



EDITORIAL

From Pluripotency to Patients: Making Induced pluripotent stem cell (iPSC) Therapies Safer

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Induced pluripotent stem cells (iPSCs) have established themselves as fundamental tools in regenerative medicine for developing individualized or universal cell-based therapies which treat various diseases including neurodegenerative and ocular conditions (1). The ability to transform adult somatic cells into pluripotent stem cells through iPSC technology allows researchers to avoid ethical issues while keeping the full potential to generate all cell types. Since their creation in 2006, iPSCs have transitioned from basic research instruments to essential clinical tools which enable disease modeling and pharmacological testing and therapeutic cell replacement (1). The advancement of these applications requires absolute safety measures to be implemented. The ongoing challenges in this field include developing mature iPSC derivatives alongside protecting genomic stability, while reducing tumor risks and developing potency tests that accurately predict clinical success rates.

Recent advances in iPSC therapies

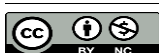
The clinical application of iPSC-derived therapies shows strong growth in the field. By December 2024 regulatory bodies worldwide approved 115 clinical trials which tested 83 humans' pluripotent stem cell (hPSC) products on more than 1,200 patients. These efforts primarily focus on ocular, neurological, and oncological indications (2). The Phase I/II trial of allogeneic iPSC-derived dopaminergic progenitors for Parkinson's disease represents a major accomplishment because it

showed both graft survival and dopamine secretion while avoiding tumor development (3). BlueRock Therapeutics advanced its iPSC-derived dopaminergic therapy bemdaneprocel to Phase III during early 2025 marking a vital step toward neurodegenerative therapy approval. The initial human trials of allogeneic iPSC-derived corneal endothelial substitutes for bullous keratopathy achieved a significant breakthrough by restoring corneal clarity through tissue replacement that eliminates donor dependency (4). The development of autologous iPSC-derived platelets continues to move forward which demonstrates the potential for mass-producing immunologically safe treatments.

The development of iPSC-derived natural killer (NK) cells shows increasing popularity in cancer treatment (5). These cells can be engineered in controlled laboratory conditions through chimeric antigen receptor (CAR) integration to produce enhanced antitumor effects which allows them to become available treatments for both solid tumors and blood cancers (5).

Addressing safety challenges

Although significant progress has been achieved safety continues to be a primary issue because of persistent problems with cell development and genetic control and tumor generation and potency measurement (6). Functional Maturation: The iPSC-derived cells demonstrate immature characteristics resembling fetal cells that create potential risks or reduced effectiveness in cardiac transplantation (7-



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9). The combination of prolonged cell cultivation with metabolic signaling and 3D scaffolding and simultaneous co-culture methods has demonstrated success in cell maturation (10). The application of electromechanical conditioning produces adult-like electrophysiological characteristics in cardiomyocytes (8) and astrocyte co-culture enhances both neuronal connectivity and neurotransmitter functionality (11, 12). The current standards recommend establishing specific maturity measurement criteria which correspond to therapeutic methods and associated risks including retinal pigment epithelium (RPE) phagocytic capability assessment (13) and dopamine neuron stimulus-response analysis (14).

Genomic Stability: The processes of reprogramming and editing alongside cell proliferation result in genetic variations that include copy-number variants together with oncogenic mutations such as TP53 and mitochondrial defects (15, 16). A stratified evaluation framework is recommended: routine karyotyping supplemented by high-density arrays or low-pass whole-genome sequencing (WGS) for batch release, and in-depth 30x WGS at cell bank inception to scrutinize cancer-related hotspots. New tools that combine optical genome mapping with next-generation sequencing provide enhanced detection capabilities for structural variants (17, 18). The implementation of population doubling limits together with early cell banking and donor-specific variant tracking helps minimize instability while protecting against immunogenicity and tumorigenicity concerns (19).

Tumorigenicity Controls: Trace amounts of residual undifferentiated pluripotent cells in iPSC-derived products pose a significant risk of teratoma formation upon transplantation. Advanced detection methods, including Quantitative PCR (qPCR) targeting Lin-28 homolog A (LIN28A) and Octamer-binding transcription factor 4 (OCT4) and antigen-based flow cytometry (e.g., TRA-1-60/SSEA-4), surpass conventional techniques (20, 21). In vivo teratoma models in immunocompromised mice, refined with spiking validations, define sensitivity thresholds (22). Proactive measures encompass purification protocols, selective cytotoxicity, and safety mechanisms like inducible caspase-9 for controlled cell elimination (23). Recent global regulatory dialogues emphasize standardized

tumorigenicity assessments to harmonize evaluation practices. Non-integrating microRNAs switches further enable targeted removal of risky cells, bolstering safety profiles without permanent genomic changes.

Potency Assays: Regulatory bodies require tests which evaluate the therapeutic power which relates to action mechanisms and serves as release and stability testing methods (24). The best assays would evaluate dopamine production in neurons together with NK cell cytotoxic potency (25) and cardiomyocyte contractile force which should match the performance of preclinical models (26). Proteomic and transcriptomic profiling together with strict validation processes create precise methods to track changes over time. The development of novel biomarkers for neural stem cell therapies demonstrates how laboratory-based assessments can serve as indicators of therapeutic effectiveness in living organisms.

iPSC therapies in biomedical research and application

Induced pluripotent stem cells (iPSCs) revolutionized research methods by enabling disease-specific models of neurodegenerative conditions and heart diseases and cancers (27). High-throughput gene disruption along with multiplexed epigenomic modifications drive functional genomic research and chromatin domain manipulations help scientists understand advanced genome organization (28). The therapeutic functions of iPSCs include both direct cell replacement and paracrine signaling which releases neuroprotective factors. The application of CRISPR-Cas9 requires strict monitoring to prevent unexpected effects because it may create problems with cell replication.

Future Perspective

The rising adoption of iPSC therapies demands the proper balance between innovative approaches and safety measures. Absolute risk elimination is unattainable, and excessively stringent criteria could impede patient access. The establishment of comprehensive registries will support tailored risk-benefit evaluations for each indication to drive continuous improvement. Stakeholders need to dedicate their focus toward developers publishing confirmed potency protocols and genomic standards

along with journals requiring uniform safety documentation and regulators establishing agreement on WGS and multiple assay standards and funders supporting reference standards for tumorigenicity and potency as well as clinicians leading registry participation for outcome tracking. The ongoing development of this field shows great potential to bring about change yet continuous monitoring is required for both ethical aspects related to germline editing and unintended consequences. iPSC therapies can advance from laboratory promise to clinical reality through careful adoption of maturation enhancements together with stability safeguards and risk mitigation strategies.

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References

1. Takahashi J. iPSC-based cell replacement therapy: from basic research to clinical application. *Cytherapy*. 2025;27(7):835-42.
2. Dayana I. USA: REPROCELL. 2025. Available from: <https://www.reprocell.com/blog/current-landscape-of-fda-stem-cell-approvals-and-trials-2023-2025>.
3. Sawamoto N, Doi D, Nakanishi E, et al. Phase I/II trial of iPSC-derived dopaminergic cells for Parkinson's disease. *Nature*. 2025;641(8064):971-7.
4. Tabar V, Sarva H, Lozano AM, et al. Phase I trial of hES cell-derived dopaminergic neurons for Parkinson's disease. *Nature*. 2025;641(8064):978-83.
5. Sun J, Elliott M, Souza-Fonseca-Guimaraes F. Engineered iPSC-derived natural killer cells: recent innovations in translational innate anti-cancer immunotherapy. *Clin Transl Immunol*. 2025;14(7):e70045.
6. Dhaiban S, Chandran S, Noshi M, et al. Clinical translation of human iPSC technologies: advances, safety concerns, and future directions. *Front Cell Dev Biol*. 2025;13:1627149.
7. Shiba Y, Fernandes S, Zhu WZ, et al. Human ES-cell-derived cardiomyocytes electrically couple and suppress arrhythmias in injured hearts. *Nature*. 2012;489(7415):322-5.
8. Ronaldson-Bouchard K, Ma SP, Yeager K, et al. Advanced maturation of human cardiac tissue grown from pluripotent stem cells. *Nature*. 2018;556(7700):239-43.
9. Yang X, Pabon L, Murry CE. Engineering adolescence: maturation of human pluripotent stem cell-derived cardiomyocytes. *Circ Res*. 2014;114(3):511-23.
10. Guvendiren M, Fung S, Kohn J, et al. The control of stem cell morphology and differentiation using three-dimensional printed scaffold architecture. *MRS Commun*. 2017;7(3):383-90.
11. Zheng H, Feng Y, Tang J, et al. Astrocyte-secreted cues promote neural maturation and augment activity in human forebrain organoids. *Nat Commun*. 2025;16(1):2845.
12. Hwang S, Lee Y, Jun SB. Co-culture platform for neuron-astrocyte interaction using optogenetic modulation. *Biomed Eng Lett*. 2022;12(4):401-11.
13. Hirami Y, Mandai M, Sugita S, et al. Safety and stable survival of stem-cell-derived retinal organoid for 2 years in patients with retinitis pigmentosa. *Cell Stem Cell*. 2023;30(12):1585-96.e6.
14. Schweitzer JS, Song B, Herrington TM, et al. Personalized iPSC-Derived Dopamine Progenitor Cells for Parkinson's Disease. *N Engl J Med*. 2020;382(20):1926-32.
15. Merkle FT, Ghosh S, Kamitaki N, et al. Human pluripotent stem cells recurrently acquire and expand dominant negative P53 mutations. *Nature*. 2017;545(7653):229-33.
16. Taapken SM, Nisler BS, Newton MA, et al. Karyotypic abnormalities in human induced pluripotent stem cells and embryonic stem cells. *Nature Biotechnol*. 2011;29(4):313-4.
17. Budurlean L, Tukaramrao DB, Zhang L, et al. Integrating Optical Genome Mapping and Whole Genome Sequencing in Somatic Structural Variant Detection. *J Pers Med*. 2024;14(3).
18. Garcia-Heras J. Optical Genome Mapping: A Revolutionary Tool for "Next Generation Cytogenomics Analysis" with a Broad Range of Diagnostic Applications in Human Diseases. *J Assoc Genet Technol*. 2021;47(4):191-200.
19. Cerneckis J, Cai H, Shi Y. Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications. *Signal Transduct Target Ther*. 2024;9(1):112.
20. Wu Y, Zhang Z, Wu S, et al. Estimating residual undifferentiated cells in human chemically induced pluripotent stem cell derived islets using lncRNA as biomarkers. *Sci Rep*. 2023;13(1):16435.
21. Kuroda T, Yasuda S, Matsuyama S, et al. Highly sensitive droplet digital PCR method for detection of residual undifferentiated cells in cardiomyocytes derived from human pluripotent stem cells. *Regen Ther*. 2015;2:17-23.
22. Sato Y, Bando H, Di Piazza M, et al. Tumorigenicity assessment of cell therapy products: The need for global consensus and

- points to consider. *Cytotherapy*. 2019;21(11):1095-111.
23. Sahillioglu AC, Schumacher TN. Safety switches for adoptive cell therapy. *Curr Opin Immunol*. 2022;74:190-8.
 24. Salmikangas P, Carlsson B, Klumb C, et al. Potency testing of cell and gene therapy products. *Front Med (Lausanne)*. 2023;10:1190016.
 25. Liu E, Marin D, Banerjee P, et al. Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors. *N Engl J Med*. 2020;382(6):545-53.
 26. Ali SA, Mahmood Z, Mubarak Z, et al. Assessing the Potential Benefits of Stem Cell Therapy in Cardiac Regeneration for Patients With Ischemic Heart Disease. *Cureus*. 2025;17(1):e76770.
 27. Sharma A, Sances S, Workman MJ, et al. Multi-lineage Human iPSC-Derived Platforms for Disease Modeling and Drug Discovery. *Cell Stem Cell*. 2020;26(3):309-29.
 28. Laurenti E, Göttgens B. From haematopoietic stem cells to complex differentiation landscapes. *Nature*. 2018;553(7689):418-26.