CellPress

Cell Stem Cell Forum

A Decade of iPS Cells

10 Questions: Clinical Outlook for iPSCs

Cell Stem Cell Editorial Team[1,*]
[1]*Cell Stem Cell*, Cell Press, 50 Hampshire Street, 5th Floor, Cambridge, MA 02139, USA
*Correspondence: stemcell@cell.com
http://dx.doi.org/10.1016/j.stem.2016.01.023

In an interview, we recently asked four leaders in the field to share their insights with us on the clinical outlook for hiPSCs. We present highlights from their responses here.

Induced pluripotent stem cells (iPSCs) have great potential for improving our understanding of human disease and regenerative medicine, but as with any innovation in medicine, there are many hurdles to overcome on the road to the clinic. To get a sense of the challenges the field faces and the opportunities ahead, we asked four leaders in the field, Kevin Eggan (KE), Malin Parmar (MP), Masayo Takahashi (MT), and Shinya Yamanaka (SY), ten questions about the clinical outlook for iPSCs. This article contains excerpts from our email interview, and the full transcripts are available in the Supplemental Information.

CSC: In your mind, what are the most promising therapeutic applications for hiPSCs currently in development?

SY: One promising application is iPSC-based cell therapy. The work led by Dr. Masayo Takahashi at Riken Center for Developmental Biology (CDB) is generating a lot of interest, since it is the first clinical research that uses the transplantation of 100% iPSC-derived cell sheets. At CiRA we are eagerly awaiting similar studies for Parkinson's disease and blood transfusions. These studies require a much larger number of cells than the one by Dr. Takahashi. Her team's work was revolutionary for many reasons, and one is that it reprogrammed the patient's own somatic cells to create retinal cells for treatment. However, autologous transplants are not financially feasible at present. Future studies will use allogeneic transplants. Demonstrating allogeneic transplants of iPSC products has tremendous potential for clinical use.

Another development of strong interest is drug discovery. iPSCs have demonstrated promise for not only drug discovery but also drug repositioning. Drug repositioning would bring drugs out faster for clinical use.

Accordingly, CiRA is working with a number of companies that aim to realize cell therapies and/or drug development using iPSCs.

KE: I would currently break this down along two distinct lines. For use in transplantation medicine, at the moment, a large push is being made in forms of macular degeneration using pigmented epithelial cells made from both iPSCs and human ESCs. With an ongoing clinical trial of human ESC-derived cardiac cells for myocardial infarction, one would think that similar efforts with iPSC-derived cardiac cells can't be far behind. The field of directed differentiation of stem cells has progressed remarkably over the last several years with production of nervous system cell types leading the way. If I had to guess which areas will see a great deal of focus in the near future, I would say Parkinson's disease and the epilepsies. The ease of transplanting blood types for many disorders will make this increasingly attractive as time goes on and more high-quality differentiated cells are made.

Another important utility of iPSCs has become their use in the identification of candidate drugs through mechanistic studies or chemical screening. This strategy has radiated throughout academic and industrial settings. There seem to be many drug candidates moving toward the clinic discovered by this approach. Again the ease of generating large quantities of neuronal and cardiac cell types has put indications impacting these cells in the lead. One example is a compound we found to normalize the physiological properties of iPSC-derived motor neurons from ALS patients. There is currently a clinical trial underway to determine if this drug can rescue known electrical changes in the brains of individuals with this form of neural degeneration.

CSC: Do you think it's valuable to bank iPSCs for clinical purposes? What do you think are the main considerations to keep in mind?

MP: I think it makes sense to bank iPSCs from individuals with specific diseases to create a resource for the scientific community to use for understanding the disease pathology and to develop better differential diagnostics and new treatment strategies.

In terms of generating large banks with the intention for the cells to be used for cell therapy, I am less convinced this is a good strategy. One has to keep in mind that it is a very resource-demanding task to create and maintain such a bank under GMP conditions and that each differentiated therapeutic cell product made from a line in that bank will still have to go through safety and efficacy testing prior to use. If that same amount of resources was put into addressing key issues remaining to enable the use of patients' own cells or cells from matched donors to create therapeutic cells directly without a banking step, personalized cell therapy could become a reality.

SY: Seeing the success of blood banks, it would be wonderful if we could do something similar with iPSCs. CiRA is currently building an iPSC bank—the iPS Cell Stock for Regenerative Medicine—and we distributed one quality-assured iPSC line to a pharmaceutical company and a medical organization last year. Our banking system collects blood or skin cells from healthy donors with HLA homozygous alleles and generates iPSC lines. We predict that ~100 such lines would cover a majority of the Japanese population. Banking iPSCs can save time and cost because the quality of iPSC lines can be assured before they are needed for treatment. In addition, target cells derived from the iPSCs can be provided more quickly to patients than cells made from patient-specific iPSCs.

CellPress

Kevin Eggan, *Harvard University* (top left); Malin Parmar, *Lund University* (top right); Masayo Takahashi, *Riken* (bottom left); Shinya Yamanaka, *Kyoto University/ Gladstone Institutes* (bottom right).

Another important consideration is the impact of minor antigens and other immunological mechanisms. We have observed beneficial effects of MHC matching in monkey models, but these need to be proved by clinical studies.

***CSC:* On a related note, what are your thoughts on the value of autologous versus allogeneic approaches? Where do you think the community should be focusing its efforts? What do you think will be more feasible or safe?**

MT: Autologous approaches have a strong advantage compared to allogeneic approaches because they do not require immune suppression, and the first patient enrolled in our clinical trial was treated with autologous cells and showed no immune rejection. However, allogeneic approaches have a significant advantage when it comes to cost.

Overall, I think the community should be focusing at the moment on allogeneic approaches, to develop standard treatments that will be applicable to the many, many desperately waiting patients.

In terms of feasibility and safety, whether autologous or allogeneic approaches should be employed depends on the end products and this should be evaluated on a case-by-case basis. I think it is wrong to think of regenerative medicine in a homogenous way. We should consider each disease and case separately.

MP: For neurological disorders immune rejection is less of a concern than for a number of other diseases. In my opinion, all first-in-human trials have to be conducted with cells that are first put through rigorous safety and efficacy testing prior to use in patients. This can be done with either allogeneic ESC-based or allogeneic iPSC-based grafting. As iPSCs encounter some additional concerns relative to ESCs due to their derivation via reprogramming, I think the most straightforward strategy would be to use ESCs. However, looking into the future, one can envision matched donor cells or personalized treatments, and those would only really be possible via cellular reprograming.

***CSC:* What are the pressing technical challenges that need to be addressed for full clinical potential to be reached?**

KE: While major progress has been made in developing strategies for directed differentiation of many cell types, it is still unclear how many of these will transfer well to culture conditions that comply with clinical requirements. I think that many groups will be surprised by what a challenge this will be. Still, I think that many of these challenges are only technical and that through time and effort they will be overcome. Another major challenge will be around reproducibility. Most differentiation schemes make heterogeneous mixtures of cells whose cellular constituents fluctuate in abundance from run to run. This is sort of like baking a fruitcake and having the abundance of cranberries, raisins, and currents change every time you make it. Better methods will need to be developed in many cases to allow the target cells of interest to be purified for downstream use.

MP: In my field we now have very good protocols for cell differentiation and we know we can generate cells that function on par with human fetal DA neurons from PSCs. The challenges that lie ahead are associated with meeting the regulatory requirements for cell production as well as safety and efficacy testing prior to use in patients. Related to this is the need to develop much better markers that predict the in vivo therapeutic efficacy and authenticity of grafted cells.

***CSC:* Where do you see the biggest gaps in our understanding of the basic science of iPSCs? In other words, what are the basic research questions that we still need to resolve for clinical translation?**

MP: A key issue remaining to be addressed is how we precisely and finely control the identity of the cellular products derived from PSCs so that we can generate cells that are very similar to the cells normally found in our bodies. Related to this is the challenge of determining the identity of cells generated in a dish. In the brain, for example, cell identity is often governed by anatomical location and projections and this is lost in vitro. We therefore need much more refined methods for determining the exact identity and functional potential of cells generated from stem cells.

KE: There are many ways to go with this question; I think that one of the largest holes in our knowledge relating to use of iPSCs in transplantation studies centers around what happens to the cells after transplantation. Where do they go after transplantation? How well do differentiated cells survive, function, and integrate over the very long term after transplant? While many studies of function in vitro have been performed, transplant studies are still scarce in rodent models and rare in large animals. There needs to be considerable progress in that area. Additionally, in many cases a deep understanding of the detailed biology of the human differentiated cells we are trying to make from human iPSCs is lacking. For many scientists there are real challenges in obtaining the primary counterparts of cells that they wish to produce from human iPSCs and too often we rely on analogies with cells readily isolated from rodents. I hope in the future more effort will be applied to compare human iPSC-derived cell types to their actual human counterparts.

***CSC:* What do you view as the major regulatory challenges that the field faces for clinical use of hiPSCs?**

MT: We still need to develop a more sophisticated and comprehensive approach to thinking about and developing cell therapies that more fully considers the treatment as a whole. Regenerative medicine is a medicine that sometimes requires surgery. It is not completed only with cells.