Published in final edited form as:

World Neurosurg. 2011 ; 76(3-4): 270–275. doi:10.1016/j.wneu.2010.12.055.

Introduction to Induced Pluripotent Stem Cells: Advancing the Potential for Personalized Medicine

Johnathan D. Ebben, Michael Zorniak, Paul A. Clark, and John S. Kuo

Brain Tumor Research Laboratory, Department of Neurological Surgery, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin, USA

Abstract

Induced pluripotent stem (iPS) cell technology has enormous potential to advance medical therapy by personalizing regenerative medicine and creating novel human disease models for research and therapeutic testing. Before this technology is broadly used in the clinic, we must realistically evaluate its disease modeling and therapeutic potential. Recent advances including the use of iPS cells to successfully model spinal muscular atrophy in vitro, as well as new techniques in generating iPS cells with recombinant proteins have accelerated the prospects of iPS cells for clinical use in regenerative therapy. This review explores the development and limitations of iPS cell technology, presents a critical comparison of iPS cells and embryonic stem cells, and discusses potential clinical applications and future research directions.

Keywords

Embryonic stem cells; iPS cells; Regenerative therapy; Stem cell biology

THE DEVELOPMENT OF IPS CELLS

Induced pluripotent stem (iPS) cell technology grew out of a need to develop research strategies with the goal of creating individualized, patient-specific stem cell treatments, while developing a better academic understanding of the flexible identity of stem cells (1). Previous efforts had already been made to develop patient-specific embryonic stem (ES)–like cells through methods such as nuclear transfer, involving either the fusion of ES cells with somatic cells or the transfer of somatic nuclear contents into an oocyte (19). Unfortunately, both of these methods pose unique challenges. Somatic nuclear transfer technology raised many bioethical questions, and continues to be a challenging procedure on a technical level. Likewise, fusing ES cells with somatic cells poses technical challenges that have hindered this technique. In Japan, Takahashi and Yamanaka in the Yamanaka group boldly hypothesized that ES cell–like behavior could be induced without fusing ES and somatic cells by reproducing the signaling that occurs during somatic nuclear transfer and ES fusion, thereby conferring totipotency or pluripotency on the treated cells (17). These researchers further theorized that these factors were likely the same as those involved in the epigenetic regulation and maintenance of ES cell characteristics. Of particular interest were several transcription factors, including Oct3/4, Sox2, and Nanog, all of which play a key

© 2011 Elsevier Inc. All rights reserved.

To whom correspondence should be addressed: John S. Kuo, M.D., Ph.D., [j.kuo@neurosurgery.wisc.edu].

Conflict of interest statement: M.Z. was supported by the Neuroscience Training Program NIH NRSA GM007507 grant. P.A.C. was partially supported by a NIH T32 postdoctoral fellowship in the University of Wisconsin Stem Cell Postdoc Training Program. This work was supported by funding to J.S.K. from the Department of Neurological Surgery, Graduate School, and Medical School at the University of Wisconsin, HEADRUSH Brain Tumor Research professorship and the Roger Loff Memorial Fund for GBM Research.

role in the maintenance of ES cells (9, 17). The Yamanaka group analyzed a total of 24 separate genes believed to play a role in ES development and maintenance to develop a final “cocktail” of transcription factors that were necessary to induce the formation of pluripotent cells. A number of these genes raised concern because of their implication in on-cogenesis, including c-Myc, Stat3, E-Ras, Klf4, and beta-catenin, all of which are involved in rapid cell proliferation. After experimenting with different combinations of transcription factors, Oct3/4, Sox2, c-Myc, and Klf4 were found essential to the development of iPS cells, which were first successfully derived from mouse fibroblasts (Figure 1). However, even when this transcription factor cocktail was optimized, cell transformation rates remained low. This technical challenge, combined with the necessary oncogenic c-Myc and Klf4 factors, created a potential hurdle to therapeutic application of iPS cell technology (17). In addition, the process to generate and culture iPS cells developed from transformed mouse fibroblasts can take between 15 and 20 days (15).

To prove the pluripotency of these newly generated cells, which demonstrated a morphology and a genotype similar to ES cells, a number of critical tests were conducted, including the ability of the cells to form teratomas (nontumor masses containing all of the distinct primary germ lines) as well as viable chimeras with injection into mouse blastocysts.

Since the early studies performed on mouse fibroblasts, iPS cells were also successfully derived from human adult and fetal fibroblasts by the Thomsen group in Madison, Wisconsin, United States. More definitive evidence came when iPS cells were successfully generated using the same cocktail of transcription factors as previously described by Park et al. and Takahashi et al. in fetal human tissue (14, 16). Subsequently, iPS cells were successfully derived from adult human fibroblasts, obtained from a skin biopsy (8). This advancement has revolutionized our understanding of cellular identity as well as expanded our tool kit for cell replacement therapies.

iPS TECHNOLOGY OFFERS DISTINCT ADVANTAGES

For years, researchers had been working with ES cells that demonstrate a great deal of plasticity and have many of the same capabilities of iPS cells. However, the development of iPS cells brings a number of potential advances that could not have been achieved through the use of ES cells alone. The key to the utility of ES cells is their inherent plasticity. iPS cells offer cellular plasticity with some distinct advantages in a clinical setting. First, iPS cells do not engender the same immune rejection risks when used therapeutically, since they are autologous cells that are unique to each patient (13). Because iPS cells are derived from individual patient cells, iPS cells also offer scientists an opportunity to model disease in vitro on a patient-by-patient basis, enabling screening for individual genomic differences that may aid in disease progression, or even for pharmacologic screens to determine which pharmacologic agents are ideal for each individual (2). Additional research will be significant in unlocking the potential of iPS cells.

FINE-TUNING iPS CELL ENGINEERING

Despite their utility in both the research and ultimately clinical settings, there are still significant barriers and obstacles that must be overcome before iPS cell technology becomes relevant for human therapeutics. One of the principal barriers lies in the methodology used to create iPS cells. Generating the pluripotent state can be particularly dangerous because of the use of transcription factors that are highly linked to oncogenicity, such as c-Myc and Klf4. Typically, viruses have been used to deliver these transcription factors, which presents a number of unique problems. The use of viral vectors to deliver reprogramming factors raises potential issues over the incorporation of viral DNA into the genome that could dampen iPS clinical applicability. Integration of the vector can result in insertional

mutations that can alter the function of iPS cells, and which can lead to tumorigenesis in certain cases (10).

Beyond the limitations of transfection vectors, iPS technology also faces a serious limitation in terms of dependence on a defined set of transcription factors that are associated with oncogenicity to reach the pluripotent state. There has been progress on this front, as dangerous transcription factors such as c-Myc that are linked to on-cogenesis have been found to be dispensable to the generation of the pluripotent state. Reprogramming of human skin fibroblasts to pluripotency has been achieved with only two factors, Sox2 and Oct4, through the use of a histone deacetylase inhibitor (5). This technique raises the possibility that iPS cells could be generated through chemical means that does not require the direct or indirect use of oncogenic factors. However, one particular problem that arises when iPS cells are developed without c-Myc is significantly decreased transformation efficiency.

Efforts have been ongoing to develop methods of increasing transformation efficiency, without having to resort to transcription factors such as c-Myc. One of the avenues that has been explored is the use of microRNAs, short sequences of RNA that act on a posttranscriptional basis to regulate genetic expression, which also appear to be intimately tied into the regulation of pluripotency. It appears that some microRNAs, such as microRNA-294, are part of the body's natural pluripotency regulation framework, with important consequences for iPS technology. When microRNA-294 is exogenously applied to developing iPS cells that have not been transfected with factors such as c-Myc, the microRNA acts to dramatically increase the efficiency with which fibroblasts are transformed to iPS cells (6). It should be noted that factors such as Oct4, Sox2, and Klf4 were still necessary. It is hoped that as additional progress and understanding of the microRNA regulation of cell state is refined that this method could be further applied to increase transformation efficiency and potentially decrease the number of other transcription factors that must be applied.

Significant progress has also been made in developing alternative methods of delivery for reprogramming factors, in developing new vectors that minimize concerns over viral integration into the genome, and in utilizing recombinant proteins, rather than viral vectors to induce pluripotency (21). In particular, a recent approach that involved using viral vectors derived from Epstein–Barr virus has shown promise (20). This vector, known as oriP/EBNA enabled the development of iPS cells that exhibit no trace of the viral genome or of any transgenic genes. Initially, viral DNA was incorporated into first-generation iPS cells that were derived; however, over time, cultured iPS cells gradually lost their episomal vectors and any trace of Epstein–Barr viral DNA or other exogenous genetic material. iPS cells free of exogenous DNA were successfully isolated and then cultured to expand subclones that exhibited no trace of transgenes and met basic criteria of iPS cells, including successful formation of teratomas, and display of similar morphology to ES cells and a genotype that also exhibited key ES characteristics (20). Still, this approach also has limitations; the efficiency with which fibroblasts were successfully transformed to a pluripotent state was relatively low, and in this study, c-Myc was used to enhance the transformation efficiency. As fibroblast culture techniques improve, it may be possible to address low transformation efficiency by culturing large amounts of fibroblasts, providing readily available iPS cells in spite of low overall efficiencies (20).

Other innovative approaches that prevent integration of viral genes or genetic modification of the host cell have also been developed, allowing for transfection without the use of viruses. These vectors are generated by splicing together the required pluripotency factors with peptide 2A sequences. The peptide 2A sequences allow all of the required pluripotency factors to be spliced together into a single plasmid, which can then be introduced to host

cells. The peptide 2A sequence acts by a mechanism that has not yet been entirely elucidated to prevent translation of specific sequences of DNA. Its use also allows for the transgene to be subsequently excised, once the pluripotency-promoting factors have been administered using the transposase enzyme (7, 11).

One of the most significant advances that also aims to tackle the problems of viral transfection may be a new technique that eliminates the use of any genetic material in the generation of iPS cells. Oct4, Sox2, Klf4, and c-Myc protein were fused together, along with a polyarginine protein transduction domain that was subsequently solubilized and introduced to target cells. The recombinant protein was successfully taken up by target cells, and a pluripotent state was generated. The resulting iPS cells that were morphologically similar to ES cells exhibited pluripotency markers and were capable of generating chimeras (21). Since the debut of induced pluripotency, scientists have found creative ways to engineer and reengineer iPS cells.

HARNESSING iPS CELLS TO DEVELOP IMPROVED DISEASE MODELS

With these ongoing efforts to ameliorate the serious challenges to the clinical use of iPS cell technology, through the use of safer vectors and safer means of inducing pluripotency, research has focused on developing clinical applications for iPS cells that harness their full potential. One of the many benefits that iPS technology can offer is the development of robust and personalized models of disease. In a proof-of-principle experiment, a team successfully cultured iPS cells from the fibroblasts of an 82-year-old adult amyotrophic lateral sclerosis patient, and then directed them to differentiate into motor neurons (2). Similarly, a group at the University of Wisconsin subsequently successfully generated diseased iPS cells from the skin fibroblasts of a patient suffering from spinal muscular atrophy, a leading inherited genetic disease that often leads to infant mortality. These iPS cells were generated and expanded in culture from the isolated fibroblasts, and directed to differentiate into motor neurons. Importantly, these differentiated cells demonstrated selective deficits compared with motor neurons generated by an individual not affected by spinal muscular atrophy (3). This experiment was the first to develop iPS cells from a patient suffering from a genetically inherited disease while replicating the deficit in that cell type (3). This process may enable scientists to better model diseases and disease development in vitro, allowing a better understanding of disease progression and potential therapeutic strategies. There is also hope that this type of robust model would allow for a more efficacious pharmacologic discovery as well that could revolutionize the way disease is treated (Figure 2) (2, 3).

iPS cell modeling of disease and disease progression could also further the dream of personalized medicine, by allowing doctors and scientists to model the developmental course of a degenerative disease within each patient—an unimaginable feat as of 5 years ago. The prospect of developing patient-specific iPS cells raises a host of possibilities, including modeling an individual patient's disease state in vitro, as well as personalized pharmacologic screens to determine the best therapeutic course, and individual genomic testing that may enable scientists and clinicians to attack the core genetic elements of the disease state.

There is hope that the development of iPS cells from individuals affected by other diseases could also be of clinical and research utility. Already, there are efforts underway to model many diseases that involve Mendelian inheritance (and some that involve more complicated inheritance) using iPS cells, including juvenile-onset, type 1 diabetes mellitus, Down syndrome, and others (12).

NEW CLINICAL APPLICATIONS

Although iPS cells have produced much excitement in the scientific community, the prospect that one cell type might be directly transformed into another is also tantalizing. The development of iPS technology has taught us much about the regulatory mechanisms that determine cell state and plasticity—vital building blocks of any effort to develop class switching (transforming a differentiated cell of one lineage into a cell of a different lineage). In particular, this strategy could be highly useful for diseases such as certain subtypes of diabetes, where insulin-secreting pancreatic beta cells have been largely destroyed, whereas other pancreatic cells remain. Application of a defined set of transcription factors (i.e., Ngn3, Pdx1 and Mafa) has allowed for the functional transformation of pancreatic exocrine cells to cells that resemble insulin-secreting beta cells in terms of morphology and function, having been shown to produce and secrete insulin in in vivo mouse models (22). It is also hoped that as a clearer picture of the cellular machinery that is used to maintain a given cell state comes into view, we will be able to more easily manipulate that machinery to transition terminally differentiated cells between different lineages.

This approach allows for the transformation of existing cells to a desired cell type without reverting to an early embryonic state, which can offer a number of therapeutic advantages. It should also be noted that the Zhou group transformed pancreatic exocrine cells under in vivo rather than in vitro conditions. This technique may have allowed the cells to develop in their niches, allowing them to more fully integrate into the pancreas and respond to pancreatic signaling (22).

APPLICATION OF iPS CELLS TO DISEASE STATES—TREATING SICKLE CELL ANEMIA IN MICE

Recent progress with iPS technology in providing clinical proof-of-principle experiments that show the usefulness of the technology have not been solely confined to diabetes and pancreatic models. Significant iPS cell work has also been done in developing therapies and proof-of-principle demonstrations in sickle cell anemia models. In a human sickle cell model, where mice are genetically modified to express homozygous human β^S mutations in the hemoglobin beta chain, scientists have provided additional support for the efficacy of iPS-based therapy as a viable sickle cell treatment. The overall treatment strategy involved culturing and deriving iPS cells from mouse fibroblasts, along the lines of the methods employed by Takahashi and Yamanaka (17). After the successful generation of iPS cell lines that were shown to produce teratomas and viable chimeras, the genetic defect in the hemoglobin beta chain was corrected by homologous recombination, accomplished with viral vectors. Using a specific combination of factors known to play a role in the differentiation of ES cells, the corrected iPS cells were directed to form hematopoietic progenitor (HP) cells, which were then transplanted back into the irradiated sickle cell mice to determine efficacy of the HP cells in generating healthy erythrocytes that could reverse the symptoms of sickle cell anemia (4). The irradiated mice that were successfully infused with the iPS-derived HP cells demonstrated remarkable improvements in terms of reticulocyte count (an indicator of sickle cell anemia) as well as overall red blood cell count and in urine concentration defects (caused by the interference of sickle cells with normal renal function). The treated mice also experienced weight gain and improved respiration, demonstrating further recovery from sickle cell anemia.

Importantly, none of the treated mice developed a malignancy despite the introduction of HP cells derived from iPS cells that were created with c-Myc. However, it is important to note that despite the efficacy of the treatment, concern remains that a future malignancy could develop, especially in view of the viral vectors that were used in this experiment,

necessitating additional trials and careful monitoring of mice to evaluate potential safety concerns, should similar therapies be applied to human trials at some point in the future (4). The Hanna group provided one of the first proof-of-principle studies indicating a successful treatment modality could be developed using iPS technology, although this experiment and model must be replicated and verified by other groups. This discovery has generated broad excitement and provided impetus to other iPS researchers to expand the range of tested iPS therapeutic models.

iPS CELLS AND PARKINSON DISEASE IN A RAT MODEL

In that vein, other groups have attempted to replicate the therapeutic success enjoyed by the Hanna group in an effort to expand the spectrum of diseases to which iPS cells can be applied. Recent successes in rat models of Parkinson disease (PD) have provided another case study of the promise of iPS technology. Death of midbrain dopamine-producing neurons causes the motor deficits experienced by PD patients. Developing replacement dopamine cells that can integrate themselves synaptically into the recipient brain could provide an advance in the treatment of the symptoms and development of PD. Because of their plasticity and ability to undergo directed differentiation, iPS cells are a promising candidate to accomplish this task (Figure 3). Wernig et al. (18) provide data that suggest recovery in rat models of PD, using iPS cells. The Wernig group successfully cultured iPS cells from rat fibroblasts, using the same defined factors previously detailed by Takahashi et al. (17). Because of their similarity to ES cells in terms of morphology, proliferative ability, and differentiation, Wernig et al. applied a differentiation protocol that had already been developed from ES cells to induce neuronal differentiation. By applying Sonic Hedgehog and FGF8, more specific differentiation into the midbrain dopamine-producing neuronal subtype was achieved. On implantation of the differentiated, midbrain dopamine-producing cells, which had been engineered to produce green fluorescent protein, successful synaptic integration was visualized through green fluorescence and immunolabeling. Labeling also revealed that the grafted cells expressed similar traits to midbrain dopaminergic neurons, in morphologic terms. Analysis of the behavior of the rats that had received the iPS treatment demonstrated marked improvement. In a typical rat where the midbrain dopamine-producing cells have been lesioned, a clear rotational bias was evident when stimulated with amphetamines. In the case of the iPS cell-treated rats, such a bias was not evident in four of five cases (18).

Although the results reported by the Wernig group demonstrate another potential therapeutic avenue where iPS cells could be successful, more work must be done to both substantiate the research and to apply it in other disease models.

FUTURE OF iPS CELLS IN NEUROSURGICAL THERAPIES

iPS cells have an immediate impact by generating new human cell-based disease and pharmacologic models that could be of enormous potential benefit in developing novel disease treatments. Yet, significant challenges and obstacles remain to iPS cell technology and use in personalized therapies. As time progresses and innovative research continues, there is great hope that these obstacles can be overcome, allowing iPS cells to approach clinical relevancy and to have a genuine and substantial impact on the lives of patients. These advancements challenge clinicians and surgeons to bridge the gap from basic science to translational therapies. Discussions regarding delivery of cellular therapies into humans have begun, but must continue in order to foster safe and functional treatment options for patients with debilitating neurologic diseases and disorders. Neurosurgeons will play an essential role in the development and delivery of clinically relevant iPS therapies.

Abbreviations and Acronyms

ES	Embryonic stem
HP	Hematopoietic progenitor
iPS	Induced pluripotent stem

References

1. Constantinescu S. Stemness, fusion and renewal of hematopoietic and embryonic stem cells. *J Cell Mol Med.* 2003; 7:103–112. [PubMed: 12927049]
2. Dimos JT, Rodolfa KT, Niakan KK, Weisenthal LM, Mitsumoto H, Chung W, Croft GF, Saphier G, Leibel R, Goland R, Wichterle H, Henderson CE, Eggan K. Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. *Science.* 2008; 321:1218–1221. [PubMed: 18669821]
3. Ebert AD, Yu J, Rose FF Jr, Mattis VB, Lorton CL, Thomson JA, Svendsen CN. Induced pluripotent stem cells from a spinal muscular atrophy patient. *Nature.* 2009; 457:277–280. [PubMed: 19098894]
4. Hanna J, Wernig M, Markoulaki S, Sun CW, Meissner A, Cassady JP, Beard C, Brambrink T, Wu LC, Townes TM, Jaenisch R. Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin. *Science.* 2007; 318:1920–1923. [PubMed: 18063756]
5. Huangfu D, Osafune K, Maehr R, Guo W, Eijkelenboom A, Chen S, Muhlestein W, Melton DA. Induction of pluripotent stem cells from primary human fibroblasts with only Oct4 and Sox2. *Nat Biotechnol.* 2008; 26:1269–1275. [PubMed: 18849973]
6. Judson RL, Babiarz JE, Venere M, Blueloch R. Embryonic stem cell-specific microRNAs promote induced pluripotency. *Nat Biotechnol.* 2009; 27:459–461. [PubMed: 19363475]
7. Kaji K, Norrby K, Paca A, Mileikovsky M, Mohseni P, Woltjen K. Virus-free induction of pluripotency and subsequent excision of reprogramming factors. *Nature.* 2009; 458:771–775. [PubMed: 19252477]
8. Lowry WE, Richter L, Yachechko R, Pyle AD, Tchieu J, Sridharan R, Clark AT, Plath K. Generation of human induced pluripotent stem cells from dermal fibroblasts. *Proc Natl Acad Sci U S A.* 2008; 105:2883–2888. [PubMed: 18287077]
9. Masui S, Nakatake Y, Toyooka Y, Shimosato D, Yagi R, Takahashi K, Okochi H, Okuda A, Matoba R, Sharov AA, Ko MS, Niwa H. Pluripotency governed by Sox2 via regulation of Oct3/4 expression in mouse embryonic stem cells. *Nat Cell Biol.* 2007; 9:625–635. [PubMed: 17515932]
10. Okita K, Ichisaka T, Yamanaka S. Generation of germline-competent induced pluripotent stem cells. *Nature.* 2007; 448:313–317. [PubMed: 17554338]
11. Okita K, Nakagawa M, Hyenjong H, Ichisaka T, Yamanaka S. Generation of mouse induced pluripotent stem cells without viral vectors. *Science.* 2008; 322:949–953. [PubMed: 18845712]
12. Park IH, Arora N, Huo H, Maherali N, Ahfeldt T, Shimamura A, Lensch MW, Cowan C, Hochedlinger K, Daley GQ. Disease-specific induced pluripotent stem cells. *Cell.* 2008; 134:877–886. [PubMed: 18691744]
13. Park IH, Lerou PH, Zhao R, Huo H, Daley GQ. Generation of human-induced pluripotent stem cells. *Nat Protoc.* 2008; 3:1180–1186. [PubMed: 18600223]
14. Park IH, Zhao R, West JA, Yabuuchi A, Huo H, Ince TA, Lerou PH, Lensch MW, Daley GQ. Reprogramming of human somatic cells to pluripotency with defined factors. *Nature.* 2008; 451:141–146. [PubMed: 18157115]
15. Stadtfeld M, Maherali N, Breault DT, Hochedlinger K. Defining molecular cornerstones during fibroblast to iPS cell reprogramming in mouse. *Cell Stem Cell.* 2008; 2:230–240. [PubMed: 18371448]
16. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell.* 2007; 131:861–872. [PubMed: 18035408]

17. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006; 126:663–676. [PubMed: 16904174]
18. Wernig M, Zhao JP, Pruszak J, Hedlund E, Fu D, Soldner F, Broccoli V, Constantine-Paton M, Isacson O, Jaenisch R. Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. *Proc Natl Acad Sci U S A*. 2008; 105:5856–5861. [PubMed: 18391196]
19. Wilmut I, Schnieke AE, McWhir J, Kind AJ, Campbell KH. Viable offspring derived from fetal and adult mammalian cells. *Nature*. 1997; 385:810–813. [PubMed: 9039911]
20. Yu J, Hu K, Smuga-Otto K, Tian S, Stewart R, Slukvin II, Thomson JA. Human induced pluripotent stem cells free of vector and transgene sequences. *Science*. 2009
21. Zhou H, Wu S, Joo JY, Zhu S, Han DW, Lin T, Trauger S, Bien G, Yao S, Zhu Y, Siuzdak G, Scholer HR, Duan L, Ding S. Generation of induced pluripotent stem cells using recombinant proteins. *Cell Stem Cell*. 2009; 4:381–384. [PubMed: 19398399]
22. Zhou Q, Brown J, Kanarek A, Rajagopal J, Melton DA. In vivo reprogramming of adult pancreatic exocrine cells to beta-cells. *Nature*. 2008; 455:627–632. [PubMed: 18754011]

Figure 1.

Generation of induced pluripotent stem (iPS) Cells. Typically skin fibroblasts are obtained from a patient and cultured to produce a stable cell line. Variations of four transcription factors are introduced via different transfection technologies to induce pluripotency. Three criteria are used to evaluate their similarity to embryonic stem cells: 1) in vitro differentiation into multiple cell types, 2) genotyping to look for defined embryonic markers, and 3) generation of teratomas that resemble the three germ layers in embryogenesis (not shown).

Figure 2.

Induced pluripotent stem (iPS) Cells are Amenable for Personalized Disease Modeling and Drug Screening. iPS cell technology advances our ability to personalize medicine. We can now take fibroblasts from a patient with Parkinson disease, for instance, differentiate the cells into dopaminergic neurons, and study the pathophysiology of the disease in a dish. Because these differentiated cells are from a renewable stock of iPS cells, large drug screens can be performed to find an appropriate drug to treat the unforeseen malady in each patient. Tailor-made therapies can be designed for these patients without removing surgically inaccessible tissues.

Figure 3.

Induced pluripotent stem (iPS) Cell Replacement Therapies. As embryonic stem cells have been purported for cellular replacement therapies, iPS cells broaden the pool of material that can be used for these treatments. Whether a patient has a traumatic brain injury or Parkinson disease, iPS cells can potentially be used to treat these conditions. In a patient with germline genomic deficiencies, iPS cell technology offers the possibility to correct the disturbance before being delivered to the patient.