FEATURE ARTICLE

An Instant Update on Stem Cell Therapy

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Abstract

Stem cell therapy, a cutting-edge technology, aims to replace damaged cells with healthy ones. Stem cells possess the remarkable ability to multiply and differentiate into various cell types, making them ideal candidates for regenerative medicine. This therapy holds promise for treating a wide range of conditions and injuries. In this review, I will delve into the historical context of stem cell research and therapy, provide updates on clinical trials for different conditions, address the challenges faced in stem cell therapy, and explore strategies to overcome these obstacles. Additionally, I will discuss the ethical and legal implications associated with stem cell therapy. A lesson plan for teaching the challenges and ethical issues of stem cell therapy is found at the end of the review.

Key Words: *stem cell; stem cell therapy; regenerative medicine; pluripotent; bioethics.*

○ Introduction

Stem cell therapy is a modern technology that aims to replace damaged cells with healthy new ones. Stem cells are unique cells that have the ability to proliferate and differentiate into numerous cell types, making them ideal candidates for regenerative medicine. Stem cell therapy has the potential to treat various conditions and injuries such as age-related macular degeneration, cardiovascular conditions, diabetes, liver conditions, osteoarthritis, Parkinson's disease, burn wounds, and gum deterioration (Hoang et al., 2022).

Stem cell therapy is still in its early stages as there are multiple challenges that need to be overcome by further research before it can be widely used. These include tumorigenesis, immunogenicity, and optimizing cell delivery methods. Despite these challenges, stem cell research is a rapidly evolving field that has the potential to revolutionize the way we approach healthcare and medicine. Researchers are actively developing new treatments for an increasingly long list of conditions (Hoang et al., 2022). In this review, I will provide a brief history of stem cell research and therapy, an update on the status of clinical trials for various conditions, challenges of stem cell therapy, and strategies to overcome them. I will also discuss the ethical and legal issues of stem cell therapy. The review also contains a lesson plan for teaching the challenges and ethical issues of stem cell therapy.

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○ A Brief History of Stem Cell Research and Therapy

The term "stem cell" was first used by Theodor Heinrich Boveri and Valentin Häcker in 1888 to describe the ability of a fertilized egg to give rise to all cells of an organism. In 1902, Franz Ernst Christian Neumann and Alexander A. Maximow isolated hematopoietic stem cells from bone marrow and demonstrated that they could differentiate to form all types of blood cells (Gurusamy et al., 2018). In 1956, Edward Donnall Thomas performed the first successful allogeneic hematopoietic stem cell transplant when bone marrow cells were transplanted from the identical twin of a patient suffering from leukemia. Dr. Thomas was awarded half of the 1990 Nobel Prize in Physiology or Medicine for this development (Nobel Prize Organization, 2023).

From the 1960s to 1970s, Friedenstein and coworkers isolated mesenchymal stem cells as part of loose connective tissue from the umbilical cord, bone marrow, and adipose tissue (Stefańska et al., 2020). Both hematopoietic stem cells and mesenchymal stem cells are classified as adult stem cells, which are multipotent and hence can differentiate to form only a limited range of specialized cells that build the tissue in which they reside. The specialized cells replace cells that are lost due to tissue turnover or injury, thus maintaining tissue homeostasis (Gurusamy et al., 2018).

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In 1981, two biologists, Sir Martin John Evans and Matthew Kaufman, cultivated mouse embryonic stem cells (ESCs) for the first time in the laboratory. In 1998, James Thomson isolated human ESCs from the inner cell mass of embryos and grew them in the laboratory. The isolation, cultivation, characterization, and differentiation of human ESCs was a major milestone in the history of stem cell research, and it spawned a prolonged, high-stakes bioethical debate in the USA (Eguizabal et al., 2019).

Another major breakthrough in the field of stem cell research came when Shinya Yamanaka generated mouse induced pluripotent stem cells (iPSCs) from mouse fibroblasts by introducing genes encoding four transcription factors namely *Oct3/4*, *Sox2*, *Klf4*, and *c-Myc*. One year later in 2007, his research group applied the same technique to reprogram human fibroblasts into human iPSCs. The resulting iPSCs display features and advantages similar to ESCs but avoid the ethical issues resulting from the destruction of embryos. Dr. Yamanaka was awarded half of the 2012 Nobel Prize in Physiology or Medicine for the discovery that specialized cells could be reprogrammed to become pluripotent (Nobel Prize Organization, 2023).

○ Conditions Targeted by Stem Cell Therapy

Approximately 2,000 clinical trials involving stem cells have been recorded in the National Institutes of Health clinical trial registry (National Institutes of Health, 2023). Stem cell therapy has been explored for numerous conditions; however, there are very few conditions for which it has been approved and shown to be effective. The most common stem cell treatment is bone marrow transplantation, which is used to treat patients with cancers or disorders of the blood and immune system. These procedures are widely accepted as safe and effective by medical professionals. All other applications of stem cells have yet to be supported by clinical trials and are considered experimental. Early results from these trials indicate that stem cell therapy holds great promise for the future of regenerative medicine. Below is an update on the status of clinical trials for the major conditions.

Clinical Trials with Promising Outcomes

Age-related macular degeneration (AMD) is an eye disorder that can blur a person's central vision. AMD affects the macula, which is at the center of the retina. The retinal pigment epithelium (RPE), a layer of cells in the macula, is essential for the health and function of the retina's photoreceptor cells. In AMD, damage to and the progressive loss of RPE cells can lead to the death of photoreceptor cells and blindness. The global prevalence of AMD was estimated to be 196 million people in 2020 and is projected to increase to 288 million by 2040 (Maeda et al., 2021). Researchers have demonstrated that transplantation of RPE cells derived from pluripotent stem cells is safe and can improve vision in patients with AMD. Currently, they are exploring various methods of delivering RPE cells into the eye (Kashani, 2022). One approach involves implanting a monolayer of RPE cells into the eye. These "sheets" have shown promise; the RPE cells appear to be stable and do not migrate to other parts of the eye. Another approach is the injection of RPE cells as a suspension into the eye. RPE sheet transplantation is generally more invasive than RPE cell suspension and, thus, carries a slightly higher risk of surgical complications. Researchers are optimizing the methods for delivering RPE cells into the eye before clinical application can be considered.

Cardiovascular conditions (CVCs) are the leading cause of death globally, claiming an estimated 17.9 million lives each year (World Health Organization, 2023a). CVCs are composed of a group of disorders affecting the heart and blood vessels, including acute myocardial infarction, congestive heart failure, coronary heart condition, and rheumatic heart condition, among others. Demurtas et al. (2021) conducted a meta-analysis of 23 randomized controlled clinical trials involving 1,764 patients to evaluate the effects of stem cell therapy on CVCs. They discovered that stem cell therapy is associated with a significant improvement in left ventricular ejection fraction and a reduction in major adverse cardiovascular events. They concluded that stem cell therapy shows promise as a treatment for CVCs; however, further research is necessary to determine the optimal stem cell type, dosage, and delivery method.

According to the International Diabetes Federation (2023), approximately 537 million people (1 in 10) were affected by diabetes in 2021. This number is projected to increase to 783 million (1 in 8) by 2045. Diabetes is often caused by the autoimmune destruction of pancreatic insulin-producing β cells in type 1 diabetes, or by the dysfunction of these cells in type 2 diabetes. Consequently, a curative treatment for diabetes could potentially be achieved through the autologous transplant of stem cell-derived β cells, enabling patients to attain insulin independence. Currently, patients still face autoimmune attacks on their transplanted β-cells. Two strategies are being explored to protect the β cells from autoimmune attacks. The first involves encapsulating the β cells within a porous matrix that allows the passage of molecules such as glucose and insulin, while shielding the β cells from immune attacks (Neumann et al., 2023). The second strategy involves genetically modifying the stem cells. Human leukocyte antigen (HLA) mismatching is a major molecular mechanism of immune rejection in transplants. By eliminating *HLA* genes from stem cells, immune compatibility can be enhanced, thus preventing immune attacks (Chen et al., 2020). While there is considerable optimism that stem cell therapy will become clinically viable for patients with diabetes, its safety has yet to be conclusively established.

Osteoarthritis is the most common joint disorder worldwide. As of 2019, approximately 528 million people globally were living with osteoarthritis (World Health Organization, 2023b). In this condition, joints become painful as the cartilage thins and bones rub against each other. A systematic review of 14 randomized controlled clinical trials involving 408 patients indicates that autologous mesenchymal stem cell therapy yields positive outcomes for patients with knee osteoarthritis (Wiggers et al., 2021). Furthermore, no harmful effects have been observed in patients within four years following stem cell therapy, including death, infection, diarrhea, central nervous system disorders, arrhythmia, dermatitis, vascular disorders, and fever. However, the review notes significant heterogeneity in the sources, methods of preparation, and dosages of the injected stem cells.

Clinical Trials with Controversial or Unknown Outcomes

Liver conditions account for two million deaths annually and are responsible for 4% of all deaths (Devarbhavi et al., 2023). Numerous stem cell clinical trials are underway for various liver conditions, including inherited metabolic liver disorders, acute liver failure, and chronic liver conditions. For inherited metabolic liver disorders such as Crigler-Najjar syndrome, researchers have replaced malfunctioning hepatocytes with genetically corrected

iPSC-derived hepatocytes (Smets et al., 2019). Although these clinical studies' results are encouraging, the long-term functionality of the transplanted hepatocytes remains to be established. Recently, researchers have used stem cell-derived hepatocytes to engineer external devices that can function as bio-artificial livers for treating acute liver failure (Wang et al., 2021). Currently, scientists are investigating the effectiveness of human mesenchymal stem cell-based bio-artificial livers for patients with acute liver failure (Feng et al., 2023). However, no detailed data has been published to date. Zhou et al. (2020) conducted a systematic review and meta-analysis of 24 randomized controlled clinical trials involving patients with chronic liver conditions. In all trials, there were no significant benefits observed for alanine aminotransferase and prothrombin levels, and 13 trials reported adverse events.

Parkinson's disease (PD) is a progressive chronic neurodegenerative disorder characterized by the death of dopaminergic neurons in the substantia nigra of the midbrain. PD affects more than 10 million people worldwide. The G-Force PD is a global initiative aimed at coordinating research on human stem cell-based therapies for PD. Research groups across Europe, Japan, and the USA are working to establish reproducible and scalable protocols for producing and transplanting stem cell-derived dopaminergic neurons that meet "Good Manufacturing Practice" standards (Barbuti et al., 2021; Takahashi, 2020). However, detailed data regarding these protocols has not been published yet. Apart from the G-Force PD consortium, other researchers are evaluating the efficacy and safety of transplanting dopaminergic neurons into the putamen of PD patients, which is a round structure located at the base of the forebrain. Recently, a single case involved autologous transplantation of iPSC-derived dopaminergic neurons into a PD patient (Schweitzer et al., 2020). It is important to note that this study involves only one isolated case. Consequently, the results may not be reliable or meaningful. Nonetheless, clinical measures of PD symptoms improved 18 to 24 months after transplantation, and the grafted cells survived for two years without any adverse effects.

○ Challenges of Stem Cell Therapy

There are three major challenges that must be overcome before stem cell therapy can be applied to benefit more patients; they are tumorigenesis, immunogenicity, and optimizing cell delivery methods.

Tumorigenesis

Tumorigenesis presents a significant challenge in stem cell therapy, especially when employing pluripotent stem cells such as ESCs and iPSCs. These cells have the capacity to differentiate into cell types of the ectoderm, mesoderm, and endoderm, offering immense therapeutic potential. However, this same pluripotency poses risks. Achieving 100% differentiation during in vitro processes and eliminating all undifferentiated cells are challenging. Even a small number of undifferentiated cells in the transplanted cell population can lead to teratomas—tumors composed of tissues from all three germ layers (Lezmi & Benvenisty, 2022).

Tumorigenesis in pluripotent stem cells, particularly iPSCs, is attributed to genomic instability. This instability can lead to mutations that contribute to tumorigenesis. Additionally, the local microenvironment at the transplantation site is pivotal in determining the fate of transplanted cells. Inappropriate signals or cues from the host tissue may promote the proliferation of undifferentiated cells, further contributing to tumorigenesis (Lezmi & Benvenisty, 2022).

To minimize the risk of tumorigenesis, researchers are investigating various strategies (Wuputra et al., 2020). One method involves using techniques such as fluorescence-activated cell sorting or magnetic-activated cell sorting to enrich specific differentiated cell types for transplantation, thus reducing the risk of tumorigenesis. Researchers are also refining differentiation protocols to achieve more complete and efficient differentiation of pluripotent stem cells, minimizing the presence of undifferentiated cells in the final product. This necessitates a thorough understanding of the molecular signals that drive differentiation pathways. Furthermore, genetic engineering techniques are being explored to alter stem cells in ways that improve their safety profile. For instance, strategies are being developed to trigger apoptosis in undifferentiated cells or to introduce "suicide genes" that can be activated should tumorigenesis occur.

Immunogenicity

Immune rejection and achieving immune compatibility are critical challenges in stem cell therapy, particularly in allogeneic transplantation. Immune rejection can occur through cell-mediated and antibody-mediated mechanisms. Cell-mediated rejection involves the activation of T cells, which can directly attack and destroy transplanted cells. Antibody-mediated rejection involves the production of antibodies that lead to the destruction of transplanted cells (Perkey & Maillard, 2018).

Researchers are exploring various strategies to mitigate immune rejection. One such strategy is matching the HLA of the donor and recipient (Perkey & Maillard, 2018), which can significantly reduce graft rejection ("host-versus-graft") and graft-versus-host disease (GVHD), where T cells from the graft attack recipient cells. However, finding a perfect HLA match is challenging due to the high degree of polymorphism in *HLA* genes. Even with a full HLA match, there is still a risk of graft rejection and GVHD because of minor histocompatibility antigens on the cell surface of transplanted tissues.

Another strategy for mitigating graft rejection is the global suppression of the host immune response. Drugs such as calcineurin inhibitors, de novo purine synthesis inhibitors, and glucocorticoids have led to long-lived graft acceptance in many patients, but come with potential side effects such as increased susceptibility to infections. An alternative is lymphodepletion, where drugs such as cyclophosphamide and fludarabine are administered to patients to kill T cells prior to infusion of stem cells, creating an environment conducive to graft persistence (Nissani et al., 2021). However, lymphodepletion increases the risk of infections due to compromised immune function. Additionally, cyclophosphamide can cause hemorrhagic cystitis, pericarditis, and neurotoxicity, while fludarabine may result in fevers and neurotoxicity.

Another way to reduce graft rejection is minimizing the immunogenicity of stem cells. For instance, researchers have used gene editing to knock out genes (*b2M* and *CIITA*) necessary for HLA expression in stem cells, rendering the edited cells less recognizable by the host's T cells and less likely to be attacked by the host immune system. The resulting hypoimmunogenic stem cells still retain their normal self-renewal capacity and differentiation potency (Chen et al., 2023). Additionally, other researchers have genetically modified stem cells so that the differentiated cells they produce can express immune inhibitory proteins, PD-L1 and CTLA4Ig, while the stem cells cannot. This makes the differentiated cells immunotolerant to the host immune system, while the potentially tumorigenic stem cells remain vulnerable to immune elimination (Zhu

et al., 2023). This strategy allows stem cell-derived differentiated cells to persist in the host without tumorigenesis, despite a lack of immune matching. All three strategies have shown promising results in preclinical studies and hold great potential for enhancing the therapeutic efficacy of stem cell therapy.

Optimizing Cell Delivery Methods

Optimizing the delivery methods for stem cell therapy presents a multifaceted challenge. It necessitates a thorough understanding of the unique requirements of each therapeutic application. Advances in delivery technologies, biomaterials, and a deep understanding of the microenvironment within the target tissue or organ are critical for overcoming these challenges and maximizing the potential of stem cell therapy in various clinical contexts.

Achieving precise and efficient delivery of stem cells to their intended site of action remains a formidable task. Different conditions or injuries require cell delivery to specific tissues or organs. Ensuring that an adequate number of cells reach the target site is crucial for therapeutic success. Some scientists have genetically engineered stem cells to express specific homing receptors, enhancing their ability to migrate toward the target tissue (Liesveld et al., 2020). Additionally, imaging technologies such as magnetic resonance imaging or bioluminescence imaging allow scientists to track the location, distribution, and viability of transplanted cells. Real-time monitoring enables fine-tuning of the delivery method (Nucci et al., 2020).

The microenvironment of the target tissue significantly influences the survival, integration, and functionality of transplanted stem cells. When designing delivery methods, it is essential to consider the complex biochemical and biomechanical cues specific to the target tissue. Proper engraftment and functional integration of transplanted cells depend on addressing these cues. Some researchers employ biomaterials and scaffolds to enhance stem cell delivery and retention within the target tissue. These materials provide structural support, mimic the extracellular matrix, and release bioactive factors that promote cell survival and integration (Zhao et al., 2021). Alternatively, microscale technologies, such as microfluidic devices, provide precise control over the flow of nutrients and oxygen to stem cells. By creating microenvironments that mimic that of the target tissue, successful engraftment becomes more likely (Yu et al., 2023).

○ Ethical Issues of Stem Cell Therapy

Stem cell therapy is a pioneering field in medicine with the potential to revolutionize treatments for a variety of conditions and injuries. However, it is also the center of intense ethical debates. A particularly contentious issue is the use of ESCs. Obtaining ESCs requires the destruction of embryos, which raises ethical concerns regarding the sanctity of human life. Critics contend that embryos have moral status and deserve the same ethical considerations as fully developed humans. In contrast, proponents highlight the significant therapeutic potential of ESCs in treating numerous conditions (Volarevic et al., 2018).

While iPSCs present an alternative to ESCs without the ethical dilemmas of embryo destruction, they introduce their own ethical challenges. These include risks such as abnormal reprogramming, tumorigenesis, and the production of germ cells (Volarevic et al., 2018). Abnormal reprogramming can lead to unintended mutations during the creation of iPSCs, potentially impacting their functionality and safety. The production of germ cells refers to the generation of artificial sperm or eggs from iPSCs, which could be utilized for reproductive or research purposes, prompting concerns over the moral status, genetic integrity, and parental rights of any resulting progeny. Addressing these ethical issues is crucial before iPSCs can be broadly applied in stem cell therapy.

The commercialization of stem cell therapy raises significant ethical concerns (Riordan et al., 2023). A primary concern is the potential conflict between the pursuit of profit and patient welfare. As stem cell therapies become commercialized, there is a risk that financial interests may prioritize over patient well-being, leading to the promotion of treatments without adequate scientific validation or consideration for long-term safety. Another concern is the disparity in access and affordability across various socioeconomic groups. Cutting-edge treatments may become disproportionately available to those who can afford them, thereby exacerbating existing healthcare inequalities. Ethical considerations must ensure that stem cell therapies are accessible to individuals across different income levels and backgrounds. Additionally, the rapid commercialization of stem cell therapy may outpace regulatory frameworks, leading to inadequate scrutiny of the efficacy, safety, and quality of stem cell products.

Establishing and enforcing ethical guidelines for commercial entities involved in stem cell therapy is crucial (Riordan et al., 2023). Governments, regulatory agencies, research institutions, healthcare providers, biotechnology companies, and insurers all have roles in setting standards that uphold ethical principles and encourage innovation. These guidelines should give precedence to patient safety and emphasize the importance of transparency, responsible marketing, and compliance with regulatory standards. Independent monitoring and ethical review boards are instrumental in ensuring that the commercialization of stem cell therapies is ethically sound.

Informed consent in the context of stem cell therapy raises several ethical concerns (Lomax et al., 2020). First, stem cell therapy often involves abstract scientific concepts and novel medical interventions. Effectively communicating the intricacies of these treatments to patients is a significant challenge. Ensuring that patients fully grasp the risks, benefits, and uncertainties of stem cell therapy is essential for obtaining valid informed consent. Second, as stem cell therapy is still experimental, there are uncertainties about its long-term efficacy and safety. Informed consent is difficult when data on potential benefits and risks is scarce. Patients should be informed about the experimental nature of the treatment and the possibility of unexpected outcomes. Third, patients seeking stem cell therapy often suffer from serious medical conditions and may feel an urgent need to consider all treatment options. In such cases, there may be considerable pressure to agree to experimental treatments. Therefore, it is essential to balance hope with realistic expectations and ensure that patients make informed decisions without feeling coerced or misled.

Improving informed consent requires public education and awareness. Promoting scientific literacy can contribute to a more informed public capable of making decisions aligned with their best interests. Improving informed consent also requires the development of educational materials accessible to patients. Additionally, healthcare providers must be adequately trained to communicate the complexities of stem cell therapy. Constant monitoring and feedback, informed by patient experiences, can refine the consent process (Lomax et al., 2020).

○ Legal Issues of Stem Cell Therapy

The utilization of ESCs in stem cell therapy presents intricate legal challenges, primarily stemming from ethical considerations related to their origin. The legal discourse also revolves around the moral status of ESCs, balancing their potential for research against the ethical implications of their developmental capabilities. Legal frameworks vary significantly across jurisdictions, reflecting diverse societal values and ethical stances (International Society for Stem Cell Research, 2021). While some countries outright prohibit research on human embryos, others permit it under stringent conditions. For example, certain regulations allow the use of imported ESCs but not their creation and use within the country's borders. In the USA, while stem cell research is legal, it is subject to restrictions, especially regarding the funding and use of ESCs; these restrictions vary widely from state to state (Wikipedia, 2024).

Advances in stem cell research have facilitated the development of embryoids from pluripotent stem cells. These cells differentiate and self-organize into three-dimensional structures that resemble early-stage embryos but are not fully developed. Embryoids are used to provide insights into early embryogenesis. Researchers can now create embryoids with more complex features. Consequently, the distinction between embryoids and embryos is becoming increasingly blurred. This raises questions about the moral status of human embryoids and has prompted calls for a reevaluation of existing legal frameworks (Iltis et al., 2023). As scientific progress continues, it is imperative that the legal framework adapts to address these ethical considerations, ensuring that stem cell research and therapy align with societal values and legal norms.

○ Conclusion

Stem cell therapy is a promising field of regenerative medicine that aims to utilize stem cells to treat various conditions and injuries. Stem cells are unique cells capable of dividing and differentiating into specialized cell types, such as blood cells, nerve cells, heart cells, and bone cells. They can be derived from various sources, including bone marrow, umbilical cord blood, and embryos. However, stem cell therapy faces several challenges and controversies, including immune rejection, tumorigenesis, safety concerns, ethical issues, and regulatory hurdles. Therefore, more research and clinical trials are necessary to establish the efficacy and safety of stem cell therapy for diverse applications. Stem cell therapy has the potential to revolutionize medicine and improve the quality of life for millions of people worldwide in the future.

○ Lesson Plan

Lesson Outcomes:

1. Analyze the challenges associated with stem cell therapy and explore potential strategies to overcome them.
2. Examine the ethical considerations surrounding stem cell therapy and propose viable strategies to address these concerns.

Duration: 60 minutes

Level: College

Materials:

1. Journal article titled "An Instant Update on Stem Cell Therapy"
2. Section titled "Stem cells" on the Genetic Science Learning Center (2024a) website
3. Video titled "Unlocking Stem Cell Potential" on the Genetic Science Learning Center (2024b) website
4. Computer notebook equipped with BioGPT

Prior Knowledge:

1. Students should have completed the following readings as homework before the class:
   a. Journal article titled "An Instant Update on Stem Cell Therapy"
   b. The section titled "Stem Cells" on the Genetic Science Learning Center website
2. An understanding of the key bioethical principles: autonomy, justice, beneficence, and non-maleficence (Varkey, 2021)
3. A solid grasp of the norms for classroom discussions (MIT Teaching + Learning Lab, 2024)

Lesson Introduction (5 minutes)

1. Start with the video titled "Unlocking Stem Cell Potential" to engage the students' interest.
2. Proceed with a real-world case study on stem cell therapy. Take, for example, Christopher Reeve, who rose to fame as Superman and was an acclaimed actor and a passionate advocate for various humanitarian causes. After a horse-riding accident in 1995 that led to paralysis from the neck down, Reeve became a champion of stem cell research, believing firmly in its potential to treat spinal cord injuries and other medical conditions.

Lesson Development (50 minutes)

1. **Group Discussion & Presentation 1** (25 minutes)
   Divide the students into small groups and assign each group a specific challenge. Instruct them to investigate the cause of the challenge and brainstorm strategies to address it. Each group should then present their findings using PowerPoint slides.
   a. Tumorigenesis
   b. Immunogenicity
   c. Optimizing the delivery of stem cells to the intended site of action
2. **Group Discussion & Presentation 2** (25 minutes)
   Divide the students into small groups and assign each group a specific ethical issue. Instruct them to research why the issue is ethically contentious and to brainstorm strategies to address it. Each group is then expected to present their findings using PowerPoint slides.
   a. The use of embryonic stem cells
   b. The commercialization of stem cell therapy
   c. The importance of informed consent

Lesson Conclusion (5 minutes)

1. The instructor will recapitulate the key aspects of the challenges and ethical dilemmas associated with stem cell therapy.
2. The instructor will address and clarify any questions raised by the students.

References

Barbuti, P. A., Barker, R. A., Brundin, P., Przedborski, S., Papa, S. M., Kalia, L. V., & Mochizuki, H. (2021). Recent advances in the development of stem-cell-derived dopaminergic neuronal transplant therapies for Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, *36*(8), 1772–1780.

Chen, S., Du, K., & Zou, C. (2020). Current progress in stem cell therapy for type 1 diabetes mellitus. *Stem Cell Research & Therapy*, *11*, 1–13.

Chen, Y., Zhou, Y., Zhou, Z., Fang, Y., Ma, L., Zhang, X., Xiong, J., & Liu, L. (2023). Hypoimmunogenic human pluripotent stem cells are valid cell sources for cell therapeutics with normal self-renewal and multilineage differentiation capacity. *Stem Cell Research & Therapy*, *14*(1), 1–15.

Demurtas, J., Fanelli, G. N., Romano, S. L., Solari, M., Yang, L., Soysal, P., López Sánchez, G. F., Grabovac, I., Smith, L., Zorzi, A., Luchini, C., & Veronese, N. (2021). Stem cells for treatment of cardiovascular diseases: An umbrella review of randomized controlled trials. *Ageing Research Reviews*, *67*, 101257.

Devarbhavi, H., Asrani, S. K., Arab, J. P., Nartey, Y. A., Pose, E., & Kamath, P. S. (2023). Global burden of liver disease: 2023 update. *Journal of Hepatology*, *79*(2), 516–537.

Eguizabal, C., Aran, B., Chuva de Sousa Lopes, S. M., Geens, M., Heindryckx, B., Panula, S., Popovic, M., Vassena, R., & Veiga, A. (2019). Two decades of embryonic stem cells: A historical overview. *Human Reproduction Open*, *2019*(1), 1–17.

Feng, L., Wang, Y., Fu, Y., Yimamu, A., Guo, Z., Zhou, C., Li, S., Zhang, L., Qin, J., Liu, S., Xu, X., Jiang, Z., Cai, S., Zhang, J., Li, Y., Peng, Q., Yi, X., He, G., Li, T., & Gao, Y. (2023). A simple and efficient strategy for cell-based and cell-free-based therapies in acute liver failure: hUCMSCs bioartificial liver. *Bioengineering and Translational Medicine*, *8*(5), 1–19.

Genetic Science Learning Center. (2024a). Stem cells. Retrieved January 4, 2024 from https://learn.genetics.utah.edu/content/stemcells/

Genetic Science Learning Center. (2024b). Unlocking stem cell potential. Retrieved January 4, 2024 from https://learn.genetics.utah.edu/content/stemcells/scfuture

Gurusamy, N., Alsayari, A., Rajasingh, S., & Rajasingh, J. (2018). Adult stem cells for regenerative therapy. *Progress in Molecular Biology and Translational Science*, *160*, 1–22.

Hoang, D. M., Pham, P. T., Bach, T. Q., Ngo, A. T. L., Nguyen, Q. T., Phan, T. T. K., Nguyen, G. H., Le, P. T. T., Hoang, V. T., Forsyth, N. R., Heke, M., & Nguyen, L.T. (2022). Stem cell-based therapy for human diseases. *Signal Transduction and Targeted Therapy*, *7*(1), 1–41.

Iltis, A. S., Koster, G., Reeves, E., & Matthews, K. R. W. (2023). Ethical, legal, regulatory, and policy issues concerning embryoids: A systematic review of the literature. *Stem Cell Research & Therapy*, *14*(1), 1–15.

International Diabetes Federation. (2023). Facts & Figures. Retrieved January 4, 2024 from https://idf.org/about-diabetes/diabetes-facts-figures/

International Society for Stem Cell Research. (2021). ISSCR guidelines for stem cell research and clinical translation. Retrieved January 4, 2024 from https://www.isscr.org/guidelines

Kashani, A. H. (2022). Stem cell-derived retinal pigment epithelium transplantation in age-related macular degeneration: Recent advances and challenges. *Current Opinion in Ophthalmology*, *33*, 211–218.

Lezmi, E., & Benvenisty, N. (2022). The tumorigenic potential of human pluripotent stem cells. *Stem Cells Translational Medicine*, *11*(8), 791–796.

Liesveld, J. L., Sharma, N., & Aljitawi, O. S. (2020). Stem cell homing: From physiology to therapeutics. *Stem Cells (Dayton, Ohio)*, *38*(10), 1241–1253.

Lomax, G. P., Torres, A., & Millan, M. T. (2020). Regulated, reliable, and reputable: Protect patients with uniform standards for stem cell treatments. *Stem Cells Translational Medicine*, *9*(5), 547–553.

Maeda, T., Sugita, S., Kurimoto, Y., & Takahashi, M. (2021). Trends of stem cell therapies in age-related macular degeneration. *Journal of Clinical Medicine*, *10*(8), 1–20.

MIT Teaching + Learning Lab. (2024). Discussion guidelines. Retrieved January 4, 2024 from https://tll.mit.edu/teaching-resources/inclusive-classroom/discussion-guidelines/

National Institutes of Health. (2023). NIH Clinical Research Trials and You. Retrieved January 4, 2024 from https://www.nih.gov/health-information/nih-clinical-research-trials-you/finding-clinical-trial

Neumann, M., Arnould, T., & Su, B. L. (2023). Encapsulation of stem-cell derived β cells: A promising approach for the treatment for type 1 diabetes mellitus. *Journal of Colloid and Interface Science*, *636*, 90–102.

Nissani, A., Lev-Ari, S., Meirson, T., Jacoby, E., Asher, N., Ben-Betzalel, G., Itzhaki, O., Shapira-Frommer, R., Schachter, J., Markel, G., & Besser, M. J. (2021). Comparison of non-myeloablative lymphodepleting preconditioning regimens in patients undergoing adoptive T cell therapy. *Journal for Immunotherapy of Cancer*, *9*(5), 1–12.

Nobel Prize Organization. (2023). All Nobel Prizes in Physiology or Medicine. Retrieved January 4, 2024 from https://www.nobelprize.org/prizes/lists/all-nobel-laureates-in-physiology-or-medicine/

Nucci, M. P., Filgueiras, I. S., Ferreira, J. M., de Oliveira, F. A., Nucci, L. P., Mamani, J. B., Rego, G. N. A., & Gamarra, L. F. (2020). Stem cell homing, tracking and therapeutic efficiency evaluation for stroke treatment using nanoparticles: A systematic review. *World Journal of Stem Cells*, *12*(5), 381–405.

Perkey, E., & Maillard, I. (2018). New Insights into graft-versus-host disease and graft rejection. *Annual Review of Pathology: Mechanisms of Disease*, *13*, 219–245.

Riordan, N. H., Gerardo Jiménez Arias, L., & Coronado, R. (2023). Ethics of international stem cell treatments and the risk-benefit of helping patients. In D. Kitala (Ed.), *Possibilities and limitations in current translational stem cell research* (pp. 1–21). IntechOpen.

Schweitzer, J. S., Song, B., Herrington, T. M., Park, T. Y., Lee, N., Ko, S., Jeon, J., Cha, Y., Kim, K., Li, Q., Henchcliffe, C., Kaplitt, M., Neff, C., Rapalino, O., Seo, H., Lee, I. H., Kim, J., Kim, T., Petsko, G. A., Ritz, J., . . . Kim, K. -S. (2020). Personalized iPSC-derived dopamine progenitor cells for Parkinson's disease. *New England Journal of Medicine*, *382*(20), 1926–1932.

Smets, F., Dobbelaere, D., McKiernan, P., Dionisi-Vici, C., Broué, P., Jacquemin, E., Lopes, A. I., Gonçalves, I., Mandel, H., Pawlowska, J., Kami ska, D., Shteyer, E., Torre, G., Shapiro, R., Eyskens, F., Clapuyt, P., Gissen, P., Pariente, D., Grunewald, S., Yudkoff, M., . . . Sokal, E. (2019). Phase I/II trial of liver-derived mesenchymal stem cells in pediatric liver-based metabolic disorders: A prospective, open label, multicenter, partially randomized, safety study of one cycle of heterologous human adult liver-derived progenitor cells (HepaStem) in urea cycle disorders and Crigler-Najjar Syndrome patients. *Transplantation*, *103*(9), 1903–1915.

Stefańska, K., Bryl, R., Moncrieff, L., Pinto, N., Shibli, J. A., & Dyszkiewicz-Konwińska, M. (2020). Mesenchymal stem cells - A historical overview. *Medical Journal of Cell Biology*, *8*(2), 83–87.

Takahashi, J. (2020). iPS cell-based therapy for Parkinson's disease: A Kyoto trial. *Regenerative Therapy*, *13*, 18–22.

Varkey, B. (2021). Principles of clinical ethics and their application to practice. *Medical Principles and Practice: international journal of the Kuwait University, Health Science Centre*, *30*(1), 17–28.

Volarevic, V., Markovic, B. S., Gazdic, M., Volarevic, A., Jovicic, N., Arsenijevic, N., Armstrong, L., Djonov, V., Lako, M., & Stojkovic, M. (2018). Ethical and safety issues of stem cell-based therapy. *International Journal of Medical Sciences*, *15*(1), 36–45.

Wang, J., Ren, H., Liu, Y., Sun, L., Zhang, Z., Zhao, Y., & Shi, X. (2021). Bioinspired artificial liver system with hiPSC-derived hepatocytes for acute liver failure treatment. *Advanced Healthcare Materials*, *10*(23), e2101580.

Wiggers, T. G. H., Winters, M., den Boom, N. A. C. V., Haisma, H. J., & Moen, M. H. (2021). Autologous stem cell therapy in knee osteoarthritis: A systematic review of randomised controlled trials. *British Journal of Sports Medicine*, *55*(20), 1161–1169.

Wikipedia. (2024). Stem cell laws and policy in the United States. Retrieved January 4, 2024 from https://en.wikipedia.org/wiki/Stem_cell_laws_and_policy_in_the_United_States

World Health Organization. (2023a). Cardiovascular diseases. Retrieved January 4, 2024 from https://www.who.int/health-topics/cardiovascular-diseases/#tab=tab_1

World Health Organization. (2023b). Osteoarthritis. Retrieved January 4, 2024 from https://www.who.int/news-room/fact-sheets/detail/osteoarthritis

Wuputra, K., Ku, C. C., Wu, D. C., Lin, Y. C., Saito, S., & Yokoyama, K. K. (2020). Prevention of tumor risk associated with the reprogramming of human pluripotent stem cells. *Journal of Experimental & Clinical Cancer Research*, *39*(1), 1–24.

Yu, S., Yu, S., Liu, H., Liao, N., & Liu, X. (2023). Enhancing mesenchymal stem cell survival and homing capability to improve cell engraftment efficacy for liver diseases. *Stem Cell Research & Therapy*, *14*, 1–14.

Zhao, X., Li, Q., Guo, Z., & Li, Z. (2021). Constructing a cell microenvironment with biomaterial scaffolds for stem cell therapy. *Stem Cell Research & Therapy*, *12*(1), 1–13.

Zhou, G. P., Jiang, Y. Z., Sun, L. Y., & Zhu, Z. J. (2020). Therapeutic effect and safety of stem cell therapy for chronic liver disease: A systematic review and meta-analysis of randomized controlled trials. *Stem Cell Research & Therapy*, *11*(1), 1–19.

Zhu, W., Li, M., Zou, J., Zhang, D., Fang, M., Sun, Y., Li, C., Tang, M., Wang, Y., Zhou, Q., Zhao, T., Li, W., Hu, Z., & Hu, B. (2023). Induction of local immunosuppression in allogeneic cell transplantation by cell-type-specific expression of PD-L1 and CTLA4Ig. *Stem Cell Reports*, *18*(12), 2344–2355.

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