Introduction

The over-expression of the transcription factors Oct4, Sox2, Klf4 and c-Myc, for the reprogramming of iPSCs from mouse somatic cells, by Takahashi and Yamanaka coined the term “Yamanaka factors” (1). Following on, the aforementioned factors, and/or combinations of other similar factors were extensively used to reprogram numerous human and mouse body cells into iPSCs (2-5). iPSCs depict vast dedifferentiation potency and attain features like embryonic stem cells (ESCs). In fact, ESCs and iPSCs are structurally identical, and under in-vitro conditions, these cells are capable to give rise to cells of the three germ layers (ectoderm, endoderm and mesoderm) and develop almost all cells of adult organisms. Moreover, iPSCs are capable of producing living and potent animals (6-9). This unprecedented reprogramming approach developed great interest among the scientific, academic and medical community since iPSCs offer a promising source of pluripotent cells. Further, iPSCs are generated from somatic cells obtained in a most unharmful method, maintaining the discrete genetic settings, hence are autologous in nature and exhibiting minimal immune rejection risks (10). Unlike, blastocyst-derived human ESCs, the iPSCs are exempted from ethical concerns. The original reprogramming procedures are being streamlined to overcome several critical experimental issues, like the use of integrative vectors for the administration of the transcription factors. Besides Yamanaka factors, other reprogramming factors, microRNAs and/or small molecules and epigenetic regulators have appeared to cooperate or substitute these factors for reprogramming iPSCs. Reprogrammed cells hold great potential for high throughput screens for drug discovery, toxicity tests and in-vitro models for disease. Above all, reprogramming opens up the option of remedy by using the patients own cells (11).

Herein, we review the eminent challenges and difficulties currently faced during the safe and stable clinical application of iPSCs. Furthermore, we suggest potential applications and therapeutic scenarios employing iPSCs for the betterment of human health and the improvement of the health care sector.

Challenges

The inception of iPSCs technology is conferred a landmark event in the remedial and therapeutic settings (12). The advantages associated with the application of iPSCs are notable and widely accepted, primarily due to their pluripotent capacity and their potential to create a patient-derived disease model (13). However, numerous distinguished barriers and drawbacks are hampering the use of promising cells in clinical research.

First, the generation and expansion and of iPSCs under laboratory settings, including all the necessary safety and pluripotency assessments, cost about 10-20,000 US dollars and also involves lengthy procedures (14). Likewise, the cost of clinical studies can reach up to 1 million dollars. Obviously, there is a serious need to find out a cost-effective solution to this hindrance, which would allow the iPSCs translation to the clinics.

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causes of the onset of DNA mutations in the iPSCs could be the reprogramming process, during subsequent passing of these cells, or the preexisting mutations in the primary cells (17). Alarming, many of the mutations and aberrations could lead to tumorigenic potential. The safety concerns related to the use of iPSCs in clinics are of foremost importance; hence, requires strict programming and manufacturing conditions ensure the therapeutic potential of these cells.

iPSCs-derived immunogenicity in the host is yet another main obstacle concerning their application in translational research. The landmark announcement in 2011, that aberrant gene expression in some cells differentiated from iPSCs can evoke T-cell-dependent immune response in syngeneic mice brought about general doubt regarding the potential application of these cells in clinical settings (18). Following on, Zhao and coworkers studied the immunogenic response of several distinct iPSCs-derived cells in humanized mice and reported that the different derivatives triggered different immune responses (19). Therefore, the immune responses provoked by the iPSCs and their derivatives vary with the use of different cell lines. These immune responses could be the result of epigenetic alterations exhibited by the cell lines or genetic anomalies enticing the aberrant immunogenic product (20). A robust understanding of the immune responses generated by these cells and their derivatives could be a big leap forward toward greater safety and with minimal need for immunosuppressive treatments in the case of iPSCs transplants (21).

**Prospects**

Currently, time, cost (autologous transplants) and immunogenicity (allogeneic transplants) related to iPSCs technology remain the main obstacles keeping these cells away from clinics (22). Regarding the immunogenicity issue, the possible substitution of allogeneic transplants could sort out the problem (42,43) (Figure 1). However, concerns linked to immunogenicity remain prime downside. In this regard, many scientists are advocating the HLA-characterized iPSCs biobank set up (Table 1). Consequently, this would not only offer cost-effective technology itself but also reduce the immune rejection risk and enhance the possibility of bringing the iPSCs closer to clinics (23). Evidently, the HLA system is very polymorphic, therefore taking into consideration the loci HLA-A, HLA-B and HLA-DR are sufficient to diminish the rejection risk and the doses of immunosuppression needed. Assumingly, HLA- homozygous and blood group O donors dependent iPSCs biobank would streamline the donor-recipient matching (24). Hypothetically, 140 and 150 (selected donors) HLA-homozygous iPSCs lines are enough to match 90% and 93% of Japan and United Kingdom recipients, respectively (25, 26). It is vital to note that HLA- characterized iPSCs biobank intended for a remedial application requires more rigorous safety checks and efficient manufacturing protocols to guarantee the reliability of the likely therapeutics generated (27).

Further, critical aspects required to make these cells a likely translational product include the normalization of reprogramming protocols and the application of good manufacturing practices (28). The current iPSCs production restricts their application to laboratory settings, thus limiting the broader applicability. Therefore, it is imperative to regulate the protocols for a large-scale expansion of iPSCs, since cellular therapies would require a substantial amount of them to be attainable (29). Moreover, the tracking of the iPSCs-bound toxicity, tumorigenicity, also the safety of cells, is crucial for the therapeutics (30).

The current differentiation strategies do not lead to the iPSCs-derived, specific lineage of interest, and exhibit unwanted phenotypic heterogeneity and inadequate maturity with reduced efficiency rates (31, 32). The introduction of certain vital transcription factors via viral vectors abets non-specific incorporation within the genome, ergo compromising the safety of the iPSCs and their by-products (33). One more approach, focused on imitating the embryonic development in the presence or absence of several decisive compounds in the cell culture medium, aiming to check the regulation of specific relevant cellular pathways and setting apart the pluripotency of iPSCs (34). However, the shortcomings related to the existing approaches thwart to attain absolute maturity, particularly, in cardiomyocytes, and diseases where the affected phenotype is only expressed at the terminal stage (35). To sort these limitations new approaches are being explored. For instance, some groups are working on different small molecule cocktails to achieve a more mature differentiation state, the exploitation of the cellular niche, and the adaptation of 3D techniques (36, 37).

**Conclusion**

It is quite apparent that the therapeutic potential of iPSCs goes far beyond the basic research, their leap from bench to bedside is imminent. Cellular therapies illustrate the success of this groundbreaking research with the progress of numerous ongoing clinical trials (Table 2). For instance, in disease models such as age-related muscular atrophy and Parkinson’s diseases, iPSCs demonstrated promising therapeutic ability. Over the years, iPSCs have evolved as a robust tool in the evolution of modern therapeutics (Figure 2), and can further be seen as a transitio-

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**Figure 1.** Schematic presentation of the cells from HLA-homozygous donors (red colored) can be used for cell therapies in recipients / patients who have at least one of the same HLA. In the illustration, the donor cells can be used in 3 of the 7 recipients / patients.
production, together with the need to normalize the technical protocols and expedite the scaling up of this promising technology would validate its application in clinics. The key point is that advanced and novel techniques are being investigated to understand and interpret these problems, 

Table 1. Brief information of iPSC repositories (38-41).

<table>
<thead>
<tr>
<th>Name</th>
<th>Allies</th>
<th>Geographic Region</th>
<th>Products</th>
<th>Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>California Institute for Regenerative Medicine (CIRM)</td>
<td>Fujifilm Cellular Dynamics International (FCDI)</td>
<td>United States</td>
<td>40 diseases including 239 neurodevelopmental disorders, 131 liver disease, 442 heart disease, 65 neurodegenerative disease, 175 eyes disease, 191 lung disease, and 302 controls</td>
<td><a href="https://www.cirm.ca.gov/researchers/ipsc-repository/about">https://www.cirm.ca.gov/researchers/ipsc-repository/about</a> (accessed on 30 October 2022)</td>
</tr>
<tr>
<td>Center for iPSC Cell Research and Application (CiRA)</td>
<td>ATCC, RIKEN, RUCDR</td>
<td>Japan</td>
<td>39 lines including 3 diseases: two neurodevelopmental diseases and a bone disorder</td>
<td><a href="https://www.cira.kyoto-u.ac.jp/e/research/material_1.html">https://www.cira.kyoto-u.ac.jp/e/research/material_1.html</a> (accessed on 30 October 2022)</td>
</tr>
<tr>
<td>European Bank for induced pluripotent Stem Cells (EBiSC)</td>
<td>HipSci</td>
<td>Europe</td>
<td>36 diseases, 895 iPSC lines including 359 normal control lines</td>
<td><a href="https://ebisc.org/search">https://ebisc.org/search</a> (accessed on 6 June 2023)</td>
</tr>
<tr>
<td>Human Induced pluripotent Stem Cell Initiative (HipSci)</td>
<td>ECACC, EBiSC</td>
<td>United Kingdom</td>
<td>15 disease statuses, 339 disease lines, and 496 normal lines</td>
<td><a href="https://www.hipsci.org/lines/">https://www.hipsci.org/lines/</a> (accessed on 30 October 2022)</td>
</tr>
<tr>
<td>Institute of Physical and Chemical Research (RIKEN)</td>
<td></td>
<td>Japan</td>
<td>14 disease categories including 231 diseases, 753 patients, and 3110 iPSC lines; 718 health control lines</td>
<td><a href="https://cell.brc.riken.jp/en/hps/patient_specific_ips">https://cell.brc.riken.jp/en/hps/patient_specific_ips</a> (accessed on 30 October 2022)</td>
</tr>
<tr>
<td>Human Disease iPSC Consortium Resource Center (Taiwan Human Disease iPSC Consortium)</td>
<td>BCRC</td>
<td>Taiwan</td>
<td>10 normal lines, 74 disease lines of 23 diseases</td>
<td><a href="http://ipsc.ibms.sinica.edu.tw/schedu">http://ipsc.ibms.sinica.edu.tw/schedu</a> le.html (accessed on 30 October 2022)</td>
</tr>
<tr>
<td>WiCell Research Institute (WiCell)</td>
<td>N/A</td>
<td>United States</td>
<td>1377 iPSC lines including 308 disease lines of 40 disease types</td>
<td><a href="https://www.wicell.org/home/st">https://www.wicell.org/home/st</a> em-cells/catalog-of-stem-cell-line s/advanced-search.cmsx (accessed on 30 October 2022)</td>
</tr>
</tbody>
</table>

Table 2. Current iPSC-based clinical trials (as of 2021) (43).

<table>
<thead>
<tr>
<th>Location</th>
<th>Company</th>
<th>Disease</th>
<th>Cell Type</th>
<th>Clinical Phase</th>
<th>Clinical Trial Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia, United Kingdom</td>
<td>Cynata Therapeutics Limited</td>
<td>Graft vs. host disease</td>
<td>iPSC-derived mesenchymal stem cell</td>
<td>Phase 1</td>
<td>ClinicalTrials.gov: NCT02923375</td>
</tr>
<tr>
<td>United States</td>
<td>Fate Therapeutics</td>
<td>Cancer</td>
<td>iPSC-derived Natural Killer (NK) cell</td>
<td>Phase 1</td>
<td>ClinicalTrials.gov: NCT03841110</td>
</tr>
<tr>
<td>Beijing University of Chinese Medicine</td>
<td></td>
<td>Chronic heart failure</td>
<td>iPSC-derived cardiomyocytes</td>
<td>Phase 2/3</td>
<td>ClinicalTrials.gov: NCT03759405</td>
</tr>
<tr>
<td>China</td>
<td>Help Therapeutics</td>
<td>Heart failure</td>
<td>iPSC-derived cardiomyocytes</td>
<td>Phase 1/2</td>
<td>ClinicalTrials.gov: NCT03763136</td>
</tr>
<tr>
<td>Kyoto University Hospital</td>
<td></td>
<td>Parkinson disease</td>
<td>iPSC-derived dopaminergic progenitors</td>
<td>Phase 1/2</td>
<td>ICTRP: JPRNUMIN000033564</td>
</tr>
<tr>
<td>Japan</td>
<td>Osaka University, Cuorips Inc.</td>
<td>Myocardial ischemia</td>
<td>iPSC-derived cardiomyocytes sheet</td>
<td>Phase 1</td>
<td>ClinicalTrials.gov: NCT04696328</td>
</tr>
</tbody>
</table>

nal factor to develop other remedial products of interest as platelets. Nonetheless, the application of iPSCs in clinics are still an uphill battle. Addressing and understanding their prominent downsides such as immunogenicity, genetic instability, toxicity, and the increased cost of their production, together with the need to normalize the technical protocols and expedite the scaling up of this promising technology would validate its application in clinics. The key point is that advanced and novel techniques are being investigated to understand and interpret these problems,
which will open up the way for the categorical application of this technology on a broader scale.

References


27. Arshad Jamal / Induced pluripotent stem cells, 2023, 69(11): 76-80


