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RESEARCH ARTICLE

CELL CROSS TALK IN DISEASES: "THE INTERPLAY BETWEEN STEM CELLS AND SOME INFECTIOUS DISEASES, THERAPEUTIC PROSPECTS IN LOW-INCOME COUNTRIES"

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Abstract

Particularly in low-income nations, infectious illnesses continue to be a significant global health burden. The interaction of stem cells with infectious diseases has become a fascinating field of study with bright therapeutic potential. This review article seeks to give readers an overview of how cells interact with one another in disease, with a particular focus on how stem cells interact with a few specific infectious diseases and their therapeutic potential in low-income nations. The definition and several types of stem cells are introduced at the outset of the review, with a focus on their capacity for regeneration and immunomodulation. The significance of stem cells in tissue repair and regeneration is next discussed, emphasizing their potential to lessen the damaging effects of infectious illnesses on host tissues. The article also examines the behaviour and function of stem cells as well as the direct and indirect effects of pathogens on stem cells. Examining the immune system's function in controlling the interaction between infections and stem cells helps to understand the intricate cellular cross-talk involved. The review examines the therapeutic potential of stem cell-based therapies for infectious diseases in the context of low-income nations. It addresses the potential of stem cell treatments for conditions like HIV, malaria, tuberculosis, and neglected tropical diseases while highlighting the developments and difficulties associated with applying these treatments in settings with limited resources. Overall, this review demonstrates the complex relationship between stem cells and infectious diseases and offers insights into the potential therapeutic applications of stem cell-based therapies in low-income nations. It emphasizes the requirement for additional study, teamwork, and the creation of affordable and widely available stem cell therapies to effectively combat infectious diseases and enhance healthcare outcomes in settings with limited resources.

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Introduction:-

Infectious illnesses are very prevalent in Sub-Saharan Africa. The prevalence and effect of diseases like malaria, HIV/AIDS, TB, diarrheal illnesses, and respiratory infections are significant. For instance, malaria, which is predicted to cause 200 million cases and over 400,000 deaths yearly in the region (Guerra et al., 2020), continues to be a common cause of morbidity and mortality. With over 25.7 million people living with HIV in the region, sub-Saharan Africa has also been disproportionately affected by the HIV/AIDS epidemic. Additionally, sub-Saharan Africa is responsible for around 25% of the global burden of tuberculosis, which is a serious health issue (Ekah, 2020).

The effects of these contagious diseases on people, families, and communities are extensive. They contribute to higher healthcare costs, lower productivity, and the continuation of the poverty cycle. Additionally, the burden is disproportionately placed on weaker groups, such as women, children, and residents of rural areas.

It has been difficult to fight these infectious diseases in low-income nations in sub-Saharan Africa because of several issues, including a lack of funding, a lacklustre healthcare system, poor diagnostic tools, and restricted access to necessary medications. To lessen the burden of these diseases and enhance general health outcomes in these areas, it is essential to create efficient and long-lasting therapies.

Infectious diseases still wreak havoc in low-income nations, with sub-Saharan Africa bearing a disproportionately heavy impact. Improved healthcare infrastructure, greater access to healthcare services, improved surveillance, and the creation of novel interventions to prevent, diagnose, and cure infectious diseases are all necessary components of a multidimensional strategy to address this challenge. In vitro disease models can be produced using stem cells isolated from the patient samples, reprogrammed, and differentiated into different cell types which are targets of the infectious pathogens, thus providing special benefits that aid in the understanding of the disease mechanisms and the creation of novel therapeutic approaches. These models closely mimic the patient's cellular environment, facilitating the study of disease progression, host-pathogen interactions, and the screening of potential therapeutic interventions (Teoh & Cheong, 2012).

Stem cells play a critical role in drug discovery and development for the treatment of infectious diseases. Stem cell-based models provide regulated and morally acceptable chemical screening, hastening the discovery of novel antiviral, antibacterial, or antifungal medicines. Additionally, stem cells shed light on the intricate interactions between infections and the host. Researchers get information about pathogen invasion, immune evasion, and host immunological responses by examining how stem cells and their differentiated counterparts react to infection (Scott, et al., 2013). Furthermore, stem cells show promise in approaches to regenerative therapy for infectious disorders. For instance, mesenchymal stem cells can help with tissue repair and regeneration after infection-related damage because they have immunomodulatory capabilities. Therapeutics based on stem cells, such as genetically modified stem cells that express antiviral or immune-modulating molecules, have shown potential to modify how infectious diseases are managed (Li et al., 2022).

In the context of infectious diseases in particular, stem cells play a vital role in disease research and therapy. Their uses range from disease modeling to drug development, from regenerative medicine to cell-based therapeutics to a knowledge of host-pathogen interactions.

With an emphasis on stem cells' potential as a treatment for infectious diseases in low-income nations, this review article intends to investigate and analyze the relationship between the two. The purpose of this article is to provide information on the importance of cell cross talk in infectious diseases and its implications for enhancing healthcare outcomes in settings with constrained resources.

Overview of Stem cells

Stem cells are distinct because of their amazing capacity for self-renewal and cell-type differentiation. They are essential for the growth, maintenance, and development of the body's tissues and organs (Zuk, 2010). ESCs (embryonic stem cells) and adult stem cells are the two basic types of stem cells.

Embryonic stem cells can differentiate into any type of cell in the body because they are pluripotent, which means they come from the inner cell mass of early-stage embryos (Murry & Keller, 2008). Due to their capacity to produce a variety of cell types, they have enormous potential in regenerative medicine.

The body's tissues and organs contain adult stem cells, also referred to as somatic stem cells (Leri et al., 2005). These cells can differentiate into a small number of cell types that are particular to the tissue in which they dwell because they are multipotent. Hematopoietic stem cells, which develop into blood cells, and mesenchymal stem cells, which are present in a variety of organs such as bone marrow and adipose tissue, are two examples of adult stem cells.

The ability of stem cells to regenerate and mend damaged tissue is one of its important functions. Stem cells can multiply and develop into specific cell types to replace damaged cells in tissues that have been harmed or destroyed (Leri et al., 2005). Through constant cell division and replenishment, they support tissue healing and the return of normal function, contributing to the renewal and maintenance of tissues.

Stem cells have the potential to be used in the treatment of infectious disorders in addition to tissue regeneration. To interact with the immune system and control immunological responses, they have immunomodulatory capabilities (English et al., 2010). Stem cells can control inflammation, facilitate tissue healing, and improve the body's defenses against pathogens. Indirectly battling pathogenic pathogens, several stem cell types have proven antibacterial qualities (Gorman et al., 2021). Research on the therapeutic potential of stem cells in the treatment of infectious disorders is ongoing, and encouraging preclinical and clinical trials have demonstrated their efficacy against illnesses such as host versus graft disease, sepsis, and viral infections.

Mechanisms of Cell Cross Talk in Infectious Diseases

The burden of infectious illnesses on public health continues to be a problem for the world's health, especially in low-income nations (Laxminarayan et al., 2021). Pathogenic microorganisms such as bacteria, viruses, parasites, and fungi are the origin of these diseases, which can have a wide range of symptoms and problems. Developing efficient therapeutic approaches requires a thorough understanding of the mechanisms behind cell cross-communication in viral illnesses.

Pathogens can directly impact stem cells, affecting their function, behaviour, and capacity for regeneration. For instance, some viruses can infect and interfere with the neural stem cells' ability to function, impairing neurogenesis and causing neurological issues (Baggiani et al., 2020). Additionally, pathogens can cause stem cell populations to die, which impairs their capacity for regeneration and hinders tissue healing.

The immune system can be modulated by infectious diseases, which in turn affects stem cells' behaviour and ability to fight infections. Different cytokines and signalling molecules produced by immune cells can affect the proliferation, differentiation, and migration of stem cells. In addition, pathogen-induced inflammation can provide a hostile microenvironment that impairs stem cell activity and tissue regeneration (Wynn et al., 2013).

On the other hand, stem cells can change how infections behave and reproduce, affecting how a disease develops. In order to directly target and stop the growth of infections, antimicrobial peptides, and compounds can be produced by stem cells (Byrnes et al., 2023). Additionally, stem cells have the capacity to alter the host immune response, improving infection eradication and reducing pathogen replication.

For the purpose of creating treatment approaches, it is essential to comprehend the intricate interactions that pathogens and stem cells have in infectious disorders. It may be feasible to improve stem cell activity, control immunological responses, and create new methods for treating infectious diseases by focusing on the principles of cell cross-communication.

Case Studies: Stem Cells and Infectious Diseases in Low-Income Countries

Stem cells and HIV in LIC

According to Anyangwe and Mtonga (2007), Sub-Saharan Africa is the region of the world where HIV/AIDS has the biggest influence on socioeconomic development and public health. Stem cell-based therapies have become a potential strategy in the battle against HIV/AIDS as a result of years of intensive research exploring novel therapeutic techniques.

Stem cells have certain qualities that make them desirable for HIV treatment methods. It is possible for hematopoietic stem cells (HSCs) to develop into diverse blood cell lineages, including immune cells that are essential for fending off viruses. Researchers have looked into the possibility of replacing immune cells that are susceptible to HIV with genetically altered cells that are virus-resistant by HSC transplantation.

Numerous investigations have produced favorable findings. In one instance, HSC transplantation from a donor with a rare genetic mutation that provides resistance to HIV infection was performed on a patient with HIV and lymphoma. The patient did not resume antiretroviral therapy for a significant amount of time after the transplant, and there was no sign of viral resurgence (Hutter et al., 2009).

However, there are several difficulties with using stem cell transplantation as an HIV treatment. The process is difficult, pricey, and fraught with dangers. It needs a compatible donor match, which can be difficult for people of African heritage because of the genetic variation in the area. Furthermore, many sub-Saharan African nations lack the infrastructure and qualified medical personnel required for stem cell transplantation.

Current research is concentrated on creating alternative strategies, such as gene therapy and methods for gene editing to alter the patient's stem cells and make them resistant to HIV infection. These developments have the potential to offer accessible and affordable treatment alternatives for those living with HIV/AIDS in settings with low resources.

Potential therapy options for HIV/AIDS in sub-Saharan Africa are stem cell-based therapies. Despite impressive accomplishments in the field, further study is required to enhance the security, viability, and long-term effectiveness of these strategies. To ensure the translation of scientific discoveries into efficient therapeutics that can address the unique issues faced by people living with HIV/AIDS in sub-Saharan Africa, collaboration between researchers, healthcare providers, and policymakers is crucial.

Stem Cells and Malaria: Therapeutic Prospects in LIC

Malaria continues to be a serious public health issue, especially in low-income nations where it has a severe negative impact on people's lives and healthcare infrastructure. The disease, which is brought on by Plasmodium parasites and spread by mosquito bites, affects millions of people every year and has high rates of morbidity and fatality.

In studying the progression and results of malaria, stem cells have become potential participants. Red blood cells and other immune system cells that are essential to the body's defense against the parasite are produced by hematopoietic stem cells (HSCs). According to Helleberg et al. (2005), malaria infection can have a direct impact on HSC survival and function, altering hematopoiesis and disrupting the immune system. These outcomes influence the degree and consequences of the illness.

Recent research has also illuminated the therapeutic potential of stem cells in the treatment of malaria. Adult stem cells known as mesenchymal stem cells (MSCs) have demonstrated promise in regulating the immune response and lowering inflammation brought on by malaria infection (Kalkal et al., 2021). MSCs can control the ratio of pro-inflammatory to anti-inflammatory molecules, prevent excessive immune activation, and facilitate tissue healing.

Preclinical research has shown that MSC therapy improves lifespan, lowers parasite burden, and lessens organ damage in experimental models of malaria (Kalkal et al., 2021; Hafalla et al., 2011). These findings have motivated additional research into MSC-based therapeutics in clinical trials to create secure and efficient malaria treatments.

It is significant to mention that there are various obstacles in the way of the introduction of stem cell therapy for malaria in low-income nations. The widespread adoption of such treatments faces major obstacles from a lack of healthcare infrastructure, resource limitations, and regulatory restrictions. To overcome these difficulties and guarantee equal access to stem cell-based treatments in malaria-endemic areas, cooperation between researchers, medical professionals, and policymakers is essential. Since they offer therapeutic potential, stem cells have gained attention as potential factors in the development and consequences of the deadly disease malaria. To completely comprehend the processes behind stem cell participation and to enhance stem cell-based therapeutics, more investigation and clinical trials are required. By utilizing stem cells' therapeutic potential, it may be possible to enhance outcomes, lessen complications, and lessen the impact of malaria in low-income nations.

Stem Cells and Tuberculosis: Therapeutic Prospects

With millions of cases each year, tuberculosis (TB) continues to be a global health emergency. Exploring novel therapeutic modalities is essential due to the rise of drug-resistant strains and the limits of available treatments. Therapies based on stem cells have demonstrated promise in combating the problems caused by tuberculosis.

Mesenchymal stem cells (MSCs), in particular, have shown immunomodulatory qualities that can be used for TB treatment. According to Huang et al. (2012), MSCs can control the immune system, reduce inflammation, and aid in tissue healing. According to research on tuberculosis, MSCs can stop the growth of the bacterium that causes the disease, *Mycobacterium tuberculosis* (Guilliams et al., 2013). Additionally, they can increase the effectiveness of traditional anti-TB medications, resulting in better treatment results.

Additionally, MSCs can aid in reducing tissue deterioration brought on by the immunological response to TB infection. They can encourage the repair of damaged lung tissue, which is important in cases of pulmonary tuberculosis. According to Joshi et al. (2015), MSC treatment has the potential to lessen TB-related fibrosis and inflammation of the lungs. The outcomes of patients are improved overall as a result of these consequences.

Although the therapeutic potential of stem cells in the treatment of tuberculosis is encouraging, more studies and clinical trials are required to improve treatment regimens and guarantee their safety and efficacy. It is necessary to address issues like the establishment of standardized protocols and the optimization of stem cell delivery techniques.

To advance stem cell-based TB medicines and make them available to individuals who need them, collaboration is essential between researchers, doctors, and policymakers.

The use of stem cell-based therapies in the battle against tuberculosis offers promising therapeutic possibilities. Making use of stem cells' immunomodulatory abilities, especially MSCs, holds promise for improving treatment outcomes and minimizing tissue damage. To fully realize the promise of stem cells in the treatment of tuberculosis and enhance the lives of those affected by this life-altering illness, additional research and clinical studies are required.

Stem Cells and Neglected Tropical Disease

Worldwide, millions of individuals are afflicted with neglected tropical diseases (NTDs), mainly in low-income nations. The problems faced by these disorders have shown promise for stem cell-based therapeutics and diagnostics.

Mesenchymal stem cells (MSCs) have shown immunomodulatory capabilities that can be used as therapies to fight NTDs. According to Das et al. (2019), MSCs can control the immune response, lessen inflammation, and encourage tissue healing. They have demonstrated promise in preclinical research for illnesses like schistosomiasis (Zheng et al., 2015), leishmaniasis (Duelen et al., 2019), and Chagas disease (Damesghi, et al., 2016), giving hope for better treatment outcomes.

Additionally, stem cells can be used in NTDs Diagnostics. Researchers can create illness models to better understand disease mechanisms and find possible therapeutic targets by using induced pluripotent stem cells (iPSCs) made from patient samples (Do et al., 2022). iPSCs can also be differentiated into specific cell types related to NTDs, enabling the investigation of disease development and the testing of potential therapeutics.

Though still in the early phases of development, stem cell-based treatments and diagnostics for NTDs present intriguing new ways to treat these underserved diseases. To maximize and validate the use of stem cells in both therapeutic and diagnostic procedures, as well as to ultimately improve the lives of people with NTDs, more research, clinical trials, and cooperative efforts are required.

Challenges and Opportunities for Stem Cell Therapy in Low-Income Countries

Although stem cell treatment has a great deal of potential to treat a variety of illnesses and disorders, applying it in low-income nations is fraught with difficulties. The advancement of stem cell research and therapy in these contexts is hampered by resource shortages, inadequate infrastructure, religion, conventional views, and legal restrictions. (Sivaram, 2019; Daley, 2012)

The high expense of stem cell therapy, including the acquisition, delivery, and processing of stem cells, is one significant drawback. Due to this, it becomes more challenging for low-income nations to fund these therapies and offer them to a larger population. Implementing stem cell therapy is further constrained by a lack of modern laboratory equipment and qualified workers.

Strategies are being explored to remove these obstacles and improve accessibility. Among these is the creation of networks and partnerships between researchers, doctors, and decision-makers from low-income and resource-rich places. Such partnerships promote information sharing, technological transfer, and capacity building, enabling the use of stem cell therapies in environments with limited resources.

International collaborations are also essential for closing the gap. Support can be given by businesses and institutions engaged in stem cell research and therapy through funding, education programs, and infrastructure development projects. Additionally, initiatives are being undertaken to simplify regulatory procedures and set up ethical standards unique to low-income nations, enabling the safe and efficient use of stem cell therapies (Fears et al., 2021). Overall, despite ongoing difficulties, low-income nations have a lot of room for growth in the stem cell therapy field. To remove obstacles and improve accessibility, cooperative efforts, global collaborations, and customized techniques can be used. Low-income nations can make use of the promise of this ground-breaking strategy to enhance healthcare outcomes and reduce the burden of diseases in their populations by removing the restrictions and boosting the adoption of stem cell treatment.

Future Directions and Conclusion:-

The interaction of stem cells with infectious diseases has demonstrated great promise for stem cell treatment, providing therapeutic opportunities for the management of disease in low-income nations. Future research has significant potential to advance the field in several areas, as we look ahead.

Before optimizing treatment plans, more research is required to better understand the precise processes of stem cell interactions with pathogens. It will be easier to create targeted treatments if we can better understand how stem cells influence the immune system, prevent the spread of pathogens, and encourage tissue repair.

Furthermore, the broad use of stem cell-based methods in low-income nations depends on the availability of affordable and scalable procedures. To overcome resource constraints and increase accessibility, creative cell sourcing, storage, and delivery strategies are required.

The management of diseases in low-income nations could be significantly impacted by stem cell therapy. These treatments have the potential to boost the resilience of healthcare systems in resource-constrained environments while also enhancing patient outcomes by utilizing the regenerative and immunomodulatory capabilities of stem cells.

In conclusion, the interaction between stem cells and infectious diseases offers a potentially fruitful route for therapeutic development in underdeveloped nations. Researchers and medical professionals might explore novel treatment approaches by utilizing the special qualities of stem cells. While issues with cost, infrastructure, and regulatory frameworks continue, cooperative efforts, global alliances, and ongoing research projects give hope for a future in which stem cell therapy becomes a workable and affordable option for treating infectious diseases in developing nations.

References:-

1. Anyangwe, S. C., & Mtonga, C. (2007). Inequities in the global health workforce: the greatest impediment to health in sub-Saharan Africa. *International journal of environmental research and public health*, 4(2), 93-100
2. Baggiani, M., Dell'Anno, M. T., Pistello, M., Conti, L., & Onorati, M. (2020). Human neural stem cell systems to explore pathogen-related neurodevelopmental and neurodegenerative disorders. *Cells*, 9(8), 1893.
3. Byrnes, D., Masterson, C. H., Brady, J., Alagesan, S., Gonzalez, H. E., McCarthy, S. D., ... & Laffey, J. G. (2023). Differential Effects of Cytokine Versus Hypoxic Preconditioning of Human Mesenchymal Stromal Cells in Pulmonary Sepsis Induced by Antimicrobial-Resistant *Klebsiella pneumoniae*. *Pharmaceuticals*, 16(2), 149.
4. Daley, G. Q. (2012). The promise and perils of stem cell therapeutics. *Cell stem cell*, 10(6), 740-749.

5. Das, M., Mayilsamy, K., Mohapatra, S. S., & Mohapatra, S. (2019). Mesenchymal stem cell therapy for the treatment of traumatic brain injury: progress and prospects. *Reviews in the Neurosciences*, 30(8), 839-855.
6. Dameshghi, S., Zavarán-Hosseini, A., Soudi, S., Shirazi, F. J., Nojehdehi, S., & Hashemi, S. M. (2016). Mesenchymal stem cells alter macrophage immune responses to *Leishmania major* infection in both susceptible and resistance mice. *Immunology letters*, 170, 15-26.
7. Do, T., Synan, L., Ali, G., & Gappa-Fahlenkamp, H. (2022). 3D tissue-engineered lung models to study immune responses following viral infections of the small airways. *Stem Cell Research & Therapy*, 13(1), 1-13.
8. Duelen, R., Corvelyn, M., Tortorella, I., Leonardi, L., Chai, Y. C., & Sampaolesi, M. (2019). Medicinal biotechnology for disease modeling, clinical therapy, and drug discovery and development. *Introduction to Biotech Entrepreneurship: From Idea to Business: A European Perspective*, 89-128.
9. Ekah, J. A. (2020). the hyperendemic classification of HIV/AIDS in sub-saharan africa: reasons, impacts, and response mechanisms. *ilorin journal of sociology*, 53.
10. English, K., French, A., & Wood, K. J. (2010). Mesenchymal stromal cells: facilitators of successful transplantation? *Cell stem cell*, 7(4), 431-442.
11. Fears, R., Akutsu, H., Alentajan-Aleta, L. T., Caicedo, A., De Carvalho, A. C. C., Čolić, M., ... & Ter Meulen, V. (2021). Inclusivity and diversity: Integrating international perspectives on stem cell challenges and potential. *Stem Cell Reports*, 16(8), 1847-1852.
12. Gorman, E., Millar, J., McAuley, D., & O’Kane, C. (2021). Mesenchymal stromal cells for acute respiratory distress syndrome (ARDS), sepsis, and COVID-19 infection: optimizing the therapeutic potential. *Expert review of respiratory medicine*, 15(3), 301-324.
13. Guerra, C. A., Donfack, O. T., Vaz, L. M., Nlang, J. A. M., Nchama, L. O. N., Eyono, J. N. M., ... & García, G. A. (2020). Malaria vector control in sub-Saharan Africa in the time of COVID-19: no room for complacency. *BMJ global health*, 5(9), e003880.
14. Guilliams, M., Lambrecht, B. N., & Hammad, H. (2013). Division of labour between lung dendritic cells and macrophages in the defense against pulmonary infections. *Mucosal immunology*, 6(3), 464-473.
15. Hafalla, J. C., Silvie, O., & Matuschewski, K. (2011). Cell biology and immunology of malaria. *Immunological reviews*, 240(1), 297-316.
16. Helleberg, M., Goka, B. Q., Akanmori, B. D., Obeng-Adjei, G., Rodriques, O., & Kurtzhals, J. A. (2005). Bone marrow suppression and severe anaemia associated with persistent *Plasmodium falciparum* infection in African children with microscopically undetectable parasitaemia. *Malaria Journal*, 4(1), 1-7.
17. Huang, B., Tabata, Y., & Gao, J. Q. (2012). Mesenchymal stem cells as therapeutic agents and potential targeted gene delivery vehicle for brain diseases. *Journal of controlled release*, 162(2), 464-473.
18. Hütter, G., Nowak, D., Mossner, M., Ganepola, S., Müßig, A., Allers, K., ... & Thiel, E. (2009). Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *New England Journal of Medicine*, 360(7), 692-698.
19. Joshi, L., Chelluri, L. K., & Gaddam, S. (2015). Mesenchymal stromal cell therapy in MDR/XDR tuberculosis: a concise review. *Archivum immunologiae et therapiae experimentalis*, 63, 427-433.
20. Kalkal, M., Tiwari, M., Thakur, R. S., Awasthi, V., Pande, V., Chattopadhyay, D., & Das, J. (2021). Mesenchymal stem cells: a novel therapeutic approach to enhance protective immunomodulation and erythropoietic recovery in Malaria. *Stem Cell Reviews and Reports*, 17(6), 1993-2002.
21. Laxminarayan, R., Matsoso, P., Pant, S., Brower, C., Røttingen, J. A., Klugman, K., & Davies, S. (2016). Access to effective antimicrobials: a worldwide challenge. *The Lancet*, 387(10014), 168-175.
22. Leri, A., Kajstura, J. A. N., & Anversa, P. (2005). Cardiac stem cells and mechanisms of myocardial regeneration. *Physiological reviews*, 85(4), 1373-1416.
23. Li, S., Zhu, H., Zhao, M., Liu, W., Wang, L., Zhu, B., ... & Jiang, X. (2022). When stem cells meet COVID-19: recent advances, challenges and future perspectives. *Stem Cell Research & Therapy*, 13(1), 1-16.
24. Mendicino, M., Bailey, A. M., Wonnacott, K., Puri, R. K., & Bauer, S. R. (2014). MSC-based product characterization for clinical trials: an FDA perspective. *Cell stem cell*, 14(2), 141-145.
25. Murry, C. E., & Keller, G. (2008). Differentiation of embryonic stem cells to clinically relevant populations: lessons from embryonic development. *Cell*, 132(4), 661-680.
26. Scott, C. W., Peters, M. F., & Dragan, Y. P. (2013). Human induced pluripotent stem cells and their use in drug discovery for toxicity testing. *Toxicology letters*, 219(1), 49-58.
27. Sivaraman, M. A. F. (2019). Ethical guiding principles of “do no harm” and the “intention to save lives” in relation to human embryonic stem cell research: finding common ground between religious views and principles of medical ethics. *Asian Bioethics Review*, 11(4), 409-435.

28. Teoh, H. K., & Cheong, S. K. (2012). Induced pluripotent stem cells in research and therapy. *The Malaysian journal of pathology*, 34(1), 1.
29. Trounson, A., & McDonald, C. (2015). Stem cell therapies in clinical trials: progress and challenges. *Cell stem cell*, 17(1), 11-22.
30. Wang, L. T., Liu, K. J., Sytwu, H. K., Yen, M. L., & Yen, B. L. (2021). Advances in mesenchymal stem cell therapy for immune and inflammatory diseases: Use of cell-free products and human pluripotent stem cell-derived mesenchymal stem cells. *Stem cells translational medicine*, 10(9), 1288-1303.
31. Wynn, T. A., Chawla, A., & Pollard, J. W. (2013). Macrophage biology in development, homeostasis and disease. *Nature*, 496(7446), 445-455.
32. Zheng, G., Ge, M., Qiu, G., Shu, Q., & Xu, J. (2015). Mesenchymal stromal cells affect disease outcomes via macrophage polarization. *Stem cells international*, 2015.
33. Zuk, P. A. (2010). The adipose-derived stem cell: looking back and looking ahead. *Molecular biology of the cell*, 21(11), 1783-1787.