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Induced Pluripotent Stem Cells (IPSCS) in Regenerative Medicine: Advances, Applications and Future Directions

Dawn V Tomy*, Ashly Merin George[1], Ashok Jacob Mathews[2], Harsha M[3]
MVM College of Pharmacy*[,1,3], St.Claret College[2] Bengaluru, Karnataka, India
*Email: dawnvtomy@gmail.com

ABSTRACT
Induced pluripotent stem cells (iPSCs) are reprogrammed adult cells that attain a pluripotent state, enabling their differentiation into nearly any cell type in the body. This innovative technology has transformed regenerative medicine, providing a versatile platform for drug development, transplantation, and disease modeling. iPSCs enhance drug discovery and facilitate personalized and regenerative treatments, offering significant potential for advancing therapeutic strategies. This paper discusses the latest advancements in iPSCs technology, its applications in treating various diseases, challenges in clinical translation and future perspectives in regenerative medicine.
Keywords: *Drug development, immune rejection, iPSCs, personalised medicine, regenerative treatment, stem cells.*

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INTRODUCTION

Induced pluripotent stem cells (iPSCs) are adult cells reprogrammed to a pluripotent state, allowing them to develop into almost any cell type in the body, similar to embryonic stem cells and they have revolutionized the field of regenerative medicine, offering a versatile platform for disease modelling, drug discovery and therapeutic applications. This reprogramming is achieved by introducing specific genes or factors into differentiated cells.

iPSCs provides a platform for drug development, allowing researchers to test new medications on specific cell types derived from iPSCs to evaluate their effectiveness and safety. In regenerative medicine, iPSCs hold the potential to generate cells and tissues for transplantation, offering hope for treating conditions like heart disease, Parkinson's disease and spinal cord injuries. Additionally, by creating iPSCs from individual patients, researchers can develop personalized therapies tailored to the unique genetic profiles of their diseases. Overall, iPSCs represent a major advancement in stem cell research, with the potential to revolutionize understanding of diseases, enhance drug discovery and enable personalized and regenerative treatments [1].

This review highlights the latest advancements in iPSCs technology, its applications in treating various diseases, challenges in clinical translation and future perspectives in regenerative medicine.

MECHANISMS OF IPSCS GENERATION:

The generation of induced pluripotent stem cells (iPSCs) involves reprogramming somatic cells to a pluripotent state using specific reprogramming factors.

Reprogramming Factors: The most well-known set of these factors are the Yamanaka factors: Oct4, Sox2, Klf4 and c-Myc.

Yamanaka Factors:

Oct4 (Pou5f1): It is a transcription factor essential for maintaining the pluripotency and self-renewal of embryonic stem cells. It activates genes associated with pluripotency and represses differentiation genes.

Sox2: It works synergistically with Oct4 to regulate the expression of pluripotency genes. It binds to DNA and interacts with other transcription factors to activate pluripotency-associated genes and inhibit differentiation pathways.

Klf4: It is involved in promoting pluripotency and inhibiting differentiation. It also plays a role in cell cycle regulation and apoptosis. It activates pluripotency genes and works with other factors to remodel chromatin, making it more accessible for transcription.
c-Myc: It is a proto-oncogene that promotes cell proliferation and growth. c-Myc facilitates the rapid proliferation of cells and helps in the activation of pluripotency genes [2].
Alternative Reprogramming Factors:
Nanog and Lin28: Nanog is a key regulator of pluripotency, while Lin28 is involved in the regulation of microRNAs that control cell differentiation. These factors work by activating pluripotency genes and repressing differentiation pathways.
Esrrb: Esrrb (Estrogen-related receptor beta) can replace Klf4 in the reprogramming cocktail. Esrrb activates pluripotency genes and interacts with other transcription factors to maintain the undifferentiated state.
Glis1: Glis1 (GLI-similar 1) can enhance the efficiency of reprogramming when used in combination with the Yamanaka factors. It activates a distinct set of genes that promote reprogramming and pluripotency.
Techniques for iPSCs Generation: The generation of induced pluripotent stem cells (iPSCs) can be achieved through viral and non-viral methods.
Viral Methods:
Retroviral Vectors: Retroviruses integrate their genetic material into the host cell genome, ensuring stable expression of reprogramming factors which is having high efficiency in reprogramming. But these vectors having a risk of insertional mutagenesis.
Lentiviral Vectors: Similar to retroviruses but can infect both dividing and non-dividing cells. Lentiviral vectors having high efficiency and broader range of target cells, similar risks as retroviral vectors.
Non-Viral Methods:
Episomal Vectors: Plasmid vectors that do not integrate into the host genome but exist episomally. These vectors having reduced risk of insertional mutagenesis and lower efficiency compared to viral methods.
mRNA: Synthetic mRNA encoding reprogramming factors is introduced into cells. Comparing to other methods mRNA having o genomic integration, transient expression and reduced risk of mutagenesis. But it requires repeated transfection to maintain expression.
microRNA (miRNA): Small non-coding RNAs that regulate gene expression post-transcriptionally. miRNA can enhance reprogramming efficiency and reduce the need for multiple reprogramming factors. But delivery and stability can be challenging issue for miRNA.
Small Molecules: Chemical compounds that modulate signaling pathways to promote reprogramming. This molecule can replace some reprogramming factors and improve efficiency. But identifying an effective and safe small molecule can be a complex task.

APPLICATIONS OF IPSCS IN REGENERATIVE MEDICINE
Disease Modelling and Drug Discovery: Use of iPSCs derived from patients to model diseases *in vitro.* Induced pluripotent stem cells (iPSCs) have revolutionized regenerative medicine, particularly in disease modelling and drug discovery. Somatic cells (e.g., skin fibroblasts or blood cells) are collected from a patient and reprogrammed into iPSCs using reprogramming factors like Oct4, Sox2, Klf4 and c-Myc1. These iPSCs retain the genetic makeup of the patient, making them ideal for studying disease mechanisms and testing potential treatments.
Disease Modeling: iPSCs can be differentiated into various cell types affected by the patient's disease. For example, iPSCs from a patient with a neurodegenerative disorder can be differentiated into neurons to study disease pathology. Researchers can observe disease-specific cellular phenotypes, such as abnormal protein aggregation or altered cellular functions, providing insights into disease mechanisms
Drug Discovery and Testing:
High-Throughput Screening: Patient-specific iPSCs can be used to screen large libraries of compounds to identify potential drugs that can correct disease phenotypes. iPSCs allow for the assessment of drug toxicity on patient-specific cells, improving the safety profile of new drugs.
Cell Therapy and Tissue Engineering - iPSCs represent a ground-breaking approach in cell therapy and tissue engineering for cardiovascular diseases, enabling the regeneration of damaged heart tissue through patient-specific cardiomyocytes and innovative bioengineered patches, while addressing challenges such as cell integration and immune rejection.
Cardiovascular Diseases: iPSCs-derived cardiomyocytes offer innovative solutions for treating cardiovascular diseases, particularly heart disease, through cell therapies and tissue engineering. Traditional treatments manage symptoms but don't address cardiac tissue loss, highlighting the promise of stem cell-based therapies [5]. Induced pluripotent stem cells (iPSCs) are reprogrammed to an

embryonic-like state and can differentiate into any cell type, including cardiomyocytes. They offer an ethical and patient-specific alternative to embryonic stem cells. iPSCs-derived cardiomyocytes can regenerate lost muscle function by replacing damaged or dead cells. However, challenges include ensuring the survival, integration and proper function of transplanted cells, as well as addressing arrhythmias and immune rejection [6]. Bioengineered patches made from iPSCs-derived cardiomyocytes and biomaterials can be transplanted onto damaged heart areas, providing structural support and promoting cell survival [7]. iPSCs-derived cardiomyocytes help create disease models to study heart disease and screen drug therapies, aiding in understanding patient-specific responses and identifying new therapeutic targets. They reduce immune rejection risks when using patient-derived cells, avoid ethical issues of embryonic stem cells and enhance understanding of genetic heart diseases [8].

Neurodegenerative Diseases: iPSCs-derived neurons offer promising treatments for neurodegenerative diseases like Parkinson's (PD) and Alzheimer's (AD) by replacing lost neurons and restoring function. iPSCs, reprogrammed adult cells, can differentiate into any cell type, including neurons, providing a patient-specific source for regenerative therapies. These neurons include specialized subtypes like dopaminergic neurons for PD and cholinergic neurons for AD [9]. Parkinson's Disease (PD) is a motor disorder caused by the loss of dopaminergic neurons in the substantia nigra, leading to tremors, rigidity and bradykinesia. Transplanting iPSCs-derived dopaminergic neurons into the brain shows early success in animal models by restoring dopamine production. These neurons reduce immune rejection risk and provide an unlimited cell supply. However, challenges include ensuring long-term survival, integration of transplanted neurons and addressing genetic causes of PD to prevent recurrence [10].

Alzheimer's Disease (AD) is characterized by memory loss and cognitive decline due to amyloid plaques and tangles causing widespread neuronal death especially in the hippocampus and cortex. By using **cell therapy for AD** can replace lost cholinergic neurons to improve cognitive function [11]. Recent studies showed that iPSCs-derived neurons can survive and function in animal models, with ongoing clinical trials like TRANSEURO exploring human applications. Addressing both amyloid plaque accumulation and tau pathology is necessary for effective treatment. iPSCs-derived neurons enable patient-specific models to study AD mechanisms and screen drugs, aiding in personalized therapeutic strategies [12].

Liver and Pancreatic Regeneration: Induced pluripotent stem cells (iPSCs), when differentiated into hepatocytes and pancreatic cells, offer a promising avenue for treating liver and pancreatic diseases. These cells possess several **key advantages** that make them attractive for regenerative medicine:

- **Patient-specificity:** iPSCs derived from a patient's own cells can be transplanted without the risk of immune rejection, significantly improving the safety and efficacy of treatments [13].
- **Unlimited supply:** Once established, iPSCs lines can be expanded indefinitely in culture, providing a consistent and abundant source of cells for research, drug development and clinical applications [14].
- **Disease modeling:** iPSCs can be reprogrammed to mimic the genetic makeup of patients with various liver and pancreatic diseases, enabling researchers to study disease mechanisms, identify potential drug targets and test new therapies in a personalized manner [15].
    1. **Cell Maturation**: Differentiating iPSCs into fully functional hepatocytes and pancreatic cells is complex, needing precise control of signaling pathways and culture conditions.
    2. **Immune Response**: iPSCs-derived cells may still face immune rejection, especially in autoimmune diseases like Type 1 diabetes. Mitigation strategies include encapsulation or immunosuppression.
    3. **Scalability**: Producing large quantities of iPSCs-derived cells for clinical use is challenging, requiring efficient manufacturing processes and standardized quality control measures [16].

To fully realize the potential of iPSCs-based therapies, future research should focus on:

- **Optimizing Differentiation Protocols**: Develop more efficient and reproducible methods for differentiating iPSCs.
- **Reducing Immune Rejection**: Explore strategies like encapsulation technologies and targeted immunosuppression.
- **Scalable Manufacturing**: Develop processes to produce high-quality iPSCs-derived cells in large quantities for clinical use.

Addressing these challenges could make iPSCs-derived hepatocytes and pancreatic cells a viable option for patients with limited treatment options [17].

Musculoskeletal Regeneration:

Induced pluripotent stem cells (iPSCs) offer a promising approach to regenerate musculoskeletal tissues, including bone, cartilage and muscle. These tissues are often damaged due to injuries, degenerative diseases or genetic disorders. iPSCs can be differentiated into various cell types, providing a potential solution for tissue repair and replacement [18].

Musculoskeletal tissues present unique challenges for regeneration:

1. Bone injuries require grafts which are limited by donor availability and rejection risks.
2. Cartilage damage common in osteoarthritis is difficult to repair due to its limited self-healing capacity [19].

iPSCs offer several advantages for musculoskeletal regeneration such as:

a. Patient-specificity: iPSCs can be derived from a patient's own cells, reducing the risk of immune rejection.
b. Unlimited supply: iPSCs can be expanded indefinitely, providing a consistent source of cells.
c. **Disease modeling:** iPSCs-derived cells can be used to study disease mechanisms and develop personalized treatments [20].

Bone Tissue Engineering: iPSCs are differentiated into osteoblasts and combined with scaffolds or biomaterials to create bone constructs. Challenges include achieving sufficient vascularization and ensuring proper mechanical strength.

Cartilage Tissue Engineering: iPSCs-derived chondrocytes are seeded into scaffolds to form cartilage constructs. Challenges include ensuring long-term function and preventing fibrocartilage formation [21].

Muscle Tissue Engineering: iPSCs are differentiated into myogenic progenitors or satellite cells, combined with biomaterials and 3D printing to create muscle grafts. Challenges include achieving necessary strength, contractility and proper vascularization.

Promise for Musculoskeletal Regeneration: iPSCs offer significant potential. Addressing challenges like tissue integration, maturation and vascularization can lead to effective therapies for various musculoskeletal diseases and injuries [22].

Personalized Medicine:

iPSCs and CRISPR-Cas9 represent a powerful combination for personalized medicine. iPSCs derived from a patient's own cells offers an unique opportunity to create patient-specific models of diseases and generate cells for transplantation [23]. CRISPR-Cas9, a precise gene-editing tool enables the correction of genetic mutations within these iPSCs. CRISPR-Cas9 works by targeting specific DNA sequences and introducing precise edits. It has been successfully used to correct genetic mutations in iPSCs derived from patients with various diseases [24].

Applications of iPSCs-based gene editing include:

- **Monogenic diseases:** correcting mutations in genes responsible for conditions like sickle cell disease, cystic fibrosis and Duchenne muscular dystrophy [25].
- **Neurological disorders:** targeting mutations associated with Huntington's disease and ALS [26].
- **Cancer therapy:** engineering immune cells to target cancer cells more effectively [27].
- **Metabolic disorders:** correcting mutations leading to enzyme deficiencies [28].

Challenges:

Challenges includes **e**diting accuracy (off-target effects) and Safety (ethics and long-term effects). Future potential of iPSCs can be used for d**i**sease modelling and personalized medicine, as universal transplants (reduced immune rejection) and used for gene editing with CRISPR-Cas9 offers promise for treating genetic diseases [29]. HLA-matching is crucial for iPSCs-based therapies**.** HLA are a system of proteins that determines immune compatibility. But difficulty in finding HLA-matched donors and generating autologous iPSCs. Universal donor iPSCs aim to address these challenges by modifying HLA genes. By introduction of HLA-matching can broaden applicability and reduce the cost and time [30].

Current Challenges in iPSCs-Based Regenerative Medicine:

iPSCs hold immense promise for regenerative medicine, but their potential to form teratomas is a significant concern. Teratoma formation is linked to the presence of undifferentiated iPSCs or cells that revert to a pluripotent state. To mitigate this risk, researchers are focusing on **c**omplete differentiation**,** removal of residual pluripotent cells [31], **g**enetic modifications**,** improved monitoring [32] and development of safe iPSCs lines**.** By addressing these challenges, scientists are working towards making iPSCs-based therapies safer and more effective for a wide range of diseases and conditions.

Current Challenges in Immune rejection:

Immune rejection is a significant hurdle in the clinical application of iPSCs-based therapies. The immune system's ability to recognize and attack foreign cells poses a challenge, particularly when using allogeneic iPSCs derived from a donor [33]. Autologous iPSCs derived from the patient's own cells offers a reduced risk of immune rejection due to their genetic identity. However they can be time-consuming and costly to generate and may not be feasible for all patients. Allogeneic iPSCs can be more scalable and cost-effective, but they require careful HLA matching to minimize immune rejection. HLA antigens are essential for immune recognition and mismatched HLA molecules can trigger an immune response [34].

To overcome immune rejection, researchers are exploring various strategies:

- **Genetic modification of iPSCs using HLA editing and immunomodulatory gene insertion**.
- **Immunoprotective agents** [35].
- Tolerance induction done by using regulatory T cells, mixed chimerism: **[36]** Preconditioning and desensitization and Immune modulation drugs [37]. Biomaterials and scaffold engineering can also play a role in reducing immune activation by providing a protective niche for iPSCs-derived cells. Continued research and clinical trials are essential to address the challenges of immune rejection and develop effective strategies for iPSCs-based regenerative medicine.

Current Challenges in scalability and manufacturing:

Scalability and manufacturing are critical factors in the successful clinical application of iPSCs-based therapies. Producing large quantities of high-quality iPSCs in a consistent and cost-effective manner is essential for widespread use.

Key challenges *in large-scale iPSCs production include:*

- **Consistency and quality control.**
- **Efficient reprogramming** [38].
- **Scale-up processes.**
- Reducing manufacturing costs with high-quality production.
- **Regulatory compliance with** (GMP) standards [39].

Future directions include:

- **Continued research and development** [40].
- **Collaboration with industry.**
- **Regulatory support** [42].

By addressing these challenges and leveraging technological advancements, researchers can pave the way for the successful and widespread application of iPSCs-based therapies.

Regulatory and Ethical Considerations in iPSCs-Based Therapy:

iPSCs-based therapies face a complex regulatory landscape, with different countries having specific frameworks and guidelines. These frameworks aim to ensure the safety, efficacy and ethical soundness of iPSCs-based treatments.

In the United States: The FDA oversees iPSCs therapies through the CBER. iPSCs-based products are classified as biologics and must undergo rigorous regulatory processes, including IND applications and clinical trials [43].

In the European Union: The EMA regulates iPSCs therapies under the ATMP category. The EMA requires marketing authorization applications and follows a risk-based approach to regulation [44].

In Japan: the PMDA regulates iPSCs therapies through the ASRM and PMDA. Japan offers unique pathways like conditional approval and accelerated approval for promising iPSCs-based treatments [45].

Ethical considerations in iPSCs-based therapies includes **i**nformed consent, addressing ethical concerns related to genetic modifications, ensuring ethical use of animal models for preclinical testing and ensuring equitable distribution of therapies [46]. International collaboration is essential to harmonize regulatory guidelines and ensure global consistency in the approval and oversight of iPSCs-based therapies. Challenges in the regulatory landscape include **l**ong-term safety, standardization and **a**ddressing differences in ethical standards across countries. Addressing these challenges requires ongoing research, collaboration and the development of robust regulatory frameworks [47].

Ethical Considerations in iPSCs-Based Therapy:

iPSCs-based therapies offer immense potential for regenerative medicine, but they also raise significant ethical concerns that must be carefully addressed. These concerns encompass informed consent, genetic privacy, genetic modification, equity of access, commercialization and patient safety. Informed consent is crucial to ensure that donors are fully aware of the potential uses and the associated risks by informing them about the possibility of genetic research and potential commercial applications. Genetic privacy is another important consideration thereby protecting information from unauthorized access [48]. Genetic **modification** of iPSCs raises ethical questions, particularly when it involves germline editing. While somatic cell editing is generally accepted, germline editing which can affect future generations so requires careful scrutiny. Ensuring inclusive research and addressing healthcare infrastructure challenges are essential to promote equitable access [49].

Commercialization of iPSCs technologies can lead to ethical dilemmas, so it is important to balance commercial interests with the public good. Patient safety is paramount in iPSCs-based therapies. Tumorigenicity and long-term effects must be carefully monitored and addressed [50]. Addressing **these**

ethical concerns requires robust ethical oversight through institutional review boards (IRBs), p**ublic** engagement and continued research and development [51]. By carefully considering and addressing these ethical issues researchers can help ensure that iPSCs-based therapies are developed and benefiting patients and society as a whole.

Future Directions in iPSCs-Based Therapies

iPSCs hold great promise for regenerative medicine, but their clinical use is hindered by low efficiency and safety concerns. Scientists are developing improved techniques to overcome these limitations and realize the full potential of iPSCs therapies [52]. Reprogramming techniques are improving rapidly. Non-integrative methods (like episomal vectors and mRNA) are safer and more efficient. Small molecules and direct cell-to-cell reprogramming also show promise [53]. Safety concerns related to iPSCs are being addressed through various strategies. Genomic integrity monitoring and epigenetic memory minimization are crucial for ensuring the safety and functionality of iPSCs-derived cells. Suicide gene systems and mitochondrial health maintenance are additional approaches to mitigate potential risks [54]. Improved differentiation methods are crucial for creating specific cell types from iPSCs. 3D organoid cultures and single-cell transcriptomics are advancing tissue modeling. CRISPR-Cas9 gene editing and iPSCs biobanking enable personalized iPSCs therapies [55]. Bioengineering, AI and organ-on-a-chip technology are transforming iPSCs therapies. These technologies enable more accurate disease modelling, drug discovery and personalized medicine [56]. By overcoming challenges and utilizing advancements, researchers are working to fully realize the potential of iPSCs therapies for treating various diseases. These therapies could revolutionize regenerative medicine and provide hope for patients with previously incurable conditions.

Challenges for iPSCs-Based Therapies:

iPSCs-based therapies have demonstrated significant promise in clinical trials for various diseases, but their widespread clinical application faces several challenges. These challenges include ensuring safety and efficacy, navigating complex regulatory frameworks, overcoming manufacturing and scalability hurdles and addressing commercialization concerns [57]. Safety and tumor formation remain key concerns in iPSCs therapies. Ongoing efforts are needed to minimize these risks. Regulatory hurdles, such as navigating complex guidelines and obtaining approvals, pose challenges for commercialization. Collaboration with regulatory agencies is crucial to streamline the process and facilitate the commercialization of iPSCs-based therapies [58].

Producing large quantities of high-quality iPSCs while maintaining consistency and cost-effectiveness is challenging. Advances in biomanufacturing techniques, automation and quality control are crucial for addressing these issues. Commercialization of iPSCs-based therapies presents challenges including pricing, reimbursement, intellectual property and market access. Developing sustainable business models that balance commercial interests with patient access and affordability is essential [59].

Future directions for iPSCs-based therapies includes continue clinical trials, inclusion of technological advancements like biomanufacturing, gene editing and cell culture techniques [60], addressing regulatory challenges, developing sustainable business models [61] and by addressing ethical concerns. By addressing these challenges and leveraging ongoing advancements, iPSCs-based therapies could provide personalized treatments for conditions such as Parkinson's disease, heart disease, diabetes and genetic disorders, improving quality of life and reducing the burden of disease.

CONCLUSION

Improved iPSCs generation has opened new doors in regenerative medicine**.** Patient-specific cells can be used for various applications. However, ethical and regulatory frameworks are crucial for safe and responsible development [62]. iPSCs are being integrated with other technologies to expand their potential**.** Bioengineering, AI and organ-on-a-chip platforms are enhancing their applications. While clinical progress is promising, challenges in safety, efficacy, regulation, manufacturing and commercialization must be addressed [63]. Future directions for iPSCs include**:** improving reprogramming and differentiation techniques, expanding clinical trials, addressing regulatory challenges, overcoming manufacturing hurdles and addressing ethical concerns [64]. iPSCs-based therapies have the potential to revolutionize regenerative medicine**.** By addressing challenges and leveraging ongoing advancements, they can offer hope to patients with various diseases. Key areas for future focus include **c**ontinued research in reprogramming, differentiation, gene editing, bioengineering and high-throughput screening [65]. Continued refinement of regulatory guidelines and ethical standards is essential to ensure the responsible and equitable development and use of iPSCs therapies [66].

Combining iPSCs with emerging technologies like AI and organ-on-a-chip models will enable more personalized and effective treatments by accelerating drug discovery and improving precision of therapies. Still efforts are required to scale up production, reduce costs and develop sustainable business models [67]. By addressing these areas iPSCs-based therapies have the potential to transform regenerative medicine, enable personalized medicine and thereby improve patient outcomes **t**hrough disease modelling and drug discovery [68]. Continued research, development and collaboration are essential to realize the full potential of iPSCs-based therapies and improve the lives of countless patients.

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