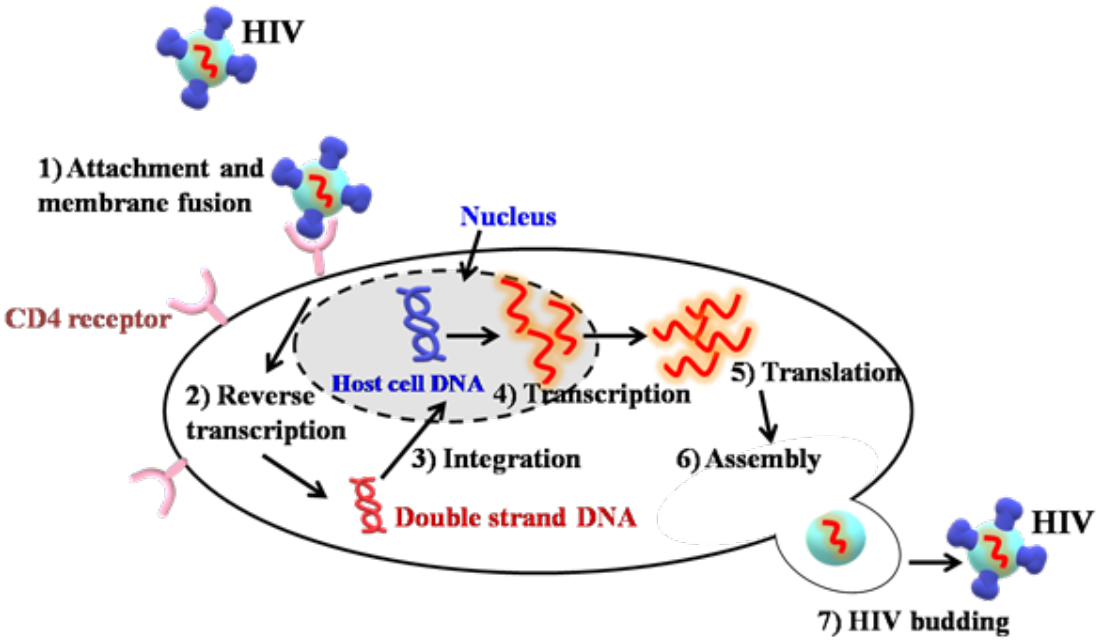

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Figure 3. Infection mode of the Human Immunodeficiency Virus (HIV) through 1. Attachment and membrane fusion; 2. Reverse transcription; 3. Integration; 4. Transcription; 5. Translation; 6. Assembly, and 7. Budding process

Stem cell therapy leaves a man 'free' of HIV

Treatment of patients with an incurable disease has always been considered in all branches of medical science. Recently, a person with HIV appeared to be free of the virus after receiving a stem-cell transplant that replaced their WBCs with HIV-resistant versions (Figure 4) [38]. The patient is barely the second person ever reported free of the virus using this technique. The patient, whose identity has not been disclosed yet, was able to stop taking antiretroviral medications with no signs of the virus even after 18 months. The stem-cell transplant technique was initially used a decade ago for Timothy Ray Brown, called the 'Berlin patient,' who is still free of a similar virus [39]. Like Brown, the latest patient (second person) also had a form of blood cancer that was not responding to chemotherapy. They needed a bone-marrow transplant, in which their blood cells would be destroyed and

Table 3. The stem cell therapies of anti-HIV research

Therapeutic Method	Notable Results	Reference
In vitro	*CCR5* ribozyme reduction and HIV inhibition in cell line	26
Clinical trial phase I/II	Transgene expression in circulating cells (anti-HIV shRNAs)	27
In vitro	HIV inhibition in cell lines	28
Humanized SCID mouse	HIV inhibition in cells from humanized mice (*CCR5* ribozyme and anti-HIV shRNAs)	29
In vitro	*CCR5* knockdown and HIV inhibition in human primary T cells	30
In vitro	*CCR5* and HIV-1 inhibition in macrophages derived from transduced hematopoietic stem and progenitor cell (HSPC)	31
Humanized BLT mouse	*CCR5* knockdown in lymphoid organs in vivo, HIV inhibition ex vivo	32
Humanized NSG mouse	HIV resistance	33
Humanized BLT mouse	Viral load reduction and HIV inhibition in lymphoid tissue	34
Humanized NSG mouse	*CCR5* knockout and HIV inhibition	35
Boston patients	Relapse	36
Berlin patient	Cured HIV	37

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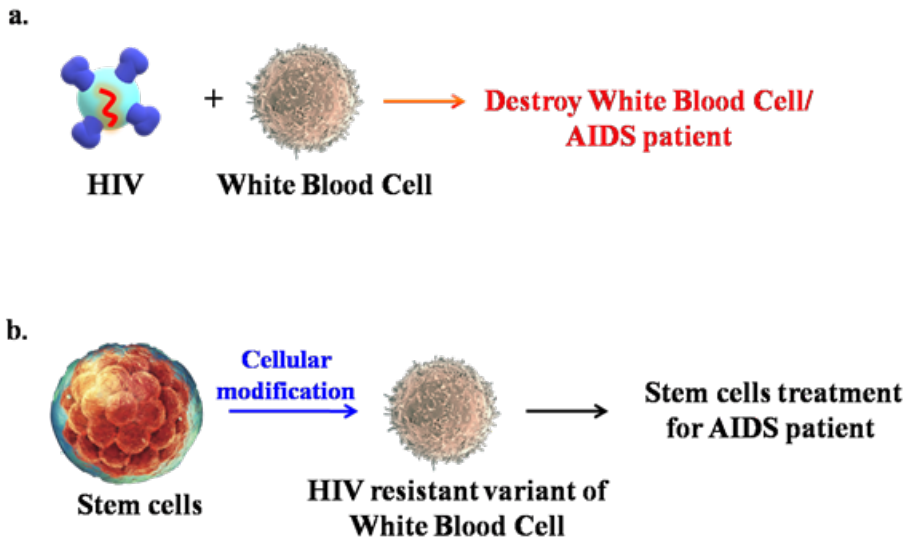

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Figure 4. The typical method to destroy a White Blood Cell (WBC) by HIV and the schematic diagram of stem cell modification to generate HIV-resistant WBC

replenished with stem cells transplanted from a healthy donor [38, 39].

However, instead of simply selecting an appropriate donor, the team led by Ravindra Gupta et al. picked a donor who had two copies of a mutation in the *CCR5* gene that gives people resistance to HIV infection [40]. Moreover, this gene codes for a receptor attached to the surface of the WBCs associated with the body's immune response. Usually, HIV binds to these receptors and attacks the cells. However, a deletion in the *CCR5* gene stops the receptors from functioning correctly. About 145 people across Europe may have two copies of this mutation.

Gupta's team described that the transplant successfully replaced the patient's WBCs with the HIV-resistant variant [41]. Cells circulating within the patient's blood stopped expressing the *CCR5* receptor that was unable to re-infect these cells with the patient's version of HIV. The team found that the virus completely disappeared from the patient's blood after the transplant. Moreover, the patient stopped taking antiretroviral drugs after 16 months. In the latest follow-up, 18 months after stopping the medication, there was still no sign of the virus.

The "London patient" was the second person cured of HIV thanks to the stem cell transplant. The researchers reported that the viral load in plasma "remained undetectable" in the London patient in all blood examina-

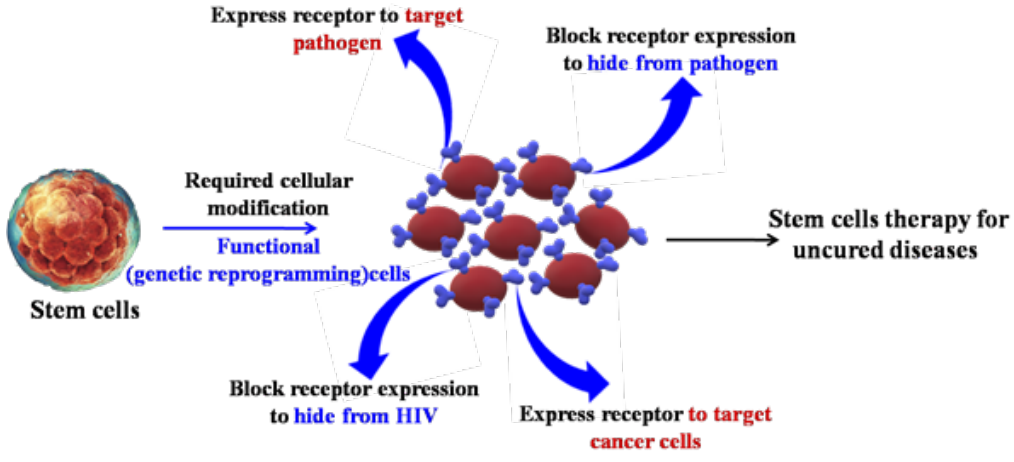

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Figure 5. An approach to use stem cells in the treatment of different incurable diseases

Table 4. The stem cell therapies of various cancer research studies

Types of Cancer	Stem Cells in Cancer Therapy	Reference
Breast cancer	MSCs (engineered to overexpress Interferon (IFN)-beta)	42
Hepatocellular carcinoma	MSCs (infected with measles virus)	43
Colon adenocarcinoma	NSCs (neural stem cells) (adenovirus transduction with a rabbit corneal endothelium (CE))	44
Metastatic lung cancer and primary lung cancer	NSCs (engineered to express CE)	45
Solid tumor	NSCs (loaded with gold nanorods)	46
Lymphomas	HSCs (allogeneic transplantation) and induced pluripotent stem cells (iPSCs) derived from T cells	47, 48
Melanoma	HSCs (genetically engineered HSCs to generate antigen-specific CD8 T cells)	49
Glioma	HSCs (modifying the proteome profile of HSCs)	50
	MSCs (retroviral transduction with CD)	51
	MSCs (loaded with Oncolytic herpes simplex virus (oHSV)	52

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tions after the transplant and did not re-emerge when the patient stopped taking antiretroviral drugs for almost two years. This finding is a prominent step in the research on HIV, which may facilitate finding potential future treatment decisions (Figure 5). However, it should be noted that this is not a common treatment for HIV. Antiretroviral therapy is the primary modality for the treatment of individuals with HIV.

Moreover, it is inspiring for many scientists and physicians to study stem cells in the treatment of different incurable diseases. The re-programming characteristics of stem cells, along with their availability, have opened a window of opportunity in research in medical sciences. It is believed that the clinical applications of stem cells will be increased soon.

Stem cells have great potential for the treatment of cancer (Table 4). The expression of different cytotoxic agents from functionalized stem cells allowed shrinkage of tumors and increased the survival rate in various preclinical studies [42-52].

Conclusions

Stem cells are a significantly interdisciplinary research area. Significant contributions are needed by biologists, genetic engineers, material scientists, and others who have developed innovative concepts and brought them to clinical application. Moreover, the advances in many other study areas can assist in the new implementation of stem cells. However, numerous challenges remain in stem cell development. However, this field should be a promising and rapidly growing research area.

Ethical Considerations

Compliance with ethical guidelines

There was no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization: Khandaker Nujhat Tasnim; Methodology: Shahadat Hossain; Investigation: All author; Writing-original draft: Sumiya Haque Adrita; Writing -review & editing, and supervision: Shazid Sharker; Funding acquisition, resources: Shahrukh Zaman Akash.

Conflict of interest

The author declared no conflict of interest.

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