



OPEN ACCESS

EDITED AND REVIEWED BY

Ranieri Cancedda,
Independent researcher, Genova, Italy

*CORRESPONDENCE

Kim C. O'Connor,
✉ koc@tulane.edu

RECEIVED 29 October 2025

REVISED 01 November 2025

ACCEPTED 21 November 2025

PUBLISHED 04 December 2025

CITATION

O'Connor KC, Stanley HJ, Bunnell BA and De Caro R (2025) Editorial: Role of induced pluripotent stem cells (iPSCs) in regenerative medicine, disease modeling and drug discovery. *Front. Bioeng. Biotechnol.* 13:1734717. doi: 10.3389/fbioe.2025.1734717

COPYRIGHT

© 2025 O'Connor, Stanley, Bunnell and De Caro. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Editorial: Role of induced pluripotent stem cells (iPSCs) in regenerative medicine, disease modeling and drug discovery

Kim C. O'Connor^{1*}, Hayden J. Stanley¹, Bruce A. Bunnell² and Raffaele De Caro³

¹Department of Chemical and Biomolecular Engineering, Tulane University, New Orleans, LA, United States, ²Department of Microbiology, Immunology, and Genetics, University of North Texas Health Science Center, Fort Worth, TX, United States, ³Section of Human Anatomy, Department of Neuroscience, University of Padova, Padua, Italy

KEYWORDS

iPSC (induced pluripotent stem cells), personalize cell therapy, disease modeling, drug discovery, regenerative medicine

Editorial on the Research Topic

[Role of induced pluripotent stem cells \(iPSCs\) in regenerative medicine, disease modeling and drug discovery](#)

Yamanaka and Takahashi's groundbreaking research on induced pluripotent stem cells (iPSCs) fundamentally transformed the field of regenerative medicine (Takahashi and Yamanaka, 2006). Genetically reprogramming somatic cells to a pluripotent state provides a virtually unlimited supply of any cell type in the body from a patient. Since their discovery in 2006, iPSCs have enabled remarkable advances in personalized cell therapies, disease models, and drug development (Nicholson et al., 2022). Yet there are still significant challenges to realizing the full potential of iPSC technology. This Research Topic highlights recent efforts to overcome some of these barriers to achieve more viable, functionally mature and effective iPSCs.

Cryostorage is essential for the transportation and long-term preservation of iPSCs in research and clinical applications. The viability and function of stem cells are threatened by transient warming events at any step along the cold chain from source to destination (Pogozhykh et al., 2017). Temperature fluctuations commonly occur when cells are moved from long-term storage in the vapor phase of liquid nitrogen at -150°C to dry ice at -80°C for temporary storage and transportation. In this Research Topic, Okuda et al. examined the impact of cycling between these temperatures on the viability of cryopreserved human (h) iPSCs. Temperature fluctuations above the glass transition temperature of -120°C for dimethyl sulfoxide, the cryoprotectant, trigger a cascade of events that culminate in cell death. Cell damage initiates with an influx of the cryoprotectant that disrupts mitochondrial cytochrome signaling and membrane potential, as well as cell attachment. These findings suggest temperature cycling causes delayed cell death from mitochondrial dysfunction rather than immediate death from loss of cell membrane integrity, as widely accepted. Understanding cellular responses to temperature fluctuations will aid in the development of



FIGURE 1
Applications of iPSC technology in personalized cell therapies, disease models and drug development. Image was generated using Whisk, an AI image remixing tool by Google Labs (labs.google/whisk).

quality control strategies, such as precise temperature controls and cell assays, to preserve the viability and function of iPSCs throughout the cold chain.

Frequently, iPSC-derived cells exhibit an immature, fetal-like phenotype upon differentiation (Baxter et al., 2015; Yang et al., 2023). Achieving functional maturity remains a critical barrier to the use of iPSCs. Josvai et al. investigated the mechanism by which hiPSC-derived cardiac fibroblasts (hiPSC-CFs) stimulate the contractile function of hiPSC-derived cardiomyocytes (hiPSC-CMs) on a 2D substrate of micropatterned extracellular matrix. Compared with monocultures of hiPSC-CMs, co-cultures of hiPSC-CMs and hiPSC-CFs exhibit larger contractile strain, increased rate of spontaneous contraction, faster kinetics, and increased contractile anisotropy and myofibril alignment. Conditioned medium from hiPSC-CFs is sufficient to improve only a subset of the contractile properties of cardiomyocytes, namely the amplitude and upstroke kinetics of contractile strain. These findings suggest that cardiac fibroblasts drive cardiomyocytes toward functional maturity through a mechanism that requires both paracrine signaling and direct cellular interactions. This research emphasizes the crucial role of cardiac fibroblasts in generating functional cardiomyocytes as cellular therapies and as *in vitro* cultures for disease modeling and drug screening.

In a related study, Gisone et al. enhanced hiPSC-CM maturation by combining co-culture with 3D hydrogels to mimic not only the composition but also the architecture of cardiac tissue. They found

that hiPSC-CMs produce higher expression of cardiac maturation markers when co-cultured with human coronary artery endothelial cells in a 3D gelatin methacryloyl hydrogel than when cultured as a classic 2D monoculture. Omics analysis yielded consistent results, which indicate an upregulation of pathways for cardiac differentiation and contraction in the 3D system. An added benefit is the increased cell viability and decreased oxidative stress of the hydrogel co-culture relative to the 2D monoculture. The improved maturation profile of hiPSC-CMs in a biomimetic environment may provide more effective cellular therapies and reliable *in vitro* models.

The clinical success of cellular therapies depends on their ability to localize and survive at the target tissue (Madsen et al., 2020; Xu et al., 2025). Using the novel Antares 2 luciferase reporter, Yuan et al. explored the fate of iPSC-derived mesenchymal stem cells (iPSC-MSCs) after injection into the knee joint cavity of arthritic rats. The reporter is a fusion of the luciferase NanoLuc to the orange fluorescent protein CyOFP, which produces exceptionally bright bioluminescence for sensitive detection in deep tissues during imaging (Yeh et al., 2017). The iPSC-MSCs significantly improved cartilage damage and persisted in the joint cavity without migrating to other sites for over 2 weeks, indicating that therapeutic effects and tissue repair occur locally rather than systemically. Imaging of dissected tissue suggested that iPSC-MSCs injected into the joint cavity are first absorbed by the loose connective tissue of the synovium before distributing to the meniscus and cartilage. This study confirms the therapeutic potential

of iPSC-MSCs to treat osteoarthritis and elucidates the underlying mechanism of joint repair.

Extracellular vesicles (EVs) are a compelling cell-free therapy in regenerative medicine that are safer, less immunogenic and logistically superior to direct stem cell use (Goo et al., 2024; Porzionato et al., 2021). A study by Palama et al. compared the aging of hMSCs and hiPSC-MSCs during long-term expansion, along with the anti-inflammatory properties of their respective EVs in an *in vitro* model of osteoarthritis. hMSC expansion leads to cellular senescence, reduced potency, and diminished anti-inflammatory properties of their derived EVs over several passages, consistent with previous reports (Izadpanah et al., 2008). hiPSC-MSCs maintain their stem cell and EV function for a longer duration than conventional hMSCs, suggesting that EVs derived from hiPSC-MSCs offer a wider therapeutic window than those derived from traditional hMSCs. The authors noted, however, variability in the biological properties across different batches of hiPSC-MSCs and their EVs. Further research is crucial to minimize batch-to-batch variability and produce reliable treatment outcomes with hiPSC-derived EV therapies.

This Research Topic showcases current research to achieve the full potential of iPSC technology. Specifically, the featured articles lay the groundwork for quality control to prevent cryoinjury, biomimetic systems to drive functional maturity, a mechanistic understanding of tissue repair, and cell-free therapies derived from extracellular vesicles. The resulting advances will deliver more effective cellular therapies, accurate disease modeling, and streamlined drug development with iPSCs. Through these and other research efforts, the day is rapidly approaching when the extraordinary promise of iPSCs becomes a reality.

Author contributions

KO: Writing – review and editing, Writing – original draft. HS: Writing – original draft, Writing – review and editing. BB: Writing – review and editing. RD: Writing – review and editing.

References

- Baxter, M., Withey, S., Harrison, S., Segeritz, C. P., Zhang, F., Atkinson-Dell, R., et al. (2015). Phenotypic and functional analyses show stem cell-derived hepatocyte-like cells better mimic fetal rather than adult hepatocytes. *J. Hepatol.* 62, 581–589. doi:10.1016/j.jhep.2014.10.016
- Goo, J., Lee, Y., Lee, J., Kim, I.-S., and Jeong, C. (2024). Extracellular vesicles in therapeutics: a comprehensive review on applications, challenges, and clinical progress. *Pharmaceutics* 16, 311. doi:10.3390/pharmaceutics16030311
- Izadpanah, R., Kaushal, D., Kriedt, C., Tsien, F., Patel, B., Dufour, J., et al. (2008). Long-term *in vitro* expansion alters the biology of adult mesenchymal stem cells. *Cancer Res.* 68, 4229–4238. doi:10.1158/0008-5472.CAN-07-5272
- Madsen, S. D., Jones, S. H., Tucker, H. A., Giler, M. K., Muller, D. C., Discher, C. T., et al. (2020). Survival of aging CD264⁺ and CD264⁻ populations of human bone marrow mesenchymal stem cells is independent of colony-forming efficiency. *Biotechnol. Bioeng.* 117, 223–237. doi:10.1002/bit.27195
- Nicholson, M. W., Ting, C.-Y., Chan, D. Z. H., Cheng, Y.-C., Lee, Y.-C., Hsu, C.-C., et al. (2022). Utility of iPSC-derived cells for disease modeling, drug development, and cell therapy. *Cells* 11, 1853. doi:10.3390/cells11111853
- Pogozhykh, D., Pogozhykh, O., Prokopyuk, V., Kuleshova, L., Goltsev, A., Blasczyk, R., et al. (2017). Influence of temperature fluctuations during cryopreservation on vital parameters, differentiation potential, and transgene expression of placental multipotent stromal cells. *Stem Cell Res. Ther.* 8, 66. doi:10.1186/s13287-017-0512-7
- Porzionato, A., Zaramella, P., Dedja, A., Guidolin, D., Bonadies, L., Macchi, V., et al. (2021). Intratracheal administration of mesenchymal stem cell-derived extracellular vesicles reduces lung injuries in a chronic rat model of bronchopulmonary dysplasia. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 320, L688–L704. doi:10.1152/ajplung.00148.2020
- Takahashi, K., and Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 126, 663–676. doi:10.1016/j.cell.2006.07.024
- Xu, Q., Zhang, C., Liu, X., Sun, Y., Li, B., Nian, S., et al. (2025). Modulation of stem cell survival and engraftment: implications for stem cell-based therapy. *Theranostics* 15, 8840–8856. doi:10.7150/thno.120805
- Yang, H., Yang, Y., Kiskin, F. N., Shen, M., and Zhang, J. Z. (2023). Recent advances in regulating the proliferation or maturation of human-induced pluripotent stem cell-derived cardiomyocytes. *Stem Cell Res. Ther.* 14, 228. doi:10.1186/s13287-023-03470-w
- Yeh, H. W., Karmach, O., Ji, A., Carter, D., Martins-Green, M. M., and Ai, H. W. (2017). Red-shifted luciferase-luciferin pairs for enhanced bioluminescence imaging. *Nat. Methods* 14, 971–974. doi:10.1038/nmeth.4400

Funding

The authors declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The authors declare that Generative AI was used in the creation of this manuscript. Figure 1 was generated using Whisk, an AI image remixing tool by Google Labs (labs.google/whisk).

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.