Stem Cell Reports
Meeting Report
OPEN ACCESS

International Coordination of Large-Scale Human Induced Pluripotent Stem Cell Initiatives: Wellcome Trust and ISSCR Workshops White Paper

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http://dx.doi.org/10.1016/j.stemcr.2014.11.006

There is growing recognition of the potential value of human induced pluripotent stem cells (hiPSC) for understanding disease and identifying drugs targets. This has been reflected in the establishment of multiple large-scale hiPSC initiatives worldwide. Representatives of these met recently at a workshop supported by the Welcome Trust in the UK and in a focus session at the 2014 ISSCR annual meeting in Vancouver. The purpose was to discuss strategies for making thousands of hiPSC lines widely available with as few restrictions as possible while retaining financial viability and donor privacy. The outcome of these discussions is described here.

Introduction

The ability to generate human induced pluripotent stem cells (hiPSCs) by direct reprogramming of somatic cells by simple overexpression of transcription factors initiated a paradigm shift in biomedical science (Takahashi et al., 2007; Yu et al., 2007). In just a few years, hiPSCs have opened new fields of investigation not only in cellular reprogramming itself but also in creating human models of inherited diseases for basic research in pathological mechanisms and drug target discovery. The increasing numbers of grant applications and publications that include hiPSCs (>7000 manuscripts have been published since 2007) are evidence of how these cells have captured the imagination of those both inside and outside this rapidly evolving field. Several large-scale initiatives have already been established to serve this growing interest and facilitate hiPSC production for studying monogenic and genetically complex disorders and understanding the causes of disease predisposition in the context of stratified medicine. Collectively, these large-scale initiatives plan to derive more than 100,000 hiPSC lines from cohorts of patients and healthy donors in Europe, North America, Brazil, China, Japan, South Korea, and Australia (Tables 1 and S1), the focus being largely on their in vitro applications in disease modeling, genetic variation, and drug development. Overall, these initiatives aim to create opportunities to address major health issues for conditions with few treatment options that lack human disease models or for which primary biopsies are difficult to access. These conditions include neurodegenerative and neurocognitive disorders, metabolic syndromes, and heart failure. To ensure that they are an appropriate return on investment, the banks are attempting to coordinate their activities with respect to donor-informed consent, material transfer agreements to academia and industry, standards of culture and characterization, and availability of donor medical history (Figure 1).

Most programs intend to create biorepositories of well-characterized hiPSC lines from different disease groups as well as healthy control individuals. The coordination of these efforts, as at the Wellcome Trust and ISSCR workshops, to discuss the conceptual, technical, ethical, and commercial challenges associated with the derivation of such high numbers of hiPSC lines, is unprecedented. This report summarizes the emerging plans to establish permanent international coordination for sharing resources, knowledge, and standards on hiPSC derivation and characterization. The ambition is that hiPSC lines in the repositories will become a shared, worldwide research resource.

Generation of hiPSC lines

Among the issues considered were the different technologies available for deriving hiPSCs.

Reprogramming Methods

This was considered the most important technical decision to be made by large-scale hiPSC initiatives, because the quality of banked lines may be highly dependent on the method used. Several methods are currently available to generate hiPSCs from somatic cells and are usually based on introducing the transcription factors *SOX2, c-MYC, OCT4, KLF4* and/or *LIN28*. Some methods introduce the transgenes on viral vectors, resulting in their integration into the genome of target cells. Other approaches use conditional integrating vectors that allow subsequent removal of the transgenes using recombinases such as Cre, although this leaves a residual loxP site (Woltjen et al., 2009). "Scarless" reprogramming is widely regarded as preferable, so that the most common approaches now used are non-integrating and rely on adenoviral (Stadtfeld et al., 2008),

Table 1. Major Large-Scale hiPSC Initiatives

Initiatives	Location	Cell Type /Derivation Technology	Characterization Assays	Open Access	hiPSC Lines
Human Induced Pluripotent Stem Cells Initiative (HIPSCI)	United Kingdom	Skin fibroblasts Sendai virus	Mycoplasma PluriTest Phenotypic assays for 3 germ layers Genotype chip Gene expression RNA sequencing Exome sequencing CHIP sequencing Methylome Proteomics	Open access data for some normals, managed access for disease and remaining normal samples Cell banking with ECACC	hiPSC lines from 500 normal and 500 diseased donors
StemBANCC/IMI	European Union	Skin biopsies and hair sample Sendai virus	Pathogen testing PluriTest Flow cytometry for Nanog SNP array Whole exome sequencing EB differentiation Proteomics	Not-for-profit, research for academia and industry	1500 hiPSC lines from 500 donors including healthy controls, diabetic patients, adverse drug responders, neurodysfunctional disorders and neurodegenerative disorders Drug screening, public-private partnership
California Institute for Regenerative Medicine	United States, California	Skin fibroblasts and PBMC Episomal plasmids	Pathogen testing Mycoplasma Pluripotency markers SNP Illumina Array PCR for episomal integration	Available for research and commercial use Derived by CDI and banked by Corriel Additional fees and royalties for commercial use	9000 lines from 3000 individuals and 11 diseases Lines for disease modeling, target discovery, drug discovery and R&D
New York Stem Cell Foundation	United States, New York	Skin fibroblasts mRNA reprogramming	25 pluripotent genes and 100 genes on scorecard assay on EB Copy number variation analysis Differentiation of beta-like cells	Open access	Repository of 2500 hiPSC lines representing diversity of US and rest of the world Generation of hiPSC lines for neurodegenerative diseases and diabetes

Sendai virus (Fusaki et al., 2009), or episomal plasmid vectors (Yu et al., 2009) to deliver the reprogramming genes. Other nonintegrating methods use synthetic modified RNAs (Warren et al., 2010) and protein-based reprogramming (Kim et al., 2009). These methods, however, still vary in efficiency, complexity, labor required, and compatibility with different somatic cell types.

Most large-scale hiPSC initiatives prefer nonintegrating methods, in order of preference: episomal plasmids, Sendai virus, and modified RNAs. These approaches all work efficiently on various somatic cell types, and the resulting hiPSC lines have been widely validated by many research groups. However, each method has specific limitations: episomal plasmids have lower reprogramming efficiencies and the potential for residual plasmid integration, Sendai viruses require higher biosafety containment levels and are relatively costly, and mRNA reprogramming is labor intensive, requiring repeated (daily) transduction and costly Pluriton medium.

The workshop consensus was that despite some shortcomings, reprogramming methods are already adequate for the purpose, with new methods rarely being more efficient than the four factors originally described by Yamanaka and colleagues. Furthermore, new methods as published have rarely been validated on the variety of cell cultures available from broad human cohorts, and thus their applicability to large-scale programs is an open question. It was concluded that an international initiative could accelerate validation of different methods by creating a network of key experts to test them and disseminate the resulting information to benefit the entire field.

Another issue discussed was how many cell lines should be derived and characterized per donor. Several initiatives are deriving three clonal lines per donor while characterizing only one. However, others prefer to derive only one polyclonal cell line that can be later subcloned into individual sublines. Later subcloning has the advantage of reducing the number of lines maintained and thus the

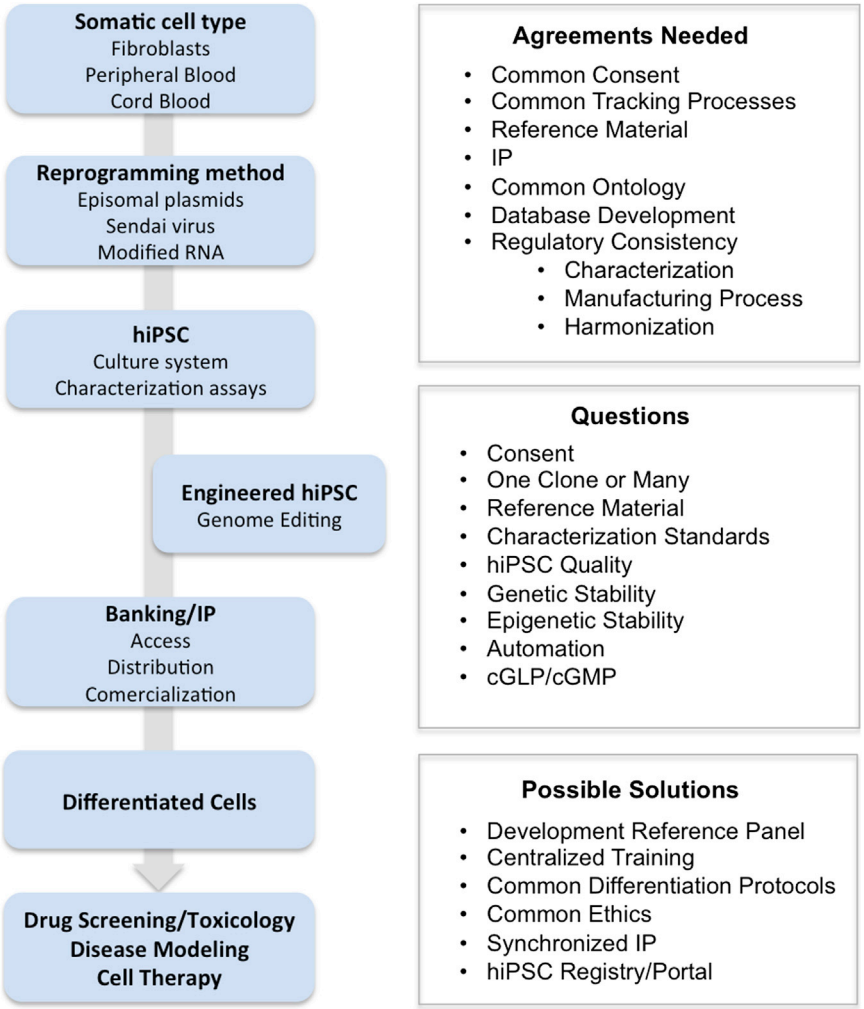

Figure 1. Workflow for Large-Scale Initiatives and Requirements for Standardization

overall costs. However, it also has the drawback of generating potentially heterogeneous populations of hiPSCs with diverse genetic anomalies, epigenetic memory, and capacity for differentiation.

Somatic Cell Type

Which somatic cell type to reprogram is another important consideration for large-scale hiPSC derivation. A wide variety of cell types from different primary tissues has already been used to generate hiPSCs, and several studies suggest that they could have variable differentiation potentials and oncogenic risk (Ghosh et al., 2010; Miura et al., 2009). Furthermore, early passage hiPSCs could retain some "epigenetic memory" of the somatic cells from which they were derived. This phenomenon has been associated with abnormal reprogramming of the DNA methylation signature of somatic cells. Epigenetic memory may have major consequences for the capacity of hiPSCs to differentiate as shown by the substantial variability in teratoma forming potential of iPSC lines derived from different adult mouse tissues (Miura et al., 2009). However, several other studies suggest that epigenetic memory can decrease over time in culture (Nishino et al., 2011). The consensus in the workshops was that hiPSCs should be passaged at least 10 times after first appearance to stabilize the pluripotent phenotype and ensure genetic stability. Characterization and differentiation at early passage (<10) was reported to be problematic and thus was systematically excluded in most of the production pipelines. However, the experience was that this precaution did not resolve variability between hiPSC lines derived from different donors; this was identified as a major challenge when working simultaneously with a large number of lines. The reasons for this variability remain unclear but were thought to originate from a combination of factors including genetic background (Rouhani et al., 2014), abnormal reprogramming, and epigenetic memory.

Taking the above into consideration, the majority of the hiPSC initiatives have chosen to use somatic cell types based on ease of accessibility and reprogramming efficiency. To date, dermal fibroblasts have been the most commonly reported in the literature and by most of the initiatives because they reprogram efficiently, are easily isolated from skin biopsies as small as 2 mm, and can be cryopreserved and banked before reprogramming. This is important because the creation of a fibroblast bank provides the opportunity to use different reprogramming methods at a later date, should this be necessary. Another cell type widely used by large-scale initiatives are peripheral blood mononuclear cells (PBMC), which can often be collected more easily from patients, especially infants, than biopsies, and may be available as frozen samples already stored in cell repositories and (cord) blood banks. The development of robust protocols for reprogramming blood cell is potentially game changing, making it possible to develop hiPSC initiatives that leverage very large existing collections, such as that of the NIMH Repository and Genomics Resource (NRGR, https://www.nimhgenetics.org) and the NINDS Repository at Coriell (https://catalog.coriell.org/1/NINDS) with tens of thousands of specimens from subjects that have extensive clinical phenotypic data associated over years of study. Kidney epithelial cells found in urine are also of increasing interest because they are entirely noninvasive to collect.

Culture System

Ideally, methods to generate and expand hiPSCs would be fully defined and not require xenoreagents. Nevertheless, Knockout Serum Replacement medium in combination with mouse embryonic feeder cells has been most widely used to date. However, most initiatives are now moving toward feeder free systems and chemically defined media such as the Essential 8 (containing eight defined factors)-vitronectin substrate culture system (Chen et al., 2011). The increasing interest in xeno-free, chemically defined media and substrates is motivated by the wish to improve robustness, reproducibility, and compatibility with clinical or good laboratory practice (GLP) applications. On the other hand, because the methods are relatively new, it is not yet clear whether there may be additional risks, for example, associated with increased genetic or epigenetic instability. The workshop delegates highlighted the importance of identifying the advantages and drawbacks of each system and of the stem cell community reaching a consensus. Indeed, the development of common culture practices among large-scale initiatives would facilitate hiPSC line standardization and reproducibility of experiments between laboratories.

Automation

Automation systems are increasingly viewed as providing opportunities to improve standardization in the generation of hiPSC lines. Several initiatives are exploring this approach for the generation of hiPSC lines. The New York Stem Cell Foundation has already automated the derivation of hiPSCs by mRNA reprogramming in 96-well plates using liquid-handling robots. This system also allows maintenance and expansion of hiPSCs as well as hiPSC differentiation into pancreatic beta-like cells. Other groups are investigating other automated culture systems with sensors to allow online monitoring and characterization of hiPSCs via metabolomics and Fourier Transform Infrared Spectroscopy (FTIR).

Characterization

Proper characterization of hiPSCs and what the criteria for this should be was identified as a major challenge by all the initiatives with delegates attending the workshop. Indeed, the main objective of these initiatives is to generate banks of high-quality hiPSC lines for a broad spectrum of users and projects. However, the diversity of assays in current use, lack of consensus on the key criteria that define utility for purpose, and budget constraints that limit implementation of expensive assays still make it difficult to define the pluripotent stem cell profile that banks can be expected to make available to users. Furthermore, identifying the best hiPSC lines remains a challenge due to still-limited understanding of the mechanisms controlling self-renewal and differentiation capacity. The consensus was therefore to divide characterization into four categories.

Pluripotency

Assays to validate the pluripotent state of hiPSCs vary in time required, cost, and accuracy. hiPSCs are usually first assessed by morphology; this approach is routinely used by the majority of the initiatives as the first step in distinguishing fully versus partially reprogrammed lines. The next evidence is the expression of markers associated with pluripotency such as OCT4, NANOG, SOX2, and TRA-1-60/SSEA-3 by immunostaining, FACS (for cell surface markers) or q-PCR (for transcription factors). It was agreed that this suffices to designate cells as reprogrammed. Although more complex in silico analyses of gene expression profiles (for example, PluriTest: Müller et al., 2011) can provide complementary information, the outcome rarely contradicts morphological and immunostaining data. Of note, though, is that PluriTest and similar algorithms will give a high pluripotency score to teratocarcinoma tumor cells and do not report differentiation potential.

Differentiation Capacity

True hiPSC lines should form derivatives of all three germ layers. Teratoma formation is historically the best and most rigorous method for demonstrating this, but as an assay it is not quantitative. Additionally, it would be practically impossible, extremely costly, and ethically

unjustifiable for repositories to generate teratomas for thousands of hiPSC lines and derivative clones. There was general agreement that teratoma assays should preferably be abandoned and that other higher-throughput, quantitative approaches, preferably in vitro based, need to be developed. The International Stem Cell Initiative (ISCI3) is addressing this issue by comparing the outcome of in vitro protocols including embryoid body differentiation under defined conditions, assessed by gene expression data; the PluriTest bioinformatics analysis of gene expression in undifferentiated hiPSCs; and a rapid immunostaining approach, with quantitative analysis of hiPSCs differentiating in teratomas. Differentiating hiPSC lines in vitro into derivatives of the three germ layers and monitoring efficacy by immunostaining for specific cell types may however be sufficient for most publication purposes, although none of the current methods can predict the ability of undifferentiated hiPSCs to differentiate into specific cell types, such as dopaminergic neurons or hepatocytes, prospectively. Additionally, the need to share and standardize differentiation protocols was recognized.

Genetic Stability

Genetic stability is becoming increasingly important among criteria for hiPSC line release because the cells regularly display karyotypic abnormalities in culture, frequently on specific chromosomes. Quality assurance should thus include systematic and regular karyotyping. However, conventional methods of karyotyping, such as G banding or chromosome painting, are time and resource consuming and thus impossible to use in pipelines producing large numbers of independent hiPSC lines. All of the initiatives plan to use genome arrays such as high-resolution SNP (single nucleotide polymorphism) and CGH (comparative genome hybridization). Exceptionally, the Wellcome Trust-funded HIPSCI program will perform exome sequencing on hiPSC lines as basic characterization, taking advantage of the unique sequencing capability of the adjacent Sanger Institute. Nevertheless, the resolution of the genome-wide methods (SNPs, CGH, Exome-Seq) can be problematic because major chromosome rearrangements may be missed if present in only a small fraction of the cell population. Each initiative has observed that genetic instability occurs naturally in hiPSCs and that 10%–30% of the lines generated could carry small amplifications/deletions. Studies have shown that at least some of the copy number variations (CNV) detected in hiPSCs may be due to mosaicism, residing in subpopulations of the source cells used to derive the hiPSCs, rather than arising as a consequence of the reprogramming methodology. Therefore, the origin and significance of these changes remain problematic and the consensus was that only major chromosomal rearrangements would likely be detrimental to in vitro applications. In addition, coordinated efforts are still necessary to collect genetic data of thousands of lines and thus enable a precise evaluation of the genetic changes specifically associated with reprogramming and/or in vitro expansion.

Epigenetic Stability

This feature of hiPSCs remains largely unexplored because it requires costly genome wide analyses of histone modifications and DNA methylation. Furthermore, the epigenome is often considered properly reprogrammed as long as the gene expression profile of hiPSC lines conform with that of other validated pluripotent stem cells lines. The HIPSCI program is the only initiative that will provide a full epigenetic profile on all of the 1000 hiPSC lines it will generate. This information will be invaluable to define the importance of the epigenetic profile on the capacity for differentiation and to establish how genetic background can influence epigenetic state.

Quality Control and Distribution

The immense resources required to generate large-scale collections of hiPSCs dictate that the most stringent quality control standards be applied to the cells before they are made widely available. The meeting participants agreed that standardized characterization should include many of the criteria mentioned above, as well as measurement of cell viability after thawing of cryopreserved cells, sterility, the absence of human pathogens (HIV-1, Hep-B, and Hep-C at a minimum), and genomic profiling. It is also critical to track cell identity to guard against potential specimen mixups or contamination by processing each hiPSC line on SNP identity panels. Historically, repositories such as RUCDR (http://www.rucdr.org) have performed all of these functions for many large-scale human genetics initiatives involving the use of nucleic acids, cell lines, and other biomaterials collected and processed from study participants. The use of centralized facilities for the identification, characterization, expansion, and distribution of hiPSC lines will be a key factor in facilitating their dissemination globally as high quality resources.

Ethical Consent/Donor Identification and Recruitment

During the workshops it was agreed that ethical consent forms acceptable for worldwide use would be ideal but that this would be practically impossible to achieve because each country has different regulatory landscapes. Nevertheless, key aspects that should be carefully considered when preparing ethical consent forms were identified because a major objective of the hiPSC initiatives is to bank lines that could be widely distributed. Indeed, the free distribution and open access of the hiPSC lines and

the corresponding data is essential for these large-scale initiatives to have maximal impact and return on investment for the scientific and industrial communities. Ethical consent needs to capture this and allow full and open access to lines and data. The availability of such data would provide vital tools for optimizing rational and economical selection of cohorts for downstream studies. Furthermore, linking medical records that document disease history and medication responses to hiPSC lines via active links safeguarded by firewall protection would create a valuable source of information for disease modeling and drug screening activities. Also, the possibility of recontacting the donor to request additional tissue samples or updates on health status would be of great value in studying disease progression. Importantly, hiPSC lines and data would ideally be available to academic and non-academic institutions. This was regarded as essential to raise interest and support from industry for the creation of hiPSC banks.

Finally, because hiPSC lines represent a unique system to study human genetics and corresponding phenotypes, several studies are already performing genome wide analyses such as whole genome sequencing. These data will allow the identification of genetic variations associated with particular diseases and greater insights into the implications for health in a way not possible in studying mice, simply because relevant SNPs and variant sequences are not necessarily conserved. This could increase understanding of the genetic basis of individual variability and its impact on disease onset and severity, thereby informing strategies to detect, treat, and prevent disease. Thus, consent forms need to enable open or controlled access to (deidentified) genetic data. Although, recent reports have shown that genome-wide data could be used to identify donors even though all of the direct identifiers have been removed, measures such as deleting any sequence related to the Y chromosome could be implemented to mitigate this risks and support open access and the distribution of the hiPSC lines and genomic data to the wider community. These points need to be explored in greater depth in the context of local legal and social frameworks and evolving technologies.

Intellectual Property

The intellectual property (IP) landscape for hiPSCs is complex, with several institutions owning patents on aspects of iPSC generation, expansion, and use, each of which could have major impacts on the freedom to use lines by commercial and academic investigators. The four "Yamanaka factors" are licensed by iPS Academia Japan. This gives full freedom to operate for academic laboratories, while reasonable license fees can be requested for commercial activity. In addition, Sendai virus is commercially available through Life Technologies under license from DNAVEC. hiPSC lines generated with this last method are covered by a strong Limited Use Label License (LULL) associated with an important IP reach through for a number of applications. Direct negotiations are usually required and each user needs to establish his/her own agreement with the owner of the IP. The use of the episomal plasmids appears to be less restrictive. Nevertheless, this method seems to be covered by several patents owned by different institutions and companies including Cellular Dynamics, which makes freedom to operate in deriving hiPSCs using episomal plasmids rather unclear. Importantly, patents may cover not only the hiPSC lines themselves but also their direct applications.

Another area of concern centers on potential restrictions associated with the use of tools such as nucleases and fluorescent reporters to make derivatives of the original hiPSC lines. Technology providers holding the rights to these tools often invoke IP reach through rights that may present obstacles for users, academic and industrial, in using or patenting derivative lines in the future. These obstacles may even impede the ability of not-for-profit repositories to distribute the lines affordably to end users. However, with respect to differentiated cells generated from hiPSCs, the situation remains unclear: several institutions, including the NIH, consider that differentiated derivatives are not covered by the claims of hiPSC derivation methods. This is a crucial point on which the international community should take a balanced view to avoid unnecessary restriction that could damage the widespread use of hiPSCs for drug screening and cell based therapies. Most of the initiatives strongly recommended that owners of intellectual property adopt a transparent and consistent position for use of their technology that would not impair the advances of the hiPSC field.

Genome Editing

Recent advances in genome editing now allow rapid and efficient introduction of genetic modifications in hiPSCs. Gene deletion, targeted introduction of fluorescent or other reporters and introduction or correction of specific mutations to generate isogenic pairs of disease and control lines, differing only in the mutation of interest, are all feasible. Transcription activator-like effector nucleases (TALENs) and clustered regularly interspaced short palindromic repeat (CRISPR)/Cas systems are preferred approaches used by several large-scale initiatives. Notably, the Wellcome Trust Sanger Institute is developing a high throughput pipeline to generate heterozygous and homozygous mutant hiPSC lines to target more than 1000 genes. The Gladstone Institute in San Francisco and Harvard University in Boston are likewise using TALENS and CRISPR/Cas to generate a large number of hiPSC lines

carrying disease-specific mutations associated with many disorders.

An important issue discussed in the workshops was the nature of controls and how to avoid misinterpretation associated with natural variability (or noise) between different hiPSC lines (Rouhani et al., 2014). Generating genetically corrected isogenic hiPSC lines would be time consuming and expensive for the initiatives, although increasingly, published studies indicate real interest in this approach. An alternative could be panels of hiPSC lines from healthy donors that could be widely available as controls, much like the original human embryonic stem cell (hESC), lines, H1, H7 and H9, are widely used as benchmarks, and that could also be used to introduce specific mutations. Workshop delegates viewed genome editing as a complementary alternative to hiPSCs derived from patients with monogenetic disorders because this bypasses the need to generate new lines and ensures a spectrum of mutations on a single genetic background. However, complex diseases involving several genes would be more challenging and there would be no data on disease severity available. Furthermore, diverse genetic (and ethnic) backgrounds might be necessary to fully understand disease mechanisms. Thus, the development of robust genome editing methods represents an important evolution for the stem cell field, and these methods are likely to be frequently used in combination with hiPSC derivation from patients in the near future.

Discussion

The topics discussed during the meetings not only covered the challenges that large-scale hiPSC initiatives are facing but also considered the issues that many groups have encountered over the past 7 years since their first discovery. These challenges range from technology of derivation, characterization, ethics, and IP to genome editing tools. As a result, a set of measures was suggested to advance the field.

Development of Reference hiPSC Panel

The distribution to the community of a panel of 10 hiPSC lines generated by different institutions in the leading countries for research in this area would be extremely useful to standardize protocols between laboratories, for the validation of new technologies, and also for experimental reproducibility. These hiPSC lines would have to be generated under broad ethical consent, fully characterized for their pluripotent state and capacity to differentiate into relevant cell types. Furthermore, the genetic stability and the compatibility of these lines with genome editing would have to be documented. Discussion and planning have already been initiated between the Wellcome Trust Sanger Institute and other organizations such as the NIH.

Training

Training was identified as a clear challenge in the field. There is still a paucity of institutions providing training to derive, maintain, characterize, and differentiate hiPSCs, although this is increasing as the field expands. Furthermore, there is a need for coordination among individual groups using different methodologies that result in divergent standards and sometimes difficulties in reproducing experimental outcomes. Ideally, training would be centralized to leading institutions, with the trainers using common methods and approaches. Concerning differentiation, training could be given by the groups developing the methods to ensure reproducibility. Organization of such training will require significant and coordinated support from funding agencies.

Common Ethics Policy

Although it would be desirable that a common, internationally recognized, consent template to derive hiPSCs was used that covered conditions of tissue donation (altruistic, voluntary, no donor benefit or feedback, academic and nonacademic users), it was considered unlikely that this could be agreed because of divergent international regulations and cultures and also local ethical committees.

Synchronized IP

A coordinated approach to negotiate licenses with major IP owners would significantly benefit the field. Repositories will play a key role as honest brokers in facilitating the implementation of these agreements so that both the providers and end users' needs, scientific and economic, are accommodated. Exchange of information on IP and license agreements signed by the initiatives would increase transparency and understanding of the necessary steps and implications on signing such documents. Another important consideration is the definition of academic versus nonacademic (commercial) research and profit versus not-for-profit use. It was pointed out during the meetings that there are several differences within Europe, US, and other countries. The attendees proposed that several categories of commercial exploitation should be defined and that the licenses should be dealt with accordingly. Regarding differentiation, the consensus was that differentiated cells should not be covered by the IP associated with methods of derivation, following the NIH perspective. The restrictive nature of licensing requirements attached to tools, reagents, and technologies will be a primary factor in driving the choices made in the earliest stages of planning large-scale projects involving hiPSCs. By virtue of their size and leadership position in the field, the initiatives will have considerable influence in driving this discussion within the community.

hiPSC Registry/Portal

The participants in both meetings agreed that the creation of large, well-characterized banks of hiPSCs must be

accompanied by the parallel construction of searchable resources that the global research community can use to easily filter and identify cell lines of interest. This could minimize the use of lines without appropriate background history, ethical consent, and poor characterization. Additionally, it would increase the speed of locating lines with a specific genotype or disease of interest and improve the exchange of information between the different initiatives. The creation of effective databases relies on achieving consensus agreement on common data elements (disease subcategory trees, representing patient selection criteria like gene variants, reprogramming and QC methods, age/gender, consent for industry use, etc.) for structuring the collections so that they can be most effectively searchable. The adoption of standardized nomenclature for hESC and hiPSC lines would aid in this effort as well (Luong et al., 2011). The need to coordinate this activity at the earliest stages was recognized, given the technical challenges in its implementation. In addition, if available as a website, this could be used as a discussion forum to collect protocols and troubleshot on a day-to-day basis. The hESReg database, originally established to provide information on all hESC lines used in EU projects, is now being expanded to include hiPSC lines (http://www.hescreg.eu). All EU-funded projects are required to register the hiPSC lines they use or generate or to use only pre-registered lines. If more widely implemented, this would serve as a useful information interface with the user community. A number of other efforts are underway, including eagle-i (https://www.eagle-i.net), the Neuroscience Information Framework (http://www.neuinfo.org), and the International Stem Cell Registry (http://www.umassmed.edu/iscr). The hiPSC initiatives were all willing to promote open exchange of hiPSC lines from their banks.

Conclusion

Large-scale hiPSC initiatives are likely to generate the majority of the lines that will become available worldwide in the coming decade. Their coordination will be essential to fully exploit these unique resources. The workshop in Hinxton, UK, and the focus session at the 2014 ISSCR annual meeting clearly identified the challenges to achieving this major task and the benefits of establishing international coordination and optimizing these resources (Figure 1). The key objectives of this coordination would be (1) to define technical standards for derivation and characterization of hiPSC lines, (2) create a panel of fully validated standard hiPSC lines originating from different centers, (3) standardize training between the different centers, (4) coordinate ethics/IP among the different initiatives, and (5) centralize resources and information on hiPSC lines derived by each initiative.

SUPPLEMENTAL INFORMATION

Supplemental Information includes two tables and can be found with this article online at http://dx.doi.org/10.1016/j.stemcr.2014.11.006.

ACKNOWLEDGMENTS

The authors would like to thank all delegates for their input into the workshops that led to the contents of this white paper (Table S2).

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