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MEETING REPORT

A Report from a Workshop of the International Stem Cell Banking Initiative, Held in Collaboration of Global Alliance for iPSC Therapies and the Harvard Stem Cell Institute, Boston, 2017

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ABSTRACT

This report summarizes the recent activity of the International Stem Cell Banking Initiative held at Harvard Stem Cell Institute, Boston, MA, USA, on June 18, 2017. In this meeting, we aimed to find consensus on ongoing issues of quality control (QC), safety, and efficacy of human pluripotent stem cell banks and their derivative cell therapy products for the global harmonization. In particular, assays for the QC testing such as pluripotency assays test and general QC testing criteria were intensively discussed. Moreover, the recent activities of global stem cell banking centers and the regulatory bodies were briefly summarized to provide an overview on global developments and issues. STEM CELLS *2019;37:1130–1135*

SIGNIFICANCE STATEMENT

International Stem Cell Banking Initiative (ISCBI) was established in 2007 with funding from the International Stem Cell Forum (www.iscbi.org), with the remit to support human pluripotent stem cell (PSC) banking centers, stem cell biologists, regulatory bodies, and others involved and/or interested in biobanking. The present report provides a summary of the key points of discussion from the 2017 ISCBI meeting, with emphasis on data standardization, quality control, and genetic for quality assurance and resource sharing. It provides a useful global perspective on developments in PSC applications and guidance on evaluation of emerging technologies for culture, characterization, safety testing, and ethical guidelines in the establishment of safe and effective stocks of stem cells for future regenerative medicine.

INTRODUCTION

The International Stem Cell Banking Initiative (ISCBI) has built a community of scientists, stem cell banks, scientific societies regulators, and developers of stem cell reagents and products from at least 24 countries. Its regular workshops are supported by a range of stakeholders including the International Stem Cell Initiative (ISCI) [1], government agencies, universities, and the ISSCR. These workshops have resulted in numerous publications of international scientific consensus on issues relating to the procurement, expansion preservation storage, and supply of human pluripotent stem cell (hPSC) lines [2, 3]. Key elements in developing the ISCBI have been the principle that all stakeholder countries should be assured of a voice in its workshops and its publications should reflect a consensus of those engaged in its discussions. The meeting was held at the Harvard Stem Cell Institute, Boston, MA, USA, on June 18, 2017, by kind permission of The Institute's Executive Director, Brock Reeve. The meeting was opened by the coordinator for the ISCBI, Prof. Glyn Stacey, who reflected on the fact that the ISCBI could now celebrate 10 years of bringing together centers around the world supplying PSC lines for research and clinical application.

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Session 1: Quality Control of hPSC Banks (Chairs: Prof. Meri Firpo [Memphis Meats, USA] and Dr. Tenneille Ludwig [WiCell Research Institute, USA])

Global Alliance for Induced PSC Therapies Quality Proposal

Dr. Joanne C. Mountford (Scottish National Blood Transfusion Service) described a proposal for quality control (QC) of Global Alliance for iPSC Therapies (GAiT) partner induced PSC (iPSC) banks. The ISCBI publication from 2015 [2] was recommended as a basis for GAiT to use as it covered the broad range of issues to be considered for the evaluation and testing of clinical-grade human iPSC (hiPSC) and human ESC (hESC) lines. The discussion that followed with ISCBI members is outlined below. It was also mentioned that the ISCBI consensus [2] also addressed a number of aspects of hPSC evaluation, including genetic stability and pluripotency assays, which because of advances in technologies and research should be kept under review and would benefit from further discussion.

Assessment of Genome Integrity and Stability

It was clear that changes at various levels occur in the genetic makeup of cells. It could be that some stem cell lines are more susceptible to such changes or that cell culture handling methods are to blame as described by Prof. Shinya Yamanaka (ISSCR presentation, Boston 2017). Various options for the kind of sequencing that should be recommended including oncogene arrays, whole exome sequencing, and whole genome analysis were discussed. Performance of analysis of selected oncogene sequences may be useful, but it was also considered that regulatory advice may be moving away from recommendation of generic lists of tests as prescriptive lists can draw attention away from the need to carry out robust science-based risk assessment. It was agreed that given the potential for genetic change during manufacturing that if genome sequencing was to be performed, it should be carried out both on cell line and the final product. It was felt that the technology and cost had reached a point at which this would be feasible. It was discussed that obtaining whole genome sequence (WGS) data on materials destined for clinical trial would be appropriate and could be particularly value retrospectively to correlate with clinical outcomes. For hiPSCs, it was agreed that it was important to evaluate or retain primary material for evaluation (cells, fibroblast cultures, or tissues) to establish whether any variant sequences detected in the resulting reprogrammed cell materials were present in the donor or had arisen in reprogramming or culture. Accordingly, assessment of genetic integrity may be most critical at the point of the final product. It was also considered valuable to collect WGS genetic stability data alongside product manufacture, not as part of QC or release testing, but for future utility to collate with clinical outcomes and patient follow-up. The ISCI had just published report from a workshop on genetic stability [4], and a further meeting on this topic was held by ISCI in October 2017 (Sheffield, U.K.) [5] and members of ISCBI were represented. The delegates strongly agreed that it would be very valuable to have consensus on good practice for hPSCs to try to minimize risk of genetic drift in different labs. Such guidance was being developed [6], and it was recommended that ISCBI members should be engaged in providing comments on the draft to be prepared in 2018.

Consideration was given to the kinds of databases needed to manage such data and a recent study of nine iPSC lines (Prof. Jeanne Loring, Scripps Research Institute, LaJolla, CA, USA) had used the cosmic database. The ISCI project [4, 5] had proposed a database to collate observations of genetic stability in hPSC cultures to provide background data to enhance understanding of genome stability in both hiPSCs and hESCs. The ISCBI delegates agreed there was a need for standardized approaches for sequencing data preparation and evaluation. Additionally, the group discussed the comparative value of RNAseq, whole exome sequencing, and whole genome analysis. It was agreed that to understand published data, it is important to know what methods for data analysis had been used, such as the types of data "filters," depth of read, etc.

Assays for Pluripotency

The teratoma assay in immune-deficient mice was still considered a powerful research tool, but it is undesirable as a QC assay because of the necessary length of the assay (6–12 weeks), requirement for use of animals, lack of reproducibility, and associated costs [2]. Group consensus was that an alternative to the teratoma assay should be identified and implemented. In order to assure uptake in the research community, such a test would need to be straightforward, simple, and low cost. Directed differentiation for cell types from the three germ lineages was useful but could be time consuming and give very specific information on a particular pathway, which may not reflect in vivo conditions.

Following a presentation on pluripotency assays by Dr. Jeanne Loring (Scripps Research Institute, USA), it was noted that a number of commercial systems were available which involved expression profiling of undifferentiated cells, Real-time polymerase chain reaction for early developmental genes in embryoid bodies and directed differentiation. Their relative strengths and weaknesses were discussed. The ISCI group, led by Prof. Peter Andrews (University of Sheffield, U.K.) and now Prof. Martin Pera (Jackson Laboratories, Bar Harbor, Maine, USA), has taken up the search for an alternative to the teratoma assay, and their results have been published in *Nature Communication* [5]. In this work, the ISCI group evaluated several options including directed differentiation, embryoid body formation, and commercially available solutions, and compared those results to the teratoma assay across multiple cell lines in a number of laboratories. The ISCI and ISCBI workshops had supported the transition away from the teratoma assay to one that gives more reproducible results and does not require direct animal use [2]. Furthermore, the ISCI data [5] now supported this position and recommended use of methods, which involve an in vitro differentiation step to evaluate pluripotent potential.

General Quality Control Testing

Most routine cell bank QC and safety tests were thought to have been covered adequately in the ISCBI document [2]. However, it was noted that the use of traditional sterility testing is known not to be able to detect all potential microbial contamination of cell cultures [7]. New molecular test methods for detection of bacterial and fungal contaminants had been developed which may prove useful in the future. The group also noted that testing for serious blood-borne viruses considered in transplantation may not be sufficient for cell therapy products, and it may be necessary to consider a wider range

of viruses through careful risk assessment of cell donors [8] and raw materials.

Costs of Cell Bank Testing

An issue raised by the ISCBI steering group for discussion was relative costs of QC and safety testing of research grade versus clinical-grade hPSC cell lines. Overall costs for research grade cell lines were estimated by Prof. Meri Firpo and Dr. Tenneille Ludwig lie in the range $80,000–200,000 per cell bank depending on the testing completed (in addition to the approximately $150,000 to prepare the cell bank), and certain testing would need to be repeated on both master and working cell banks produced for the clinical trial [2]. Testing cell banks for clinical use attracted higher costs as they would also entail use of validated protocols that would need to be verified for suitability by the testing laboratory that would also be expected to operate with accreditation to relevant standards. Some tests may have to be performed in-house but would still require method verification. It was noted that expectations of cell bank release testing would be a special focus of regulatory inspectors, whereas tests performed for information may not require such rigor but should be evaluated on a case-by-case basis.

Session 2: Free Communications from ISCBI Members (Chairs: Dr. Jung-Hyun Kim (KNIH, South Korea) and Prof. Steve Oh (A-Star, Singapore)

Introduction to GAiT

Prof. Marc Turner (GAiT Chair and Scottish National Blood Transfusion Service) and Dr. Stephen Sullivan (GAiT) introduced the GAiT project, which aims to coordinate a number of partners around the world to deliver a haplobank of iPSC lines for clinical application. GAiT is supported by an international consortium of organizations, including the Cell and Gene Therapy Catapult (London, U.K.), the Centre for Commercialization of Regenerative Medicine (Toronto, Ontario, Canada), the Korea human leucocyte antigen (HLA)-Typed iPSC Banking Initiative (Seoul, Korea), and the New York Stem Cell Foundation (New York, USA). GAiT's mission is to serve as a central, international resource for those organizations that are developing therapies from clinical-grade iPSCs and to support the expansion of this nascent field [9]. With the support of its international partners, GAiT is working to develop manufacturing, regulatory, and quality standards, as part of its goals to support the delivery of the next generation of induced PSC-based therapies (www.gait.global/).

Establishment of the International Stem Cell Foundation

Prof. Qi Zhou (Chinese Academy of Sciences, Beijing, China), the current chairman for the International Stem Cell Forum, initiated by the U.K. Medical Research Council in 2003, described the creation of a new organization the International Stem Cell Foundation (ISCF), which is aimed at developing a certification program, staff training, and international scientific exchange for stem cell banks (www.stem-cell-forum.net/). Prof. Zhou described the creation of an executive board of funding organizations and a scientific advisory board drawn from the projects initiated by ISCF funding ISCI, the ISCBI, and the ISCF Ethics Working Party and looked forward to working with these organizations in support of the PSC field.

ISCI-3 Update on a Comparative Study of Pluripotency Assays

Prof. Nissim Benvenisty (Hebrew University of Jerusalem, Israel) summarized the significant body of work which the ISCI collaborators had completed to carry out an analysis of a range of pluripotency assays including teratoma formation, embryoid bodies (neutral and induced differentiation), and bioinformatic analysis of undifferentiated hPSCs (Pluritest). In addition, teratomas were analyzed by both histology and bioinformatic analysis of gene expression (Teratoscore). The study had been completed and published [5], and key outcomes included in discussion on QC above. In summary, Prof. Benvenisty indicated that all assays used could indicate potential pluripotency but each had different end points and gave different perspectives on pluripotency. A comparison of karyological data and appearance of transformed cells in teratoma studies had also identified new information on the potential connection between genetic status and development of potentially malignant cells.

The Korean National Centre for Stem Cells and Regenerative Medicine and ISCBI Workshop, Seoul, October 2016

Dr. Jung-Hyun Kim (Korean NIH, Korea) reported the completion and operational activity of the new National Centre for Stem Cells and Regenerative Medicine in Osong, Korea (http://kscr.nih.go.kr/). The new 5,200-m^2 center has good manufacturing practice (GMP) manufacturing facility that aims to support early stage of clinical trials of cell therapies. It included seven segregated modules, each grade B. One of the modules will support products, which need viral product for the process. She also mentioned 18 new GMP-grade HLA homozygote iPSC lines, which deposited in the national stem cell bank of Korea. These lines cover approximately 44% of the Korean populations. She also gave a report on the ISCBI workshop held in Seoul in October 2016, which had been included in the report on ISCBI activity in 2016 published in *SCTM* [3].

WiCell Biobanking Activities

Dr. Tenneille Ludwig (WiCell Research Institute, USA) described the recent expansion of the WiCell bank to include 1,200 new iPSC cell lines with unprecedented diversity. Available lines are both disease-affected and apparently normal, derived from donors ranging in age from 1 month to 100 years and covering 17 ethnicities. Cell lines from affected family groups are available as well as lines derived from twins. The group also includes a "Wellderly" cohort [10]: iPS cell lines derived from individuals aged over 80 with no evidence of disease. WiCell continues to offer research grade ES and iPS materials as well as clinical grade ES cells and characterization services including contract banking, QC testing, and cytogenetic services.

European Bank for iPSCs Cell Supply for Disease Studies

Dr. Rachel Steeg (Roslin Cell Sciences, U.K.) described the European Bank for iPSCs (EBiSC) consent documents, cell processing, QC, and distribution for the European iPSC Bank of hiPSCs for disease studies. Stocks of 380 hiPSCs had been made available out of a total of 693 disease associated and control lines (www.ebisc.org/). Disease-associated lines included examples from a

wide range of disease backgrounds including neurodegeneration, metabolic disorders, and psychological syndromes.

HipSci Project Update

Dr. Alex Alderton (Sanger Institute, U.K.) described the completion of the HipSci collection of hiPSC lines. These were primarily from healthy donors and were intended for use in studies of genetic and biological diversity in humans. The hiPSC lines included a large number from the HipSci programme (www.hipsci.org/) and other from the Insignia program (www.mutationsignatures.org/insignia/). These also included cell lines from rare disease donors (www.hipsci.org/cells/), including Batten disease, macular dystrophy, and DNA repair defects such as Bloom Syndrome and xeroderma pigmentosum. The project had generated 1,000 lines over 4 years, and 522 lines were now available from European collection of cell cultures and 200 from the EBiSC catalog.

EMBL-EBI Stem Cell Data Systems

The data analysis process for over 970 iPSC lines from the EBiSC and HipSci cell line collections was presented by Dr. Peter Harrison (EMBL-EBI, Cambridge, U.K.) and the advanced search service currently being developed by EMBL-EBI. This had the capacity to identify iPSC lines of interest based on a live search of their underlying genetic variation data. The European Bioinformatics Institute (EMBL-EBI; www.ebi.ac.uk/) provides information on both disease affected and unaffected lines. Examples included donors from a very wide age range up to 100 years.

RUCDR Stem Cell Resources

Dr. Michael Sheldon (RUCDR Infinite Biologics and Rutgers University, USA) introduced RUCDR Infinite biologics (www.rucdr.org/), which has developed from biobanking activities in operation for 20 years. It processes, stores, and distributes the collections of iPSC lines from the National Institute of Mental Health and National Institute of Neurological Disorders and Stroke, which combined comprise 292 hiPSC lines and 684 fibroblast cultures including one clinical line. In addition to a full range of genomics platforms and analyses, RUCDR provides a testing service for SNP Trace for cell line identity validation and genetic analysis and now offers CRISPR gene editing. Cells are supplied internationally via country-specific MTAs.

Development of Stem Cell Lines for Clinical Applications at Takara Bio Europe

Dr. Catharina Brandsten (Takara Bio Europe - Cellartis, Sweden) outlined the work of Takara to develop hESC derivation in a GMP facility. The lines will be feeder free and in completely defined media. Takara are also manufacturing plasmid and viral vectors for reprogramming to supply clinical iPSCs projects with GMP materials.

Stem Cell Clinical Trial Update from Brazil

The activity of the Brazilian regulatory authority Agencia Nacional de vigilancia Sanitaria in stem cell-based therapy was reviewed by Prof. Patricia Pranke (Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil). There were a significant number of current Brazilian clinical trials using various stem cell types, although no activity was reported yet in PSCs. Prof. Pranke also provided details of all current stem cell clinical studies in Brazil, which are available from her at patriciapranke@ufrgs.br or the ISCBI contact (see below).

Quality Control of iPSC Lines for Clinical Use in Kobe, S. Kawamata, Foundation for Biological Research and Innovation, Japan

Prof. Shin Kawamata (Foundation for Biological Research and Innovation [FBRI], Kobe, Japan) described the work of the FBRI and the development of QC and safety tests used for hiPSC for clinical use in the Kobe Medical Centre (www.fbri-kobe.org/english/). The Kobe project had used CiRA's iPSCs seeded at low density with expansion of ×50 to ×100 per passage at CiRA. Usually mutations had been detected in cells in extended culture, for example, beyond passage 20. Accordingly, Prof. Kawamata recommended minimizing the number of mitoses of cells (and thus passages) for both clinical and research use. However, not all mutations arise during reprogramming and culture, and a specific example was reported, that is, a major deletion in X and homogenous deletion 15 chromosomes present in both donor and in the respective hiPSC. Subcutaneous transplantation of the differentiated product from these cells in NOG mice had caused no tumor formation and showed no histological abnormality after 1.5 years. The mutation in the BCOR gene reported by centre for iPS cell research and application (CiRA) in some passaged cultures of the hiPSC was not found in RPE cells in the Kobe project. Prof. Kawamata stated that genetic profile can change during long-term culture and recommended the use of comparative genome hybridisation (CGH) array to monitor genetic instability. He also commented that although WGS of final products, not iPSCs, can be useful to evaluate against long-term clinical outcomes, it was not a helpful product release test due to the difficulty in setting product release criteria. Furthermore, method interpretation and validation of test results of WGS can be quite different among institutions, and sometimes different test results were obtained from the same sample when using different institutions for WGS. Prof. Kawamata considered that standardization of WGS would be a crucial development before its routine use for product analysis can be discussed. Prof. Kawamata concluded that tumorigenicity assays on the final products, not starting material hiPSC/ESCs, should be the focus of QC analyses.

UKStem Cell Bank Release of First EUTCD-Grade Cell Lines

Dr. Jennifer Man (UKStem Cell Bank [UKSCB], U.K.) announced the release of the first panel of six hESC lines specifically derived and banked tested and stored to meet the requirements of European regulations as "starting material" for clinical trials. The pre-Accession ethics screening by the U.K. Steering Committee for the Use of Stem Cell Lines and the UKSCB Due Diligence process were also described. A total of 37 such lines are currently planned to be banked with more coming on line (www.nibsc.org/ukstemcellbank/).

New York Stem Cell Foundation Update

Dr. Michael Yaffe (New York Stem Cell Foundation [NYSCF], New York, USA) gave a presentation and video regarding NYSCF's new stem cell research facility (see nyscf.org/newhq/), where NYSCF has automated iPSC derivation, differentiation, and genome editing. Thousands of lines have been processed and donors have consented to allow clinical use of the cell lines.

Potential Application of Triple-Homozygous Cell Lines

Prof. Lygia da Veiga Pereira (Centro de Terapia, Cellular/Center for Cell Based Therapy, Sao Paolo, Brazil) reported that 1,900 different triple homozygous haplotype donors had been identified in Brazil from a national list of 20,000 donors. This appeared to represent unique genetic diversity in Brazil. L.d.V.P. described the criticality of correct collection of the primary cells. Prof. Pereira had determined that almost one-third of donors would not be suitable or not retraceable and was looking for 400 most suitable donors for clinical iPSC lines to cover populations in Brazil and other countries. Also described was ongoing work to bank peripheral blood mononuclear cells (PBMNCs) and iPSC cells derived from erythroblasts cultured from the PBMNCs.

Production of Human Embryonic Stem Cells for Clinical Use at the University of Kyoto

Dr. Eihachiro Kawase (Kyoto University, Japan) reported that the University is beginning to establish 20 clinical grade hESC lines. The production process used a Laminin fragment and defined medium (StemFit AK03N) for the surface coating for hPSC culture.

Recent ISCBI Publications

Dr. Tenneille Ludwig announced on behalf of Jeremy Crook (University of Woolongong, Australia) the launch of a book "Stem Cell Banking: Concepts and Protocols" (editors J. Crook and T. Ludwig). Written in the successful Methods in Molecular Biology series format (Springer Protocols), it includes contributions from experts in the field (including numerous authors from the ISCBI community) [11]. The proceedings of the ISCBI 2016 meetings in San Francisco and Seoul were also now to be published in *Stem Cells Translational Medicine* [3].

Summary

ISCBI Future Prospects

Prof. Glyn Stacey (ISCBI coordinator, Cambridge, U.K.) summarized recent changes to the ISCBI steering group. He offered thanks on behalf of the ISCBI community to Prof. Tsuneo Takahashi who after many years active support for ISCBI had requested to stand down from the ISCBI Steering Group. New members of the steering group were agreed, including Prof. Andreas Kurtz (Berlin Centre for Regenerative Therapies), Dr. Eihachiro Kawase (Cell Processing Facility Manager, Kyoto University), Dr. Michael Sheldon (RUCDR, Rutgers University), and Stephen Sullivan (GAiT). Prof. Stacey also reported the establishment of ISCBI as a legal entity called The International Stem Cell Banking Initiative Ltd. now registered in the United Kingdom (www.iscbi.org/). It would operate as a not-for-profit company. He also reported that ISCBI with the support of its Steering Group would continue to focus on its core aims to support coordination of PSC banks, development of consensus on best practice in this area, and training scientists in stem cell banking procedures. Ongoing issues raised for ongoing ISCBI workshop discussions included issues for QC for reporter and gene-edited hPSC lines, banking of tissue typed panels of hiPSC lines. These issues were discussed at the ISCBI 2018 meeting in Melbourne, and an independent report from that meeting is in preparation for publication.

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Disclosure of Potential Conflicts of Interest

C.B. declared employment with Takara Bio Europe. J.F.L. is a member of the Merck KGaA Bioethics Advisory Panel and has stock ownership in Aspen Neuroscience, Inc. T.L. is a coinventor and receives a share of royalties on the following stem cell media and culture related patents currently held and licensed by the Wisconsin Alumni Research Foundation (WARF): U.S. Patents 7449334, 7442548, 8426203, 8158424. M.L.T. is the Medical Director of the Scottish National Blood Transfusion Service. The other authors indicated no potential conflicts of interest.

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