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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

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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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