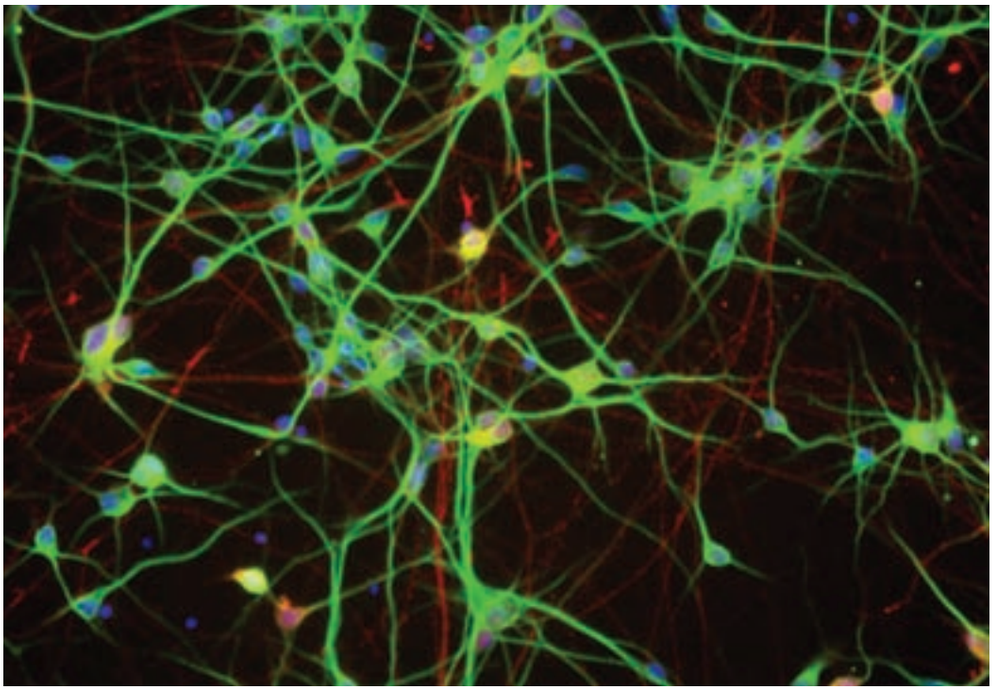
Resetting the course of drug development: stem cell banking in support of drug discovery

The discovery by Yamanaka and Thomson in 2007 that human somatic cells can be reprogrammed to a pluripotent state (ie, induced pluripotent stem cells, iPSCs) has revolutionised cell biology. Leveraging experience with human embryonic stem cells (hESC), directed differentiation of iPSCs into a number of terminal cell lineages is not only possible, but when done in a robust and consistent manner, produces cells that have been shown to be a better representative of *in vivo* biology than alternatives such as primary tissues and immortalised cell lines. A number of proof of principle experiments have demonstrated that iPSC-derived tissues from donors with pathological diseases can recapitulate disease properties *in vitro*. This advancement in iPSC-derived tissues has led to worldwide interest and investment in creating iPSC banks from a wide variety of donors to address the fundamental question about genetic diversity and its role in disease pathogenesis as well as beneficial and deleterious response to drug treatment.

By Dr Thomas J Novak, Dr Uta Grieshammer, Dr Michael Yaffe and Dr Steve Madore

Despite a significant increase in research and development budgets, the success rate for biopharmaceutical drug discovery efforts, as measured by new drug approvals per dollar spent, has been falling for the past decade. Paradoxically, this decrease has occurred during a period of expanding knowledge of the genomic changes (including genome sequences, gene expression profiles, etc) associated with disease. Many reasons have been proffered for this decline in productivity, including a shift from designing drug screening assays based on disease characteristics displayed by cells (phenotypic screens) to approaches that pursue molecular targets (target-based screens); an increase in safety margins demanded by regulators; and an expectation by third-party payers and regulators that new drugs offer significant improvements over existing therapies[1,2]. While these and other factors, including non-scientifically-based business decisions, have surely played a role in pharma's diminishing drug approval rates, another key factor has been the lack of suitable human disease tissue for use in drug discovery and development efforts. Advances in human stem cell biology may finally change that.



A robust differentiation protocol that results in a consistent supply of biologically-relevant human cortical neurons (iCell® Neurons; Cellular Dynamics International) was developed and is now being used with patient-derived iPSC lines to produce functional neurons for modelling diseases

For years, drug hunters and those studying human disease biology have had to make do with surrogates for authentic human cells. Commonly used stand-ins such as immortalised cell lines or primary animal cells often represent a poor substitute for true human biology. In the case of immortalised cell lines, the molecular changes ('transformation') that render them immortal usually cause significant alterations to their biological functionality as well. Also, it is easier to transform actively dividing cells than non-dividing cells. Therefore, many cell types of interest, such as neurons, are difficult to convert to useful cell lines. Primary human tissue and cadaveric tissue, while authentic human cells, pose even greater challenges, not least of which is low availability. Primary human tissue, such as peripheral blood, from live donors can be a good source of some cell types, but many cell types cannot be collected for medical and ethical reasons. In addition, variables such as post-mortem interval (time between death and tissue harvest) for cadaveric tissue adversely affects sample quality and reproducibility.

In an attempt to surmount these challenges, the pharmaceutical industry embraced target-based screening in the early to mid-1990s. In this model, human genes encoding protein targets of interest were expressed in easily grown cell lines such as HEK or CHO, and these recombinant cell lines were used for high-throughput compound screening and lead optimisation[3]. The high efficiency of this approach also enabled the use of larger compound libraries than before, increasing the chances of identifying active compounds. The results were often highly potent and selective compounds affecting the function of the protein target under investigation; unfortunately, many of these candidates failed in the clinic, and a recent review of new drug approvals in the 10-year period from 1999-2008 has shown that phenotypic screens were more likely to lead to a new medicine than target-based screens[4].

There are several reasons why this might happen. First, the target may not play as important a role in human disease as was previously thought. In spite of the tremendous increase in our understanding of disease biology, most complex (ie, multigenic) disorders are exceedingly complicated in biological terms and may not respond well to single points of intervention. In particular, unlike Mendelian disorders, many of the complex diseases that pharmaceutical companies are interested in treating appear to be caused by small contributions from many genes. In this scenario, no single

References

1 Pammoli, F, Magazzini, L and Riccaboni, M (2011). The productivity crisis in pharmaceutical R&D. Nat Rev Drug Discov 10(6):428-438.

2 Paul, SM, Mytelka, DS, Dunwiddie, CT, Persinger, CC, Munos, BH, Lindborg, SR and Schacht, AL (2010). How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov 9(3):203-214.

3 Walters, WP and Namchuk, M (2003). Designing screens: how to make your hits a hit. Nat Rev Drug Discov 2(4):259-266.

4 Swinney, DC and Anthony, J (2011). How were new medicines discovered? Nat Rev Drug Discov 10(7):507-519.

5 An, WF, Bowlby, MR, Betty, M, Cao, J, Ling, HP, Mendoza, G, Hinson, JW, Mattsson, KI, Strassle, BW, Trimmer, JS and Rhodes, KJ (2000). Modulation of A-type potassium channels by a family of calcium sensors. Nature 403(6769):553-556.

6 Grskovic, M, Javaherian, A, Strulovici, B and Daley, GQ (2011). Induced pluripotent stem cells- opportunities for disease modelling and drug discovery. Nat Rev Drug Discov 10(12):915-929.

7 Merkle, T and Eggan, K (2013). Modeling human disease with pluripotent stem cells: from genome association to function. Cell Stem Cell 12(6):656-668.

8 Thomson, JA, Itskovitz-Eldor, J, Shapiro, SS, Waknitz, MA, Swiergiel, JJ, Marshall, VS and Jones, JM (1998). Embryonic stem cell lines derived from human blastocysts. Science 282(5391):1145-1147.

9 Takahashi, K and Yamanaka, S (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126(4):663-676.

10 Takahashi, K, Tanabe, K, Ohnuki, M, Narita, M, Ichisaka, T, Tomoda, T and Yamanaka, S (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131(5):861-872.

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gene may play an important enough role that its modulation will have a clinically significant impact. Second, different cell types express overlapping but distinct sets of proteins, which interact in specific, but often unpredictable, ways. Screening a molecular target that is normally active in neurons in a non-neuronal cell type removes it from its native context, and in this non-native environment the target may not demonstrate normal function[5]. Hits that seem promising in such contrived systems may fail to work as expected *in vivo*, when the target protein needs to be perturbed in its native cellular milieu.

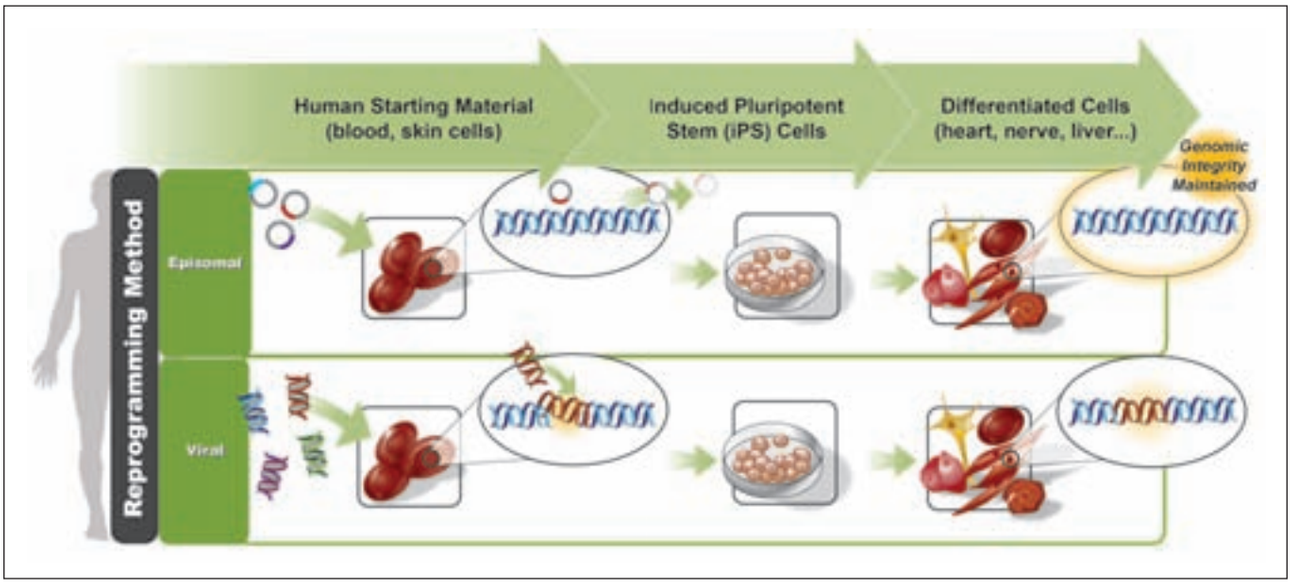
Fortunately, exciting advances in human stem cell biology are poised to address many of these problems. The ability to generate fully functional human cells from stem cells opens up new possibilities for drug discovery and development campaigns and holds the promise of improving the selection of clinically relevant drug candidates. A major contributor to that effort will be the collection of a large number of donor samples (blood or fibroblasts) that can be used to generate patient-specific iPSC lines[6,7].

iPSC potential energises discovery process

Human embryonic stem cells (hESCs) were first isolated in 1998 by Dr James Thomson[8]. These cells display the hallmarks of pluripotent stem cells as they have unlimited capacity for expansion and in principle can generate every cell type in the human body.

Efforts to understand the molecular basis of pluripotency led to the startling discovery by Yamanaka and colleagues in 2006 that the introduction of a four-gene cocktail (Oct4, Klf4, Sox2, c-Myc) into mouse fibroblasts reprogrammed them into pluripotent stem cells[9]. The production of these so-called induced pluripotent stem cells (iPSCs) set off a frenzy of activity and in 2007 both Yamanaka (who would win a Nobel Prize in 2012 for his discovery) and Thomson announced the successful reprogramming of human fibroblasts[10,11]. Progress came swiftly and today reprogramming of numerous human adult cell types to iPSCs is a well-established technique.

The reasons iPSC technology has so energised the scientific community are two-fold. First, the use of adult skin fibroblasts or peripheral blood cells as the starting material for reprogramming makes it less controversial, removing the social and political objections that accompanied hESC research. Second, while hESCs and iPSCs both have the potential to differentiate into any cell in the body, the latter possess the substantial advantage that they can be derived from adults with any disease of interest. So-called 'patient-specific' iPSC lines were first reported in 2008 by the laboratories of George Daley and Kevin Eggan at Harvard. Daley's lab generated iPSC lines from donors with a variety of Mendelian and complex (multigenic) disorders[12]. Eggan's lab not only generated patient-specific iPSC lines from two elderly sisters with Amyotrophic Lateral Sclerosis (ALS), they also differentiated them into spinal motor neurons, the cells that are affected in ALS[13]. Since then, iPSC lines have been generated from individuals



Originally the four reprogramming genes were introduced into adult cells by use of an integrating lentivirus vector. Although efficient, this method results in permanent genomic alterations at the site of viral insertion. These insertions can affect the behaviour of the resulting iPSC lines and some may even cause tumour formation *in vivo*. The CIRM Human iPSC Initiative chose to use non-integrating episomal vectors to reprogramme adult cells in order to avoid these potentially confounding problems. Note that other non-integrating methods exist as well (eg, using mRNAs encoding the reprogramming factors or the recombinant proteins themselves. Sendai virus is another vector gaining popularity)

Table 1. Large-scale banks of patient-specific iPSC lines that are completed, in development, or anticipated[1]

SPONSOR	APPROXIMATE # DONORS[2]	DISEASES
California Institute for Regenerative Medicine (CIRM)	3,000	Alzheimer's Disease; Idiopathic Pulmonary Fibrosis; Idiopathic Familial Dilated Cardiomyopathy; Blinding diseases; Infantile epilepsy; Cerebral Palsy; Viral hepatitis; Non-alcoholic steatohepatitis; Autism spectrum disorders (ASD)
UK Human iPSC Initiative ('HipSci')	1,000	Unknown; many will be chosen for genetic diversity
StemBANCC	500	Diabetes and diseases of PNS/CNS; also some donors with specific drug responses
Michael J Fox Foundation	700	Parkinson's Disease (PD)
US National Institute of Mental Health	500	Schizophrenia; Bipolar Disorder; ASD
Framingham Heart Study and Harvard Stem Cell Institute	400	Heart Attack; Stroke; Diabetes
Personal Genome Project	300-400	Unknown
NIH Undiagnosed Disease Program & NY Stem Cell Foundation	100	Undiagnosed and rare diseases
US National Institute of Neurological Disorders and Stroke & CIRM	10-20 each	Huntington's Disease; PD; Amyotrophic Lateral Sclerosis
US NIH	10-20,000	Wide-ranging (this number reflects cumulative activities funded by NIH)
Guangzhou Institutes of Biomedicine & Health (China)	10-100,000	Wide-ranging

[1] Except for the US NIH row, this table focuses on large collaborative efforts to generate patient-specific iPSC lines, usually focused on one or a few diseases. It does not include the thousands of lines that are being generated in academic and industry labs around the world.
[2] Note that most banks plan on generating multiple iPSC clones per donor. Also, the donor pool usually contains a number of matched control samples. For example, the CIRM project is generating three clones per donor and is collecting ~2,400 disease samples and ~600 controls. This is typical.

with dozens of diseases[6]. In fact, the potential of these cells is so great that numerous worldwide efforts have been launched to build large banks of patient-derived iPSC lines (**Table 1**). Some banks are also collecting samples based not on disease status, but rather to address the issue of genetic diversity in the human population. Both should prove useful to improving drug development.

Patient-specific iPSC lines have significant potential in drug discovery. Not only are these cells human, they are massively expandable. Additionally, if they express disease characteristics upon differentiation to the affected cell type, they can be easily employed for compound screens to identify potential drugs that normalise function or to better understand disease progression and/or pathophysiology. Patient-specific iPSC lines thus provide a means to run phenotypic screens in an authentic context of diseased human cells. Further, a collection of genetically diverse iPSC lines provides a means to test the safety of compounds in a more relevant system, representing the genetic diversity of future patient populations, before committing to clinical development. Both examples are discussed below.

iPSC utility in action

A 2011 review lists more than 50 diseases for which hESC or iPSC lines have been developed, although not all have been well characterised[6]. This is remarkable progress considering the first patient-specific lines were not isolated until 2008,

and it highlights the excitement and energy generated by reprogramming technology. A few examples should serve to illustrate the utility of patient-derived lines.

- Individuals with mutations in any of several ion channels show abnormal electrocardiograms and are at risk of developing fatal arrhythmias (Long QT Syndrome [LQTS]). Over a dozen genes have been implicated in LQTS and several patient-derived lines have been differentiated into cardiomyocytes and studied using electrophysiology[14,15]. These mutant cardiomyocytes accurately recapitulate the aberrant cardiac function seen in patients and thus are useful models for discovering drugs that normalise function.
- Spinal muscular atrophy (SMA) is a disease that results in premature loss of spinal motor neurons and is usually fatal by age 10 (some less severe and adult-onset forms affect mobility but not life expectancy). The severe forms have no known treatment and are due to mutations in the Survival of Motor Neuron gene, SMN1. iPSC lines derived from SMA patients can be differentiated into spinal motor neurons which are less healthy and die faster than wild-type motor neurons[16]. They have also been used in a small compound screen to identify potential drugs that prolong the half-life of SMN1.
- Alzheimer's disease (AD) is a disease with an increasing prevalence and limited treatment options. Animal models have not led to the development of a new drug since the approval of memantine (Namenda) in 2002 (Europe; 2003 US). Several groups have used AD-derived iPSC lines (from both sporadic and familial cases) to generate neurons. There were no reported electrophysiological differences between any of the neurons; however, familial AD neurons typically show increased Aβ and phospho-tau production[17]. This is not surprising given that the familial lines possess amplified copies of the APP gene that gives rise to Aβ. AD neurons also demonstrated endoplasmic reticulum and oxidative stress that was variably relieved by docosahexaenoic acid, an omega-3 fatty acid that has been clinically evaluated in AD patients[18].
- Lastly, it should be noted that patient-specific iPSC lines are not the only ones with value. Cardiomyocytes derived from iPSCs from a normal individual have been used to test drug candidates for cardiotoxicity and proarrhythmogenic activity[19,20] and many pharmaceutical companies are now including the results from such preclinical assessments in their regulatory filings. Further, the FDA is examining ways in which iPSC-derived cardiomyocytes can be used in a Comprehensive *In-vitro* Proarrhythmia Assay (CIPA) to mitigate and/or obviate the need for the clinical thorough QT study. Current *in vitro* and *in vivo* regulatory guidelines call for cardiovascular/proarrhythmia risk to be assessed through blockade of the cardiac ion channel, hERG and/or a thorough QT study in humans (ICH documents S7b and E14, respectively). While these assays have been effective in reducing the risk of drug-induced cardiac arrhythmia, they are becoming increasingly recognised by some as overly sensitive and lacking in predictivity, thus beneficial drugs are being unnecessarily scuttled before they reach the clinic or market due to false positive results. Currently the Agency, through organisations such the Health and Environmental Safety Institute (HESI) and the Cardiac Safety Research Consortium (CSRC), is examining ways in which the native biology of iPSC-derived cardiomyocytes can be leveraged to increase the predictivity of the regulatory guidelines[21]. Thus, the field is seeing an amazing and concurrent adoption of iPSC technology by both pharmaceutical and regulatory agencies.

As more cell types become available (hepatocytes, in particular) they are likely to be increasingly used in preclinical assessments of toxicity. For example, hepatocytes from genetically diverse individuals (normal or diseased) can be used to evaluate metabolic differences prior to entering the clinic. Likewise, clinical drug candidates can be ranked based on efficacy shown on a panel of genetically diverse patient-specific cell lines. The ability to conduct *in vitro* 'clinical' trials may be the most important benefit of iPSC technology.

iPSC banking: opportunities and challenges

Although banks of patient-specific lines hold great promise for the future of drug discovery, their use does not come without significant challenges. First, whatever iPSC-derived differentiated cells one chooses to use must be made to stringent specifications and perform reproducibly from batch to batch. As with all new technologies, as the commercial opportunities in this space increase, more and more companies will step in to fill the need. In time, these cells will become a commodity rather than an exotic research reagent. However, even rigorously manufactured cells are of little use unless their expected disease characteristics can be well established. This is where the large-scale banking initiatives listed in **Table 1** will play an important

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11 Yu, J, Vodyanik, MA, Smuga-Otto, K, Antosiewicz-Bourget, J, Frane, JL, Tian, S, Nie, J, Jonsdottir, GA, Ruotti, V, Stewart, R, Slukvin, II and Thomson, JA (2007). Induced pluripotent stem cell lines derived from human somatic cells. Science 318(5858): 1917-1920.
12 Park, IH, Arora, N, Huo, H, Maherali, N, Ahfeldt, T, Shimamura, A, Lensch, MW, Cowan, C, Hochedlinger, K and Daley, GQ (2008). Disease-specific induced pluripotent stem cells. Cell 134(5):877-886.
13 Dimos, JT, Rodolfa, KT, Niakan, KK, Weisenthal, LM, Mitsumoto, H, Chung, W, Croft, GF, Saphier, G, Leibel, R, Goland, R, Wichterle, H, Henderson, CK and Eggan, K (2008). Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. Science 321(5893):1218-1221.
14 Moretti, A, Bellin, M, Welling, A et al (2010). Patient-specific induced pluripotent stem-cell models for long-QT syndrome. N Engl J Med 363(15):1397-1409.
15 Itzhaki, I, Maizels, L, Huber, I, Zwi-Dantsis, L, Caspi, O, Winterstern, A, Feldman, O, Gepstein, A, Arbel, G, Hammerman, H, Boulos, M and Gepstein, L (2011). Modelling the long QT syndrome with induced pluripotent stem cells. Nature 471(7337):225-229.
16 Ebert, AD, Yu, J, Rose, FF, Mattis, VB, Lorson, CL, Thomson, JA and Svendsen, CN (2009). Induced pluripotent stem cells from a spinal muscular atrophy patient. Nature 457(7227):277-280.
17 Israel, MA, Yuan, SH, Bardy, C, Reyna, SM, Mu, Y, Herrera, C, Hefferan, MP, Van Gorp, S, Nazor, KL, Boscolo, FS, Carson, CT, Laurent, LC, Marsala, M, Gage, FH, Remes, AM, Koo, EH and Goldstein, LS (2012). Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. Nature 482(7384):216-220.

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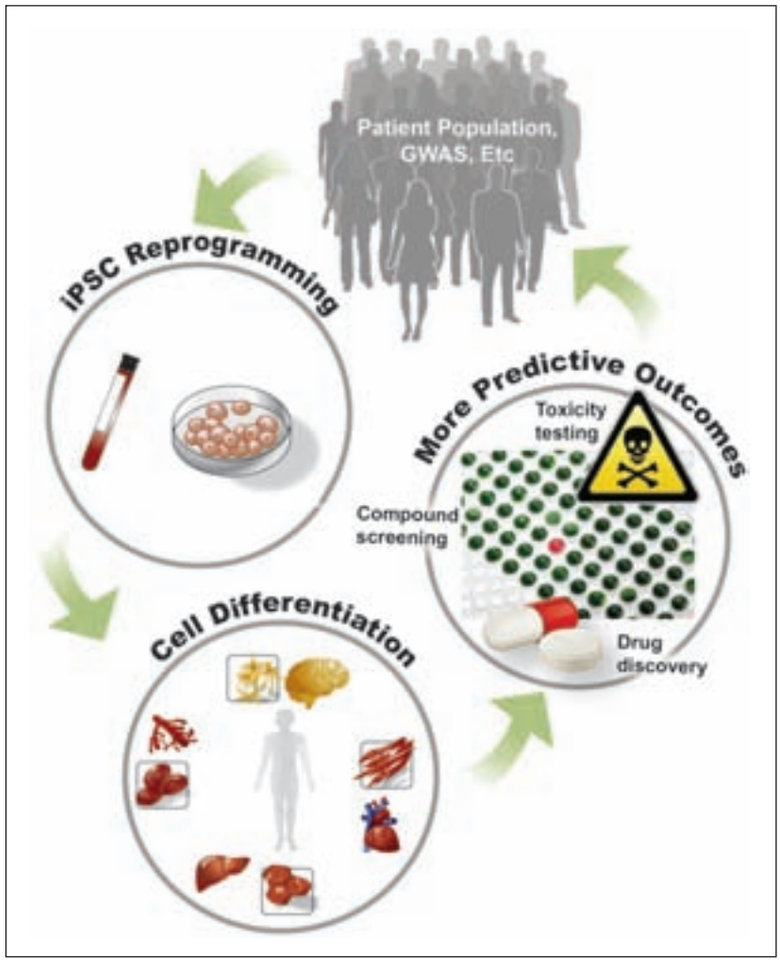

Large-scale iPSC banks can transform drug discovery by providing fully functioning human cells from numerous genetic and disease backgrounds. Donors can be chosen by various criteria, for example, HLA haplotype, the results of genomewide association studies (GWAS), the presence or absence of a particular disease, ethnicity, etc. The efficacy and safety of candidate drug molecules can then be assessed on cells derived from individuals likely to be recruited into that particular clinical trial. The results from such *in vitro* 'clinical trials' may allow tailored recruitment of those individuals most likely to benefit from the drug, thereby increasing the likelihood of a successful trial while also saving time and money.

role. The sponsors of these banks recognise that high quality clinical data must accompany each patient-derived iPSC line. Without such records it will not be possible to decide which lines to study, since even the most well-funded labs can examine only a fraction of the lines that will be generated. In some cases, additional genetic and genomic information will also need to be collected. For example, information regarding the status of known disease-causing or -modifying genes or chromosomal abnormalities will in many cases prove decisive in choosing lines for further study. Unless this data is collected and made available by the banks, this effort will fail to realise its potential. It would also be helpful if informed consent forms allowed for follow up contact with donors, including the collection of medical data that has emerged since the tissue collection occurred. Knowing which donors with a particular disease showed accelerated progression or enhanced survival would be enormously useful.

Large-scale iPSC banks will also make a significant contribution by standardising methodology. Although differentiated cells such as fibroblasts and blood can be reprogrammed to pluripotency by the introduction of a small number of genes, there are numerous methods for accomplishing that. The earliest reprogramming efforts utilised lentiviruses as gene vectors but these viruses integrate into the cells chromosomes, potentially altering cell behaviour. More recently, a number of non-integrating methods have been developed, and current banking efforts are committed to using these approaches to avoid chromosomal alterations as a confounding factor in cell behaviour[22]. Further, technological improvements now allow iPSCs to be grown without mouse feeder cells and in simpler media containing only human proteins[23].

Even assuming that the iPSC banks meet the challenges outlined above, it should not be assumed that drug discovery will immediately enter a new golden age of productivity. Several challenges exist in fully exploiting this technology. First, not all diseases are cell autonomous; that is, not all mutations exert their direct effects in the cell types that present with the disease characteristic. One well-characterised example of this phenomenon is Amyotrophic Lateral Sclerosis, or Lou Gehrig's disease, a devastating disorder in which spinal motor neurons begin to atrophy and die, with patient death usually occurring within a few years of diagnosis. In general, neurons generated from ALS-derived iPSC lines look healthy and function normally. Only when cultured in the presence of ALS-derived astrocytes (neuronal support cells) do the neurons die[24]. In fact, ALS-derived astrocytes also kill spinal motor neurons from normal individuals. In this case the interacting cell types have been identified, but this interplay between cell types may prove a challenge for other diseases. In some cases the interacting cell(s) may be known, but cannot yet be generated from stem cells due to the absence of a useful differentiation protocol.

Another reason that some diseases will be more difficult to model *in vitro* than others is that many complex diseases have both a genetic and an environmental component, the latter often completely unknown. An additional component of many diseases is time. Will it be possible to model diseases of ageing such as sporadic Alzheimer's Disease (AD), for example, without culturing cells for decades? Some early research suggests this will not be the case[17,18], but in this example very few sporadic AD lines have been studied. This leads to the next challenge – how many patient-specific lines should be studied in order to have a high level of

confidence that the disease phenotype is real and not an artifact of a given line? And how many control lines should be examined? For comparison, the examples given above generally utilised fewer than five disease lines and even fewer controls. The iPSC banks will ensure that plenty of lines are available for a particular disease, but resource constraints will limit most labs to studying only a handful. How big should that handful be? The answer to this question is unknown and will certainly vary for different diseases, but unless the patient-derived iPSC lines used in screening have been rigorously evaluated prior to selection, the results may be line-specific.

Lastly, many human diseases involve the interaction of multiple systems which will prove challenging to model in culture. In addition, diseases that affect behaviour (eg, schizophrenia, bipolar disorder) will require the development of surrogate readouts since some key features of the disease, such as negative affect and diminished executive function in schizophrenia, are complex higher order brain functions that will not easily yield to a reductionist approach. The use of surrogate markers is common in drug screening but it is fraught with uncertainty regarding the relevance of the surrogate to the disease of interest. Patient-specific iPSC lines cannot in all cases completely remove that risk.

A more prosaic challenge to the widespread adoption of patient-specific iPSC lines by pharmaceutical companies may be cost. Compared to widely used cell-based screening systems like CHO or HEK cells, iPSC-derived differentiated cells are at least an order of magnitude more expensive. In some cases, this difference may be justifiable immediately, simply because no other approach is available, or they have repeatedly failed. In other cases costs will have to come down before iPSC-derived cells are widely embraced, and this will likely occur as a result of improvements in cell culture media composition and differentiation protocols.

Conclusions

In a very short period of time, iPSC technology has become an important component of drug development. In particular, patient-derived lines are poised to play a key role in enhancing our understanding of disease etiology, improving the success of compound screens, and reducing attrition in the clinic by providing more predictive safety screens. The establishment of large banks of high quality iPSC lines accompanied by comprehensive medical and genetic information will reshape the way pharmaceutical companies approach drug discovery, and will, in time, provide tools to attack diseases with high unmet medical needs. The challenges are not insubstantial, but the progress of the past six years suggests the best is yet to come. DDW

***Dr Tom Novak** is VP, Strategic Partnerships, at Cellular Dynamics International. Previously he held a number of positions at Roche Palo Alto, including Head of Discovery Technologies. Dr Novak earned a BA in chemistry and biology from Amherst College and a PhD in molecular biology from Caltech. He began his pharmaceutical career as a scientist at Wyeth in Princeton, NJ.*

***Dr Uta Grieshammer** is a Science Officer at the California Institute for Regenerative Medicine, California's stem cell funding agency. She received her PhD from Boston University School of Medicine and did post-doctoral research at the University of California, San Francisco, interrogating the mechanisms of organ formation during embryonic development.*

***Dr Michael Yaffe** is Associate Director of Research Activities at the California Institute for Regenerative Medicine (CIRM). Prior to joining CIRM, Michael was a Professor of Biology at the University of California, San Diego where his laboratory studied cell growth and subcellular structure, with particular focus on mitochondria, the cellular power plants. He earned his PhD in Biochemistry from Harvard University and carried out postdoctoral research at the Biozentrum, University of Basel in Basel, Switzerland.*

***Dr Steve Madore** is Director of Biobanking at Coriell responsible for leading the Molecular Biology, Cell Culture and Stem Cell Laboratories. He has more than 10 years' experience in big pharma using gene expression profiling technology in support of drug discovery. He earned a BS in Microbiology in 1984 from the University of Massachusetts, Amherst and a PhD in Cell and Developmental Biology in 1991 from the State University of New York, Stony Brook.*

Continued from page 19

18 Kondo, T, Asai, M, Tsukita, K et al (2013). Modeling Alzheimer's disease with iPSCs reveals stress phenotypes associated with intracellular Aβ and differential drug responsiveness. Cell Stem Cell 12(4):487-496.
19 Guo, L, Coyle, L, Abrams, RMC, Kemper, R, Chiao, E and Kolaja, K (2013). Refining the human iPSC-cardiomyocyte arrhythmic risk assessment model. Toxicol Sci doi:10.1093/toxsci/kft205.
20 Harris, K, Aylott, M, Cui, Y, Louttit, JB, McMahon, NC and Sridhar, A (2013). Comparison of electrophysiological data from human-induced pluripotent stem cell-derived cardiomyocytes to functional preclinical safety assays. Toxicol Sci 134(2):412-426.
21 Sager, PT, Gintant, G, Turner, JR and Stockbridge, N (2013). Rechanneling the cardiac proarrhythmia safety paradigm: a meeting report from the Cardiac Safety Research Consortium. Am Heart J doi:110.1016/j.ahj.2013.11.004.
22 Yu, J, Hu, K, Smuga-Otto, K, Tian, S, Stewart, R, Slukvin, II and Thomson, JA (2009). Human induced pluripotent stem cells free of vector and transgene sequences. Science 324(5928):797-801.
23 Chen, G, Gulbranson, DR, Hou, Z et al (2011). Chemically defined conditions for human iPSC derivation and culture. Nat Methods 8(5): 424-429.
24 Di Giorgio, FP, Carrasco, MA, Siao, MC, Maniatis, T and Eggan, K (2007). Non-cell autonomous effect of glia on motor neurons in an embryonic stem cell-based ALS model. Nat Neurosci 10(5):608-614.