BSS
BIOLOGY STUDENT SOCIETY

ROOTS

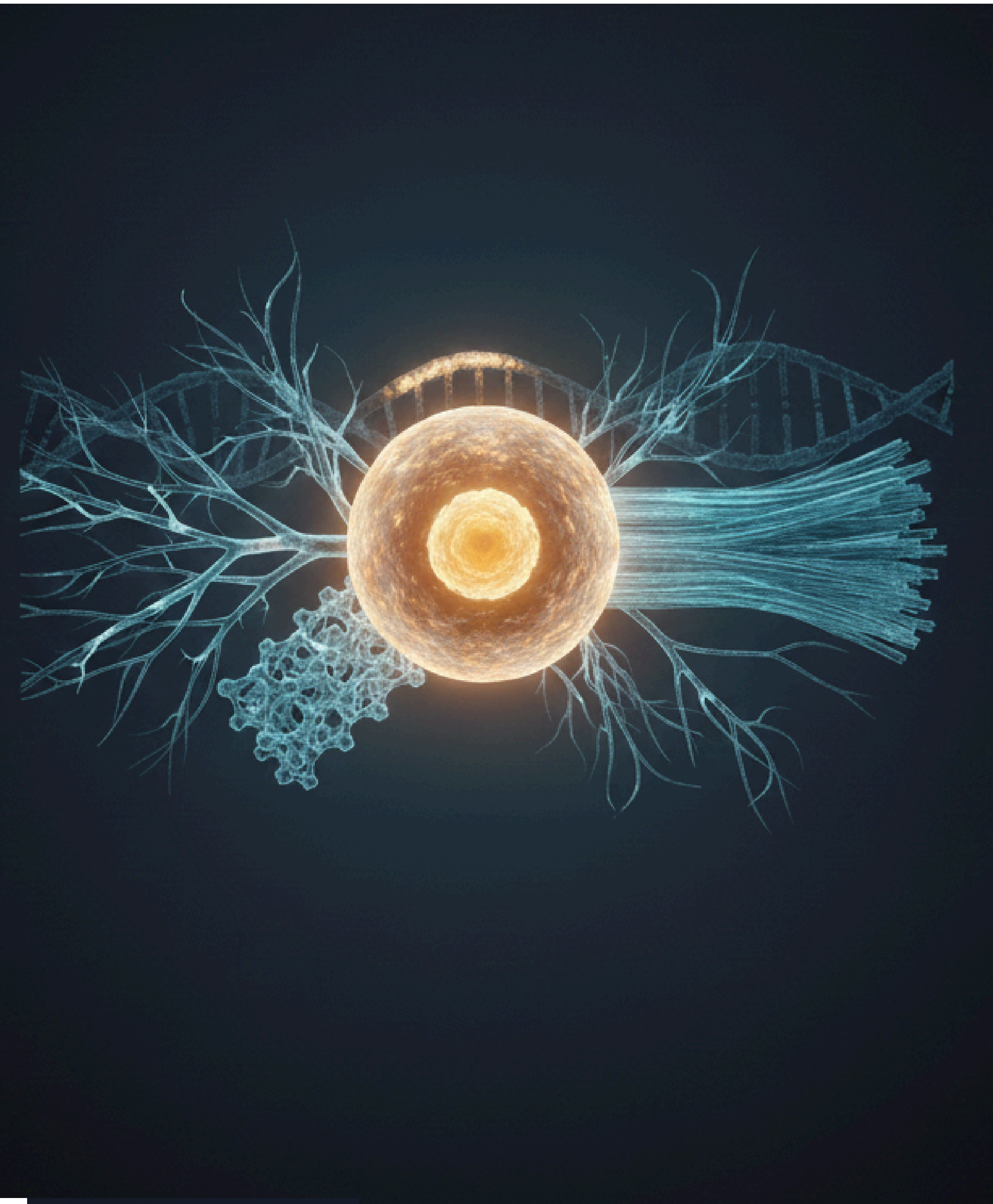
Research Outreach and Opportunities Through Science

GSR
Beirut, LB

Induced Pluripotent Stem Cells (iPSCs): Understanding the Challenges of Regenerative Medicine

Ahmad Miski

03/01/2026



Introduction

Imagine a future where a patient's crushed bones, dead nerves, and a degenerating retina can all be regenerated using their own skin cells. This imaginary scenario is becoming real with induced pluripotent stem cells (iPSCs). First, let's start by defining what stem cells and iPSCs are. Stem cells are unspecialized cells with two main roles: self-renewal to make more stem cells, and differentiation into specialized cells. During early embryonic development, stem cells play a crucial role by specializing into all types of tissues and organs, while in adults they play an equally important role in replacing damaged and dead cells.

Traditionally, stem cells have been used in regenerative medicine to restore or replace damaged tissues, most notably in bone marrow transplants to cure some blood and immune related diseases. However, the potential of stem cells is limited in traditional techniques, as not all types of stem cells can specialize into all types of tissues. There are types of stem cells that can bypass this problem, like human embryonic stem cells, but they are not used due to ethical concerns. iPSCs have the same developmental and regenerative potential as human embryonic pluripotent stem cells but bypass the ethical problems. Still, culturing iPSCs often causes mutations that later form tumors, which pose a significant barrier in the way of clinical application. This research aims to understand why iPSCs suffer a great deal of mutations and how to reduce them. Understanding these mutations is critical to the transition of iPSCs into clinical use.

Background

Stem cells gradually get specialized by passing through 4 stages or types before becoming fully specialized:

1. **Totipotent stem cells (TSCs)**, which are only found in the zygote and can differentiate into any type of cell in the body, including the placenta.
2. **Pluripotent stem cells (PSCs)**, which are found in the embryo and can differentiate into any type of cell in the body, excluding the placenta.
3. **Multipotent stem cells (MSCs)**, which are found in the adult body and can differentiate into multiple yet limited types of cells. An example is Hematopoietic Stem Cells (HSCs), which are found in the bone marrow and can develop into all blood cells.
4. **Unipotent stem cells (USCs)**, which are found in the adult body and can differentiate into only 1 type of cell. An example is muscle satellite cells which self-renew and only differentiate into mature myocytes

Stem cells have a substantial regenerative ability, and this is seen clinically in cases such as hematopoietic stem cells (HSCs). These are used in hematopoietic stem cell transplantation (HSCT), also known as bone marrow transplantation, as HSCs can differentiate into any type of

blood cell, or cells from the immune system. Human Embryonic Stem Cells (hESCs) are a type of pluripotent stem cells that showed success in initial clinical trials, yet they have two major problems that stand in the way of clinical application. First, hESCs can only be obtained from human embryos, which is a huge ethical problem. Second, the hESCs do not have the same HLA as the patient, therefore, the patient's body could reject them after transplantation. So, using hESCs is not a solution.

iPSCs offer a solution to both the ethical problem and the immune rejection of implantation, as skin cells can be taken from the patient and turned into iPSCs, and then re-differentiated into whichever type of cell that the patient needs by passing the transplantation problem. Yet iPSCs bring in a myriad of problems on their own, as when put into clinical testing iPSCs start developing mutations which may later lead to tumors. Thus, multiple studies in which iPSCs were used for therapeutic goals have had to stop while incomplete to ensure the patients safety [9,10].

Traditional uses of stem cell therapies

Stem cells have proved they can be helpful clinically, as seen in the most widely used stem cell therapy, i.e. hematopoietic stem cell transplantation (HSCT). HSCT is used as a cure for many illnesses such as blood cancers, inherited blood disorders (e.g., sickle cell anemia), and some immune system disorders (e.g., Severe combined immunodeficiency (SCID)). The process of HSCT starts by collecting hematopoietic stem and progenitor cells (HSPCs), either directly from the bone marrow, or from the blood stream in a process known as "apheresis". Afterwards, the cells are prepared for transplantation, then transplanted into the patient. Once in the patient's body, these cells migrate to the bone marrow, where they are engrafted and start producing new healthy blood and immune system cells [3].

Another type of stem cells used to treat patients is Mesenchymal stem cells (MSCs). MSCs are multipotent progenitor cells that can be derived from the bone marrow, umbilical cord, and adipose tissue. They can also differentiate into diverse types of mesenchymal cell lineages, like bone, cartilage, and fat [4]. Moreover, MSCs' therapeutic potential lies in their ability to utilize several paracrine messengers, instead of being fully engrafted, promoting tissue repair, angiogenesis, and modulation of inflammation [5]. MSCs have been approved for use against diseases such as steroid-refractory acute graft-versus-host disease and complex perianal fistulas in Crohn's disease. They are also being tested against many other conditions, such as heart diseases, strokes, spinal cord injuries, liver damage, osteoarthritis, chronic wounds, and severe lung problems like ARDS and COVID-19 [4,6].

Despite their notable capabilities, MSCs' effectiveness can vary depending on both the patient and donor's age and health. To add, since they are not fully engrafted, they do not last very

long in the patient's body, but also present some risks such as cell aging, fibrosis, or rarely, genetic changes [6,7].

The moment everything changed

The field changed forever in 2006, when Japanese scientist Dr. Shinya Yamanaka achieved something that was previously thought to be impossible when he successfully reprogrammed mouse skin cells to become pluripotent stem cells. This new type of stem cells was called induced pluripotent stem cells (iPSCs) [1]. He did so by introducing four transcription factors to mouse skin cells, and by doing so, the mouse skin cell grew like and expressed the same gene markers as embryonic stem cells; it essentially got turned back from skin cells into stem cells. Since then, little research has been done on them, merely 62 studies to be exact, only 19 of which are clinical trials [2].

So, how can a few transcription factors turn back the cellular clock? When these transcription factors are introduced to a specialized cell, they bind to the DNA and activate a few genes that are usually only active in ESCs. These genes then activate other genes related to pluripotency, which, in turn, activate other genes and so on, until all the genes related to the pluripotency of the cell are activated, and the cell returns to being a PSC [9].

So far, most of the research done on iPSCs has been dedicated to understanding how diseases alter human physiology. Traditionally, scientists have tried to understand diseases either in vitro, or through animal models which include small animals like rats, or larger animals like dogs or non-human primates. These research designs rely on mimicking the human body, and, eventually, being able to develop cures for diseases. Yet, due to physiological and genetic differences between animals and humans, these models usually could not accurately replicate what would happen in the human body. Nowadays, iPSCs are used for understanding various human diseases, such as diabetic cardiomyopathy and catecholaminergic polymorphic ventricular tachycardia [9].

The first time iPSCs were used for treating a human was done only 4 days after a health-ministry committee gave permission for the operation to go ahead [11]. In 2014, ophthalmologist Dr. Yasuo Kurimoto of the Kobe City Medical Center General Hospital had a patient in her 70s who suffered from age-related macular degeneration, a common eye disease that may lead to blindness. Dr. Kurimoto saw this as a golden opportunity to trial iPSCs on humans. First, he started by doing safety studies on both mice and monkeys to ensure that he can safely do the same procedure on a human. After the animal tests found that iPSCs' transplants were not rejected and did not lead to the growth of tumors, he got the clearance from the Ministry of Health to do the human trial. After that, Dr. Masayo Takahashi of the RIKEN Foundation for Biomedical Research and Innovation reprogrammed skin cells from the patient to produce iPSCs. Then, she

differentiated those cells into retinal pigment epithelial cells and Dr. Kurimoto implanted a 1.3 by 3.0-millimeter sheet of retinal pigment epithelium cells into the patient's eyes [11].

Fortunately, the surgery yielded good results, as RIKEN reported that the patient had no effusive bleeding or other serious problems after the surgery. It is important to note that the goal of this surgery was not to reverse the effects of the disease on the patient, but to stop further damage to the retina [11]. Four years later, it was reported that the iPSC derived sheet of retinal pigment epithelial cells remained alive under the retina with slight expansion of the pigmented area. Moreover, the patient's vision remained stable and did not require any further medications, and there were no adverse events like tumor formation to report [16].

Current uses of iPSCs

While their clinical use is still limited, iPSCs are currently being used in many ways to contribute to the healthcare system. The most common way that iPSCs are being used is for disease modeling. The major advantage that they give us is being taken from human cells, instead of animal cells, thus having the ability to simulate what would specifically happen to a human cell [17]. Since animal cells cannot always simulate what would happen to a human cell, for example, neurological diseases that do not have a specific genetic cause are much harder to study through animal cells, due to the high complexity of the human brain compared to animal brains. These limitations have hindered research around neurological diseases in the past, but nowadays, iPSCs solve that problem [17]. Some of the diseases that have been modeled using iPSCs are: Long QT Syndrome (LQTS), Dilated Cardiomyopathy (DCM), and leopard syndrome [20].

The second way that iPSCs are being used today is drug modeling and toxicity studies. Between 2009 and 2018, the average cost to make a new drug and bring it into the market was around 985 million USD, as, even after rigorous testing and animal trials, 90% of the drugs would fail the clinical test [20]. This happens because pre-clinical studies on the effectiveness and toxicity of a drug are done on animal subjects, and human specific responses may not manifest in the animals, which leads to withdrawals of the drugs late in the development process, thus increasing the cost of drug production significantly [17]. Here is where iPSCs step in as a complementary tool to traditional testing methods to ensure that the drug induces the cellular response it is designed to and that it is not toxic to human cells [17].

One more way that iPSCs are used is in cell replacement and regenerative therapy. One example of this is the case mentioned earlier of iPSCs being implanted into a patient’s eyes, which stopped the spreading of AMD in the patient’s eye. Another example of iPSCs being used in cell replacement therapy is to treat heart failure following a myocardial infarction (heart attack) [21], as myocardial infarctions are responsible for 25% of all heart failure cases [21]. Moreover, myocardial infarction survivors often experience symptoms after the heart attack due to the death

of some heart muscle cells. These symptoms include breathlessness, arrhythmia, chest pain, dizziness, and fatigue [22]. This happens because existing therapies for myocardial infarction reduce mortality rates, yet many patients progress to advanced heart failure and death [21]. Thus, a study was done to assess the safety of transplanting iPSCs in patients who suffer from ischemic cardiomyopathy, i.e. weakening of the heart muscle due to long-term poor blood flow, often following one or more myocardial infarctions. Transplantation of clinical grade iPSCs differentiated into myocardial cells into the hearts of 3 patients was done, and immunosuppressants were administered for 3 months. Then, a one-year follow-up was recorded, where it was revealed that none of the patients had any serious adverse events related to stem cell transplantation, such as tumor formation or malignant arrhythmia. This shows that the transplantation of the allogenic iPSCs was a success. Furthermore, all the patients reported symptomatic improvement, and even better, 2 out of the 3 patients reported gains in cardiac function [23].

Challenges in iPSC therapy

One of the most prevailing challenges that iPSCs are facing is the large number of mutations that iPSCs accumulate [13]. This was first seen with the same researchers and doctors that did the first iPSC transplantation into a patient suffering from AMD. When they tried to recreate the same treatment for another patient in 2015, unlike the first patient's iPSCs, this patient's iPSCs developed mutations in 3 different genes. Even though there was no evidence to suggest that cancer has developed in these cells, the fact that the iPSCs that were meant for surgery developed mutations led to major concerns from the scientific and medical communities. Thus, the surgery did not get the approval from the Japanese ministry of health to be done [12]. Moreover, multiple studies show that there is a good chance that iPSCs acquire an abnormal number of chromosomes while under in vitro development [14]. It is important to note that PSCs have an abnormally high number of mutations, many of which can cause tumorigenicity [13], especially when compared to other types of stem cells like hESCs [14]. One reason for this large number of mutations, as the inventor of iPSCs points out, is that the 4 transcription factors used to activate pluripotency genes are associated with tumorigenicity [19].

Another barrier that stands in the way of iPSCs is their cost and time to develop. As for every patient that needs to undergo iPSC treatment, multiple new lines of iPSCs have to be created from the patient's skin cells and then differentiated and tested for mutations and safety, which can take up to 4 months before any treatment can be administered [12]. Not to mention, it is estimated that the safety testing cost can reach half a million dollars per patient, and when counting for the maintenance and equipment costs, a single autologous treatment could cost up to a million dollars [12]. Yet, it is important to note that this cost may be inflated when the treatment is still in its first phase of implementation, and once we reach later stages, the cost should go down significantly as researchers will look for ways to reduce the treatment cost [12]. Additionally, not only is the

treatment costly, but starting iPSC research is as well. In general, generating and validating a research-grade iPSC line costs approximately $10,000–$25,000, and the entire process from patient recruitment to final characterization can take 6 to 9 months, with an additional 3 to 6 months required to produce large-scale iPSC derivatives [24].

Furthermore, despite iPSCs having pluripotency and the ability to differentiate into all types of cells in the body, it is sometimes difficult to fully complete these differentiations. Even when using identical protocols to differentiate iPSCs, iPSCs coming from different people can display huge differences in how quickly and how well they differentiate [25,26]. For example, efforts to differentiate iPSCs into cardiomyocytes (heart cells) found that when the concentration of cells during differentiation was changed, it caused a variation in the degree of differentiation of the cells in different lines. Another study that tried to grow retinal organoids from iPSC lines acquired from patients found out that, even though all the cell lines looked similar before differentiation, some cell lines yielded better results than others. Differences in gene expression were seen as soon as one week after the start of the differentiation process, and these differences managed to predict which cells would develop later on [27]. Therefore, new research is trying to understand how differences in cell markers early on in iPSC development of different cell lines help predict the success of differentiation. This helps scientists avoid putting time and effort into cell lines that will not result in successful differentiation [28]. Overall, these challenges must be addressed before iPSCs can reach their full potential in clinical applications.

Emerging strategies to overcome the challenges

Given the major challenges and obstacles that rise alongside bringing iPSCs into clinical use, multiple strategies have been developed to bypass, avoid, and solve current problems. First, scientists are switching from integrating reprogramming methods to non-integrating reprogramming methods to induce pluripotency. Integrating reprogramming methods, like retroviruses and lentiviruses, insert the reprogramming genes directly into the genome of the cell. This process can disrupt important genes and regulatory regions, which leads to a high chance of mutations in iPSCs. Non-integrating reprogramming methods, such as Sendai virus, episomal plasmids, and mRNA-based delivery, introduce reprogramming factors without changing the genome, allowing the cells to return to a pluripotent state without developing the risk of mutations [29].

Second, the rise in automation has significantly decreased the cost of iPSC culturing and reprogramming. One example of this is the Cell X robot platform, which has reduced human error, differentiation time, and the number of unnecessary cell lines. The Cell X robot platform has achieved this by automating generation, cloning, and differentiation of iPSCs under cGMP compatible conditions [30]. Another of these is the differentiation and culture of iPSCs into retinal

pigment epithelium (RPE) cells via TECAN robots, increasing the number of cells done at a time significantly, and making reproducing the process much easier and more precise [31].

However, the most important way of fighting the challenges that face iPSCs is allogenic iPSCs banks. So far, this article has only discussed the autologous iPSC treatments, which refers to iPSCs taken from the patient and implanted into the body of the same patient. Still, this treatment is very expensive and takes a lot of time. So, scientists all over the world are starting to take cells from healthy human beings and turn them into iPSCs and store them in banks for use on patients. Some of the iPSC banks in the world include the European Bank for induced pluripotent stem cells (EBiSC) established in 2014, Center for iPS cell research and application (iCeMS), Kyoto University established in 2010, California Institute for Regenerative Medicine (CIRM) established in 2008, and King Abdullah International Medical Research Center (KAIMRC) also established in 2008 [24,33,34]. These banks serve to collect iPSCs from people termed 'super donors', as these people have an HLA that is highly common in the population, therefore reducing the risk of the patient's immune system rejecting the iPSCs. Then, differentiated iPSCs from 'super donors' are ready to treat patients in a process called iPSC allogenic transplantation [34]. This process has its disadvantages, as they eliminate one of the advantages that iPSCs have, which is having the same genetic material as the patient. Therefore, immunosuppressant therapy would have to be given to patients after allogenic iPSC treatment. Yet, the advantages far outweigh the disadvantages, as iPSC banks allow for iPSCs taken from a small number of the population to be able to match the HLA of a large number of the population. For example, it is estimated that about 200 such iPSC lines could cover at least 90% of the U.S. and/or European population, and about 90 to 100 such iPSC lines could cover at least 90% of the Japanese population [34]. Moreover, these banks ensure that all the iPSC lines ready for transplantation are tested for genetic stability, tumorigenicity, and differentiation potential [24]. Additionally, iPSC banks increase accessibility to iPSC therapy, as new lines of cells don't have to be made for every patient, reducing cost, time, and the number of mutations in the process. Currently, iPSC banks are trying to increase the diversity of HLA types to increase accessibility for the population [24].

Conclusion

To conclude, Induced Pluripotent Stem Cells have revolutionized regenerative medicine by offering a new way of making patient-specific pluripotent stem cells without the ethical concerns associated with human embryonic stem cells. However, they are facing challenges that include mutation accumulation, tumorigenicity, high cost, and variability in differentiation that plague their clinical application. Therefore, emerging strategies like the use of non-integrating methods, automation of culturing and differentiation as well as the establishment of iPSC banks all around the globe have started to try and overcome the challenges. Specifically, iPSC banks stand out as the most promising way to make iPSCs more accessible and cost efficient with less

mutations, as they derive iPSCs from the cells of “super donors” that have a common HLA in the population. As time progresses, iPSC banks will acquire more diverse HLAs from different donors, consequently increasing the number of people who can benefit from them. With continued research standardization and improved iPSC banking, induced pluripotent stem cells are likely to reach their full potential and redefine the future of regenerative medicine.

References

1. Takahashi, K., & Yamanaka, S. (2006). *Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors*. Cell, 126(4), 663–676. https://www.cell.com/cell/fulltext/S0092-8674(06)00976-7?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867406009767%3Fshowall%3Dtrue
2. Kim, J.Y., Nam, Y., Rim, Y.A. *et al.* (2022) Review of the Current Trends in Clinical Trials Involving Induced Pluripotent Stem Cells. *Stem Cell Rev and Rep* 18, 142–154. https://link.springer.com/article/10.1007/s12015-021-10262-3
3. Aljagthmi, A. A., & Abdel-Aziz, A. K. (2025). Hematopoietic stem cells: Understanding the mechanisms to unleash the therapeutic potential of hematopoietic stem cell transplantation. *Stem Cell Research & Therapy, 16*(1), 60. https://doi.org/10.1186/s13287-024-04126-z
4. Hoang, Duc M., Phuong T. Pham, Trung Q. Bach, Anh T. L. Ngo, Quyen T. Nguyen, Trang T. K. Phan, Giang H. Nguyen, Phuong T. T. Le, Van T. Hoang, Nicholas R. Forsyth, Michael Heke, … Liem Thanh Nguyen. 2022. "Stem Cell-Based Therapy for Human Diseases." *Signal Transduction and Targeted Therapy* 7 (272). August 6, 2022. https://doi.org/10.1038/s41392-022-01134-4.
5. Merimi, M., et al. (2021). *The therapeutic potential of mesenchymal stromal cells*. Frontiers in Cell and Developmental Biology, 9, 673. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8416483/
6. Zaripova, S., et al. (2023). *Mesenchymal stem cells in autoimmune disease: Therapeutic perspectives and challenges*. International Journal of Molecular Sciences, 24(22), 16040. https://www.mdpi.com/1422-0067/24/22/16040
7. Sharma, R., et al. (2021). *Review of the potential of mesenchymal stem cells for the treatment of infectious diseases*. Frontiers in Immunology, 12, 624458. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8246252/
8. da Cruz, L., et al. (2018). Phase 1 clinical study of an embryonic stem cell-derived retinal pigment epithelium patch in age-related macular degeneration. Nature Biotechnology, 36(4), 328–337. https://www.nature.com/articles/nbt.4114
9. Sayed, N., Liu, C., & Wu, J. C. (2016). Translation of Human-Induced Pluripotent Stem Cells: From Clinical Trial in a Dish to Precision Medicine. Journal of the American College of Cardiology, 67(18), 2161–2176. https://doi.org/10.1016/j.jacc.2016.01.083
10. Yoshihara, M., Hayashizaki, Y. & Murakawa, Y. Genomic Instability of iPSCs: Challenges Towards Their Clinical Applications. Stem Cell Rev and Rep 13, 7–16 (2017). https://doi.org/10.1007/s12015-016-9680-6
11. Cyranoski, D. Japanese woman is first recipient of next-generation stem cells. *Nature* (2014). https://doi.org/10.1038/nature.2014.15915

12. Chakradhar, S. An eye to the future: Researchers debate best path for stem cell–derived therapies. *Nat Med* 22, 116–119 (2016). https://doi.org/10.1038/nm0216-116
13. Garber, K. RIKEN suspends first clinical trial involving induced pluripotent stem cells. *Nat Biotechnol* 33, 890–891 (2015). https://doi.org/10.1038/nbt0915-890
14. Pera, M. The dark side of induced pluripotency. *Nature* 471, 46–47 (2011). https://doi.org/10.1038/471046a
15. Muers, M. Reprogramming's unintended consequences. *Nat Rev Genet* 12, 230 (2011). https://doi.org/10.1038/nrg2975
16. Takagi, S., Mandai, M., Gocho, K., Hirami, Y., Yamamoto, M., Fujihara, M., Sugita, S., Kurimoto, Y., & Takahashi, M. (2019). Evaluation of Transplanted Autologous Induced Pluripotent Stem Cell-Derived Retinal Pigment Epithelium in Exudative Age-Related Macular Degeneration. *Ophthalmology. Retina*, *3*(10), 850–859. https://doi.org/10.1016/j.oret.2019.04.021
17. Cerneckis, J., Cai, H. & Shi, Y. Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications. *Sig Transduct Target Ther* 9, 112 (2024). https://doi.org/10.1038/s41392-024-01809-0
18. Mullard, A. (2023). Disease models get real. Nature Reviews Drug Discovery, 22(1), 3–5. *doi: https://doi.org/10.1038/d41573-023-00008-w*
19. Yamanaka, S. (2020). Pluripotent stem cell–based cell therapy—Promise and challenges. *Cell Stem Cell, 27*(4), 523–531. https://doi.org/10.1016/j.stem.2020.09.014
20. Nicholson, M. W., Ting, C.-Y., Chan, D. Z. H., Cheng, Y.-C., Lee, Y.-C., Hsu, C.-C., Huang, C.-Y., & Hsieh, P. C. H. (2022). Utility of iPSC-Derived Cells for Disease Modeling, Drug Development, and Cell Therapy. Cells, 11(11), 1853. https://doi.org/10.3390/cells11111853
21. Sugiura T, Shahannaz DC, Ferrell BE. Current Status of Cardiac Regenerative Therapy Using Induced Pluripotent Stem Cells. International Journal of Molecular Sciences. 2024; 25(11):5772. https://doi.org/10.3390/ijms25115772
22. NHS. (2023, July 13). Complications - Heart attack. NHS. https://www.nhs.uk/conditions/heart-attack/complications/
23. Kawamura, T., Ito, Y., Ito, E., Takeda, M., Mikami, T., Taguchi, T., Mochizuki-Oda, N., Sasai, M., Shimamoto, T., Nitta, Y., Yoshioka, D., Kawamura, M., Kawamura, A., Misumi, Y., Sakata, Y., Sawa, Y., & Miyagawa, S. (2023). Safety confirmation of induced pluripotent stem cell-derived cardiomyocyte patch transplantation for ischemic cardiomyopathy: first three case reports. Frontiers in cardiovascular medicine, 10, 1182209. https://doi.org/10.3389/fcvm.2023.1182209
24. Huang, CY., Liu, CL., Ting, CY. *et al.* Human iPSC banking: barriers and opportunities. *J Biomed Sci* 26, 87 (2019). https://doi.org/10.1186/s12929-019-0578-x
25. Tereshchenko Y, Petkov SG, Behr R. The Efficiency of In Vitro Differentiation of Primate iPSCs into Cardiomyocytes Depending on Their Cell Seeding Density and Cell

Line Specificity. International Journal of Molecular Sciences. 2024; 25(15):8449. https://doi.org/10.3390/ijms25158449

26. Nath, S. C., Menendez, L., & Friedrich Ben-Nun, I. (2023). Overcoming the Variability of iPSCs in the Manufacturing of Cell-Based Therapies. International Journal of Molecular Sciences, 24(23), 16929. https://doi.org/10.3390/ijms242316929
27. Cooke, J. A., Voigt, A. P., Collingwood, M. A., Stone, N. E., Whitmore, S. S., DeLuca, A. P., Burnight, E. R., Anfinson, K. R., Vakulskas, C. A., Reutzel, A. J., Daggett, H. T., Andorf, J. L., Stone, E. M., Mullins, R. F., & Tucker, B. A. (2023). Propensity of Patient-Derived iPSCs for Retinal Differentiation: Implications for Autologous Cell Replacement. Stem cells translational medicine, 12(6), 365–378. https://doi.org/10.1093/stcltm/szad028
28. Guo, N. N., Liu, L. P., Zhang, Y. X., Cai, Y. T., Guo, Y., Zheng, Y. W., & Li, Y. M. (2019). Early prediction of the differentiation potential during the formation of human iPSC-derived embryoid bodies. *Biochemical and biophysical research communications*, *516*(3), 673–679. https://doi.org/10.1016/j.bbrc.2019.06.081
29. Pozner, T., Grandizio, C., Mitchell, M. W., Turan, N., & Scheinfeldt, L. (2025). Human iPSC Reprogramming Success: The Impact of Approaches and Source Materials. Stem cells international, 2025, 2223645. https://doi.org/10.1155/sci/2223645
30. Bohrer, L.R., Stone, N.E., Mullin, N.K. *et al.* Automating iPSC generation to enable autologous photoreceptor cell replacement therapy. *J Transl Med* 21, 161 (2023). https://doi.org/10.1186/s12967-023-03966-2
31. Truong, V., Viken, K., Geng, Z., Barkan, S., Johnson, B., Ebeling, M. C., Montezuma, S. R., Ferrington, D. A., & Dutton, J. R. (2021). Automating Human Induced Pluripotent Stem Cell Culture and Differentiation of iPSC-Derived Retinal Pigment Epithelium for Personalized Drug Testing. SLAS technology, 26(3), 287–299. https://doi.org/10.1177/2472630320972110
32. Coriell Institute for Medical Research. (2008). *Coriell Stem Cell Biobank*. https://www.coriell.org/0/sections/collections/cscb/default.aspx
33. King Abdullah International Medical Research Center. (n.d.). *The Saudi Bank of Induced Pluripotent Stem Cells*. https://getkaimrcipsbank.org/
34. The Regents of the University of California. (2018). *HLA-indexed repository of iPSCs and iPSC-derived stem cells, and related systems and methods* (PCT Patent No. WO2018170046A1). https://patents.google.com/patent/WO2018170046A1/en