ISCBI Workshop on Management of Stem Cell Data, Genetic Testing of hPSC Lines and Cost of Goods Considerations for hPSC Banking.
25th Sept ISCBI Workshop, KNIH and Korean Biobank Campus, Osong

Workshop proceedings

Laboratory visit: Korean Biomedical Facilities

The Korean National Biobank

The meeting started with a tour of the Korean Biobank and its biomaterials processing and storage facilities, hosted by Dr. S-H Chou, Deputy Director Korean National Biobank, Korean National Institutes for Health (KNIH). Dr Chou explained the role of this facility was to hold and catalogue biosamples from regional biobanks and national population studies to provide a resource for individual researchers and programmes such as the Korean Genome Epidemiology Study (KoGE) and the Korea Association Resource (RARE) (Cho *et al.,* 2012). Delegates were impressed by the scale of this facility and in particular the biomaterials ultra-low storage area which now holds many 100,000s of biosamples from the Korean population.

Korean Centre for Regenerative Medicine and National Stem Cell Bank

Delegates were then given and introduction to the National Center for Stem Cell and Regenerative Medicine and the Korean National Stem Cell Bank (http://kscr.nih.go.kr/nscb/en/kscr/index.do) and tour of their substantial facilities of 5000m^2, hosted by Dr Jung-Hyun Kim (Deputy Director KNIH Cell Therapy Center). Dr Kim described projects to contract manufacturing organization of cell therapy products ~~nd iPSC derived products~~. This facility was also the home for an iPSC bank of homozygous

haplotype iPSC lines to provide starting materials for a range of HLA-matched cell therapies for the Korean population.

Dr Sung-Gon Kim the incoming Director for the KNIH welcomed all ISCBI delegates to KNIH and opened the meeting.

Workshop I: Management of Research Participant (Donor) Personal Data

Chair: Rosario Isasi, University of Miami, USA

Korean regulation on consent and genetic data protection, So-Young Yoo (Assistant Professor in biomedical policy and ethics, Asan University, Korea).

Dr So-Young Yoo emphasised the key criteria for obtaining medical consent in Korea and went on to introduce the key Korean legislation relating to personal data including the Personal Information Protection Act to protect the rights and freedoms of individuals and the Bioethics and Safety Act intended to prevent violation of the dignity and values of Korean citizens and also to avoid harm to humans in the performance of research. Dr Yoo described the specific requirements for the so-called Prospective and Retrospective studies using human materials and data which must be carefully documented whilst keeping materials and personal identity separate.

It was a fundamental requirement for Researchers to obtain written and fully-informed consent from donors both regarding the research and future destination of the donated materials. Researchers were also expected to restrict the use of materials and data to the original stated purposes and make other commitments including constraining the retention period of donor material and presenting plans for release of materials and data. Under the legislation, human biobanks were prohibited from any release of personal data (including genetic data) even if permitted in the donor consent.

Dr Yoo also explained that retrospective studies may be performed subject to certain criteria and approval from the researcher's institutional ethics review board. However, some challenges remained around the classification of personal sensitive information and consent waivers for retrospective studies.

Managing Cell Line USA and EU Policy Approaches, Rosario Isasi (University of Miami, USA)

Rosario Isasi JD MPH, reflected on the significant changes which can occur in public and political attitudes to ethics in general and summarised the various ethical issues for pluripotent stem cell research considered by the ISSCR Ethics Working Party. These related to management of research data findings, publication of SNP genotypes and protection of donor identity (Isasi *et al.,* 2012; Isasi *et al.,* 2014). Ms Isasi identified a fundamental difference between the EU and US, which is that unlike the EU, US law provides no fundamental right to privacy.

Ms Isasi reviewed the 4 key pieces of US legislation on personal data (US regulation 1) which fell under the jurisdiction of the Department of Health and Human Services which delegated responsibility for assuring compliance to the FDA (US regulation 2), Office of Civil Rights (US regulation 3) and the Office for Human Research Protections (US regulation 4). Isasi also reviewed the key EU Directive (GDPR, 2016) which became law in May 2018. This legislation required specific consent for future uses of personal data and hPSCs and included raw genetic data. The requirements of these two jurisdictions were also compared in terms of fundamental rights and applicable state and federal laws. This revealed that whilst there were derogated rights for national or state jurisdictions to impose stricter

standards, in the EU, there were common minimum legal criteria for personal data protection (GDPR) unlike the lack of a single federal law in the USA with significantly diverse state by state privacy laws,

Ms Isasi went on to summarise changes implemented in 2018 to the US Federal Policy for the Protection of Human Subjects (Common Rule), regarding the definition of a 'human subject' from whom an identifiable biospecimen has been obtained. Also reported were further changes which required that further information were provided as part of consent, regarding potential future research. Furthermore, identifiable biospecimens could be used in research where consent is waived or where broad consent has been obtained. In addition, certain exceptions were also permitted for research with non-identifiable biospecimens (i.e., where the biospecimen is approved for another purpose, venipuncture biospecimens or non-invasive biospecimen collection).

Ms Isasi related that under the General Data Protection Regulations (2018), research data from data subjects in the EU was also subject to GDPR when moved outside of the EU. This had significant implications for international collaborations for data management and the definitions of 'personal data.' Ms Isasi went on to compare the key issues of de-identified data and the processing and use of data.

Ms Isasi identified three areas where there were special issues for hPSC research (Morrison et al., 2017): 1) the requirement for hPSC traceability to the donor hPSC lines which means that iPSCs cannot be fully anonymized, 2) raw genetic data represents personal information and 3) data processing & control includes iPSC genetic data and health and/or biometric data that may associated with an hiPSC.

To conclude, Ms Isasi considered that it would be desirable to have a common international template for consent relating to tissues donated for hPSC research and indicated the need for researchers should consider including new elements in the informed consent process to allow for future-proofing of stem cell applications.

Japanese requirements for donor consent and data management, Dr Mika Suzuki (Uehiro Research Fellow, iPSC ethics research center, CiRA, Kyoto University, Japan)

Dr Mika Suzuki presented a personal review of Japanese requirements for donor consent and personal data management and began by explaining that hPSC were considered "high risk" regarding the donors as the cells can be used for very diverse research and products in many countries. Dr Suzuki described the structure of the Japanese Act on Protection of Personal Information which gives fundamental provisions for all work using donor personal information and guidelines for industry.

Dr Suzuki explained that individual field-specific regulations produced by three Japanese ministries have been implemented for Academic research, medical practice and commercial purposes such as personal genetic testing services. Dr Suzuki described the extensive information on the research proposed, management of personal data, potential applications and commercialisation/IP, which was required to be included in donor information prior to obtaining written fully informed consent. Dr Suzuki also went on to outline the special requirements for provision of biological samples from Japan to other countries.

To conclude, Dr Suzuki raised some key issues relating to compliance required for academic research which was mandatory but did not apply in current standards for Japanese regenerative medicine.

Regulation of cross-border data sharing in China, Yaojin Peng (Institute of Stem Cell and Regeneration, Chinese Academy of Sciences, Beijing)

Dr Yaojin Peng outlined the key groups he was working with at the National Stem Cell Resource Centre (CAS, Beijing) and other stem cell research centers across China as part of the Alliance for Stem Cell Resource Centers which had been launched in 2019. He went on to explore how China's genetic materials and data might be shared with other countries under the general provisions for protection of personal data and its control under the Cybersecurity Law of 2016 and General Principles of Civil Law (2017). Peng identified that there were four key legal instruments relating to health data. He went on to describe regulations on the Ethical Review of Biomedical Research Involving Humans (PRC regulation 1, 2016) and the introduction of new legislation on the Administration of Human Genetic Resources (PRC regulation 2, 2019). Under the new genetic resources legislation "genetic materials" included organs and cells containing genomes, genes and other genetic substances, furthermore, "information" included data obtained from the use of genetic materials. It was fundamental to these laws that materials and personal information should be kept separate.

Dr Peng reported that licenses for collecting of genetic resources, their preservation and international collaboration involving them (PRC regulation 2. 2019), must be obtained with approval by the Ministry of Science and Technology. Furthermore, non-Chinese entities wishing to use Chinese genetic resources, must cooperate with a Chinese educational and/or research entity under a MOST license and comply with Chinese laws and regulations, including customs requirements. Such cooperation is also required to be subject to ethics review in China and the cooperating country.

In moving on to fundamental issue of informed consent Dr Peng noted that all uses of Chinese genetic resources shall respect the privacy of genetic resource providers (*i.e.* donors), requires written informed consent and must protect the lawful rights and interests of donors. Consent must be completed before the genetic resources are donated.

Pluripotent stem cell data management, Dr Andresa Kurtz (BCRT, IBMT-Fraunhofer Institute, Sarbrukken and Charite Universitat Medizin, Berlin, Germany)

Dr Andreas Kurtz emphasised the importance of data standards to assure interoperability of different data systems and that a crucial step was to decide on the data format to be used (Wilkinson *et al.,* 2016). Dr Kurtz explained that other aspects of data such as definitions, structure, manipulation, data exchange/transmission, use and management, are also important to be standardised.
Dr Kurtz described the convention for establishing a critical identifier, standard name and Biosamples ID for hPSCs registered in the hPSCreg database which had been previously reported by Kurtz *et al.,* (2018) and proposed as a standard for the pluripotent system cell community (www.iscbi.org/documents). He reflected on the importance of data standards the lack of which was holding the field back. Dr Kurtz went on to explain that variation in validation criteria for stem cell lines limited data reliability. Furthermore, there was currently a lack of traceability and interoperability in stem cell data and went on to explore a data model for stem cells including a variety of cell characteristics (e.g., cell markers, pluripotency, genotypic identity and genomic constitution). He also believed that current knowledge was sufficient for cell level models whilst also acknowledging the plasticity and complexity of stem cell lines and thus, the need for ongoing review of the models based on new science. As Dr Kurtz concluded he previewed ongoing work in hPSCreg to develop a registry of clinical trials using differentiated hPSCs (Kobold *et al*., 2020) and that hPScreg would continue to engage stakeholders to accommodate their 'use cases' to make the hPSCreg system a true standard.

The SKIP Database and Minimum Guidelines for Stem Cell Bank Data. Prof Wataru Fujibuchi (Centre for iPSC Research and Application, Kyoto University, Kyoto, Japan)

Prof Wataru Fujibuchi introduced the SKIP stem cell data project initiated and formerly run by Professor Toru Masui of Keio University. This database held information on over 5000 cell lines

including 857 from Japan of which 16 had been certified on hPSCreg. He described a project to establish Minimal Information About a Cellular Assay for Regenerative Medicine (Sakurai et al., 2016), which dealt with donor information, reprogramming and differentiation respectively and had been presented at the Seoul ISCBI workshop in 2016 (Kim *et al.,* 2017). The third stage of MIACARM would address the data structures needed for cell differentiation somatic cells and in vitro stem cell-derived cell types. Prof Fujibuchi also addressed a range of projects capturing cell ontogenies and reported the launch of the International Cell Type Authentication Committee that would deliver MIACARM III (recently published by Panina *et al*., 2020) that would develop proposals for international ontological standards and a reference molecular code for all human cell types. An ICTAC working draft outline had been developed at an ICTAC workshop in Berlin 2019. In conclusion, Prof Fujibuchi invited ISCBI members to engage with the ISCTAC and development of MIACARM III.

Data Workshop Discussion

In discussion on withdrawal of donor consent Prof Glyn Stacey commented that under the Human Tissues Act (2004)[1] in the UK, withdrawal of consent only applied to the original donor tissue and not to any in vitro derivatives involving cell replication (including hPSC lines) or disruption of donor cells such as DNA or protein extraction. However, he went on to say that conditions of withdrawal may vary in other European countries and there had been cases of hESC lines being withdrawn from distribution for research purposes following withdrawal of donor consent. Dr Andreas Kurtz added that across the EU it was required to assure that donors were made aware of their consent withdrawal rights. Examples of further information on consent issues were mentioned including hPSCreg cell line certification (www.hpscreg.eu) required for use of hPSC lines in European Commission funded research and discussion on the GAiT website (www.gait.global). Repurposing of donated tissue was a challenging issue which had been reported on by the ISCF Ethics Working Party (Lomax *et al.,* 2013). Rosario Isasi MPH confirmed that in the USA it was possible to consent for unforeseen future use. Mr Xiangjun Kong (Zephrym) commented that it was usual for national laws to promote broad consent which is agreed between the recipient and the donor with donors right protected by their ability to withdraw donated tissue. However, Andreas Kurtz, a member of the EU Group on Ethics (EGE), said that broadening of consent had been discussed at the EGE but at some point the consent might be considered too broad to assure it is fully-informed consent. Dr Yaojin Peng raised the issue that consent was not a legal contract and delegates agreed there was typically a need for some other measure of robustness of the consent an examples included the European Commission hPSCreg certification process (www.hpscreg.eu), the UK ethics Steering Group for the use of embryonic stem cells [2], the NIH stem cell registry[3] and the Spanish Istituto Carlos III ethics review process[4].

Discussion moved on to the kinds of data that were needed for hPSC research and development which had been addressed by ISCBI (Andrews et al., 2015) and which would include nature of consent and its review for suitability for stem cell research, permissible donor information including medical history and scientific and technical details of cell line derivation (including date the donor tissue was put into culture and characterisation, as required for hPSCreg certification. Also considered was feedback to the donor on use of the cell line and while some organisation on the USA were considering feedback on the use of a specific cell line to the donor many stem cell banks including UK Stem Cell Bank and the UK Biobank project had excluded this in the consent process. Dr Stephen Sullivan reflected on the discussions in the presentations on data regulation, which clearly meant that access to certain kinds

[1] https://www.hta.gov.uk/policies/human-tissue-act-2004
[2] https://mrc.ukri.org/research/policies-and-guidance-for-researchers/uk-stem-cell-bank-steering-committee/
[3] https://stemcells.nih.gov/research/registry.htm
[4] https://stemcellforum.org/about_the_iscf/members/instituto_de_salud_carlos_iii_spain.cfm

of data, especially sensitive personal data, would be regulated and controlled and may only be accessible by an independent data access committee. Dr Steve Oh also pointed out that hPSCreg had published a standard cell line unique identifier system which would be important for all ISCBI community members to adopt (Kurtz *et al.,* 2018) to avoid confusion due to lack of consistency in cell one naming in publications and occasional identical naming of different cell lines (Luong *et al.,* 2012, Kurtz *et al.,* 2018). Two key outputs from the workshop were agreed:

1) It was agreed by delegates that a further understanding of international diversity in how stem cell line data was managed would be extremely beneficial. In order to progress this Dr Kurtz and Ms Isasi agreed to coordinate and distribute to speakers on data regulation and some other national experts, the four key questions already identified in the ISCBI agenda:
    a. What regulations apply to obtaining donor consent, donor personal data and the use of pluripotent stem cell lines?
    b. What kinds of donor data would be considered private and should be protected?
    c. What key requirements are applied for obtaining consent from donors of cells/tissues to be used in the derivation of stem cell lines?
    d. What requirements if any, apply to the collection, handling and sharing/dissemination of data from pluripotent stem cell lines and donor specific data including genetic data?

    This would enable a map of international diversity and potential blocks on stem cell research to be established which could be used by the stem cell community.
2) ISCBI would ensure that a copy Professor Fujibuchi's presentation on the ICTAC would be circulated to all ISCBI members so that they could engage with this initiative and provide data to assist in its development.

Session II: Reagents and testing services for stem cell banks for manufacture of cell therapies.

Chairs: Shin Kawamata, Kobe Medical Centre, Kobe, Japan and Glyn Stacey, ISCBI, UK and Beijing Stem Cell Bank, IOZ-CAS, Beijing, China.

ISCBI workshop summary on qualification of reagents for manufacture of hPSC-based products. Glyn Stacey, ISCBI, UK.

Glyn Stacey summarised the extensive discussion from the June 2019 ISCBI meeting for which full proceedings are available to ISCBI members on request to admin@iscbi.org

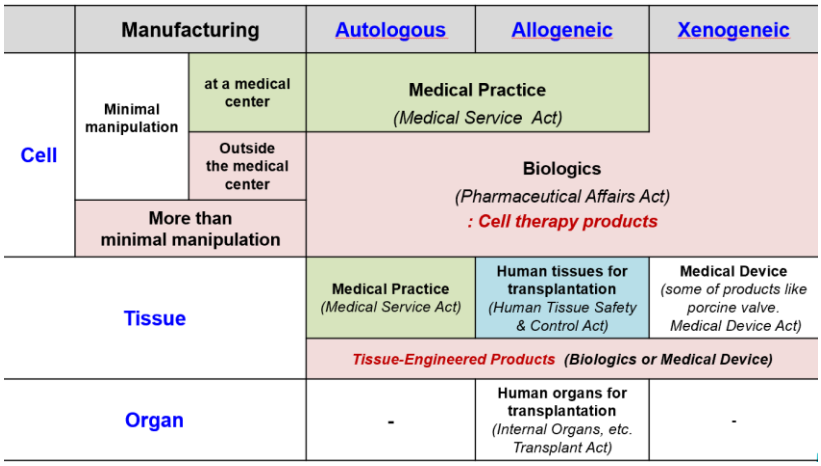
Regulation of Cell and Gene Therapy Products in Korea. Kyoung Suk Choi MFDS C&GT Prod division

Dr Kyoung Suk Choi started by giving the Ministry of Food and Drug Substances (MFDS) description of a cell-based medicinal product as a product "manufactured through physical, chemical, and/or biological manipulation, such as *in vitro* culture of autologous, allogeneic, or xenogeneic cells." However, she also indicated that certain procedures were exempted, but only where a medical doctor performs minimal manipulation of autologous or allogeneic cells, which does not raise safety concerns

in the course of surgical operation or treatment at a medical center. Examples of such minimal manipulation were cited as "… simple separation, washing, freezing, thawing, and other manipulations," which maintained the biological properties of the cells (MFDS notification Article 2[5]). Specific examples not included in the MFDS definition of minimal manipulation included, proliferation of cells as a result of cell culture, cell activation using growth factors and gene transduction.

Choi went on to summarise the Korean laws which governed development and delivery of cell and gene therapies in Korea (Figure 2). Key legislation was the Pharmaceutical Affairs Act and Riles for the Safety of Pharmaceuticals which were implemented under the MFDS approvals process and supported by MFDS industry guidelines.

Figure 2. The Application of Gene and Cell Therapy Regulations in Korea



These are applied to legal instruments specific to particular types of cell or tissue as follows:

- Cord blood: Umbilical Cord Blood Control and Research Act
- Blood products : Blood Management Act
- Human derived cell & tissue : Bioethics and Safety Act
- Human tissues regulated under HTSCA : cartilage, bone, ligament, tendon, skin, heart valves, blood vessel, fascia, amnion

Dr Choi moved on to specify a gene therapy product under Korean regulation as "a medicinal product which contains either, genetic material to influence gene expression or cause genetic modification, or genetic material-transduced cells" (MFDS notification Article 2, Revised in 2017 – see above).

Looking to the future Dr Choi indicated that MFDS task forces had been launched to develop new legislation and guidance for other advanced therapeutic cell-based products starting in 2020.

The clinical trials process was described by Dr Choi which was broadly equivalent to other jurisdictional approaches with preclinical development followed by phase I & II clinical trial of an Investigational

5 https://www.khidi.or.kr/board;jsessionid=14CTf8hY11qL42qtPvVp2MQ2RG1gdVtprThwyr4rYBR1X4dknyRf!495014750?menuId=MENU02291&siteId=SITE00032

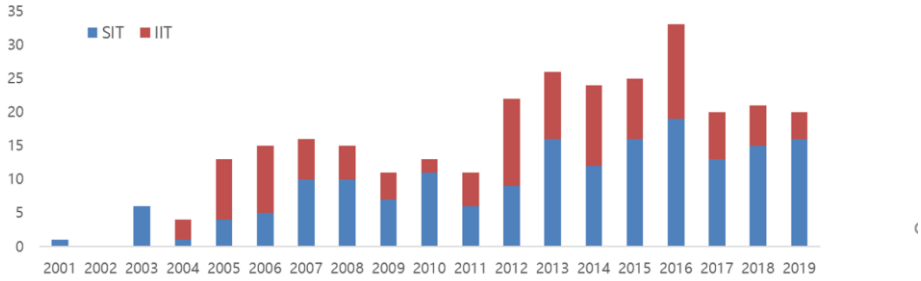
New Drug (IND) subject to MFDS review and phase III, followed by NDA review and approval prior to phase IV clinical trial (for details see http://nedrug.mfds.go.kr).

Dr Choi described an expedited regulatory process for cell therapy products for life-threatening or severe and irreversible disease *(MFDS Notification, Article 24[6]) after phase II, where t*he product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. There was clear benefit in that this process could help speed up patients' access to new medicines, and potentially have a greater choice of therapies. However, Dr Choi also recognized that such an approach could involve uncertainties where there was less evidence of efficacy and safety than for drugs approved via the standard pathway. Dr Choi went on to describe the detailed documentation required for MFDS review of IND proposals and also the new Advanced Regenerative Medicine and Advanced Biopharmaceuticals Safety and Support Act to be enacted in 2020 (*postscript:* this law was enacted in August 2020, see WEBLINK). The new regulation would see a split in regulatory oversight responsibilities between the Ministry of Health and Welfare who would oversee 'clinical research' applications of regenerative medicines and the MFDS who would oversee clinical trials of commercial advanced biopharmaceuticals. 'Clinical research' included patient low-high risk applications but high risk trials would still require approval by the MFDS. There would also be a division of responsibilities between MOHW and MFDS for provision of conditional approval for cell processing supply, medicinal product manufacturing, regenerative medicines and biopharmaceuticals and safety control.

The growing numbers of cell therapy trials and market authorisations in Korea were outlined by Dr Choi (summarised in Figure 3, Table 3, Table 4 and Table 5) and went on to list the 20 regulatory guidance documents designed to assist product developers which are shown in Table 6 and can be found at http://mfds.go.kr/index.do?mid=5689. Dr Choi also summarized the 16 cell therapy products with Market authorisation which exceeded the numbers in the EU (Table 5).

Figure 3 and Table 3. Regulatory activity for cell therapies in Korea since 200

SIT: Sponsor initiated trial IIT: Investigator initiated trial

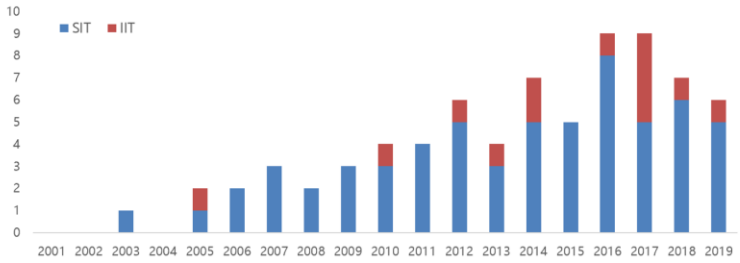


Clinical trial No.		Cell Type			
		Stem Cell	Immune Cell	Somatic Cell*	Xenogeneic Cell
SIT	177	109	41	25	2
IIT	119	70	40	9	0
Total	296	179	81	34	2

* keratinocytes, fibroblasts, chondrocytes, osteoblast, etc.

[6] https://www.mfds.go.kr/eng/brd/m_18/down.do?brd_id=eng0003&seq=71448&data_tp=A&file_seq=1

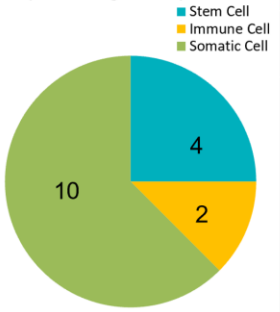
Table 4. Regulatory activity for gene therapies in Korea since 2001



Vector type									
Plasmid	Adenovirus(AV)	AAV	Plasmid +AV	Vaccinia virus	mRNA	Retrovirus	HSV	Bacteria	Total
In vivo									
30	8	0	1	9	2	1	3	1	55
Ex vivo									
1	5	4				9			19

Table 5 Market Authorisations for cell therpoy products in Korea

- Market Authorization
(as of Aug. 2019)



	Product	Year	Conditional Approval	Indication
Stem Cell Products	Neuronata-R Inj.	2014	Orphan	Amyotrophic Lateral Sclerosis
	Cupistem	2012	Orphan	Crohn's disease
	Cartistem	2012		Knee cartilage repair
	Hearticellgram-AMI	2011		Myocardial infarction
Immune Cell Products	Immunecell-LC	2007	Cancer	HCC
	CreaVax-RCC	2013		RC (Export only)
Somatic Cell Products	Cartilife	2019	autologous chondrocytes	Articular cartilage defect of knee
	Rosmir	2017	autologous skin cells	Nasojugal groove
	KeraHeal-Allo	2015		Burn wounds
	Cure-skin	2011	autologous skin cells	Acne scar
	Queencell (min. manipulation)	2010		SC adipose tissue deficiency
	RMS ossron	2009		Local bone formation
	KeraHeal	2006	autologous skin cells	Burn wounds
	Kaloderm	2005 2010		Burn wounds Diabetic foot ulcer
	Holoderm	2002	autologous skin cells	Burn wounds
	Chondron	2001	autologous chondrocytes	Articular cartilage defect

Table 6. Korean Regulatory guidelines for cell and gene therapies issued by the MFDS

- Guideline on Quality Assessment for Gene-editing based Advanced Therapy Medicinal Products (2018
- Guideline on Quality, Non-clinical and Clinical Assessment of Extracellular Vesicles Therapy Products (2018)
- Considerations on Design and Analysis of Clinical Trials for Conditional Approval (2018)
- Frequent Asked Questions and Answers on Advanced Therapy Products (2018)
- Guideline for Non-clinical Assessment of Gene Therapy Products (2017)
- Guideline for Cell-based Combination Products Using Scaffold : 3D Bio-Printing Products (2017)
- Guideline for Nomenclature of Drug Substance of Cell Therapy Products (2017)
- Guideline on Eligibility Determination for Donors of Cell Therapy Products (2016)
- Guideline on Design of Early-phase Clinical Trials of Cell and Gene Therapy (2015)
- Guideline for Follow-Up of Patients Administered with Gene Therapy Products (2016)
- Guideline on Sponsor-Investigator Trials of Cell Therapy Products for Academic Purpose (2015)
- Guideline for assuring the quality and nonclinical evaluation of therapeutic DNA vaccines (2015)
- Considerations in Tumorigenicity Assessment of Stem Cell Therapy Product (2014)
- Considerations in Biodistribution Assessment of Stem Cell Therapy Product (2014)
- Guideline on Assessment of Stem Cell Products(2014)
- Guideline on Release test for Cell Therapy Products (2014)
- Guideline on Mycoplasma test using PCR method (2012)
- Guideline on Adventitious Virus Test for Biological Products for Human Use (2010)
- Considerations for Validating Analytical Method for Biodistribution of Gene Therapy Products Using qPCR (2010)
- Considerations for Evaluation of Dendritic Cell Therapy Products for Cancer Treatment (2005)

Some of the key concerns held by the MFDS for the safety testing were explained by Dr Choi to include:

- The needs for strict aseptic processing and strict microbiological control of raw materials of human and animal origin
- Short shelf life of non-frozen products which will require development of alternative testing methods, in-process testing with representative samples and an investigation plan where positive microbiology tests arise.
- Small batch sizes for some cases which do not permit adequate samples for QC testing and may require in-process control.
- Variation in cell source which would require the establishment of minimal criteria to ensure safety, efficacy and consistency of product.

Dr Choi also reflected on the absence of procedures for inactivation or removal of exogenous agents during manufacturing of cell-based therapy products and emphasized the need to prevent raw materials of biological origin from being contaminated by infectious agents including TSEs, by review of animals of origin, processing and evidence to assure their microbiological safety.
TSE. Donor cells were also discussed as potential safety risk and Dr Choi indicated the need for three levels of donor assessment:

- donor screening (medical history),
- donor testing for serious pathogens including HTLV1/2 and hCMV for leucocyte rich materials and *N gonorrhoeae* and *C trachomatis* for cells from reproductive tissues and
- donor eligibility review including review of completion and documentation of donor screening and testing, documentation of these procedures and assurance of archiving and traceability.

Finally, Dr Choi reviewed the wide range of safety testing required for regenerative medicines by MFDS which were expected to be performed according to Korean, European or US Pharmacopeial methods.

In conclusion, Dr Choi drew attention to the new regenerative medicine regulation now being introduced in Korea to accelerate patient access to novel therapies, the significant number of approved cell therapy products which currently exceeded the approved gene therapy products in many other countries, the critical need to assure microbiological safety and control of product variation.

Assuring the quality of karyological testing, Koji Tajino, Chromocenter Inc., Japan

Dr Koji Tanjino presented the experiences of Chromocenter in providing standardised karyological testing using Geimsa-banding, Quinacrine-banding and mFISH, over more than six years. He summarised some of the key aspects of validating karyological analysis at all stages of processing from cell culture, cell fixation and sample preparation, staining image capture and analysis. Three hPSC cell lines were used to validate SOPs for all these stages and to avoid variation when new batches of reagents were used, three batches of all critical reagents were compared in parallel to enable selection of equivalently performing reagents. However, Tajino reported that a key challenge of providing quality data is assuring the quality of cells available for analysis and significantly variable and often suboptimal cell fixation conditions used by clients for preparation of individual cell lines. This meant that results were often compromised due to absence of metaphase cells, highly condensed chromosomes or chromosome dispersion during fixation.

Dr Tajino indicated that in Chromocenter experience 400 band level karyotype analysis had been sufficient to precisely detect the majority of chromosome variations precisely. In fact, 300 band level analysis had also proven a useful approach which yielded faster results but could still indicate the presence of chromosomal variants. However, Dr Tajino also recognized that occasionally, even 400 band level analysis cannot find karyotypic variants. He went on to summarize genetic testing data since 2013 which had shown that the frequency of gaps and breaks in mesenchymal stromal cell chromosomes appeared to occur more frequently than in hiPSCs, but noted that chromosome gap and break analysis had not been mentioned in many stem cell banking regulations. Dr Tajino observed that such observed genetic effects are often used to test the genetic impact of mutagens and proposed that they may also be useful indicators of suboptimal cell culture and genetic instability. He also pointed out that a potential benefit of Q-banding over G-banding was that the Q-banding is not so adversely affected by cell debris and may be valuable where this arises, as the Q-band pattern is often very similar to G-banded chromosomes. On reviewing the value of mFISH pseudo-colouration of chromosomes Chromocenter's experience was that this technique had the capability to readily detect minor genetic changes including small insertions. However, Dr Tajino also reported that it could be difficult to detect break points, inversions and duplications.

Session II workshop discussion

Open discussion was invited on the key issues for determining suitability of testing services for stem cell lines intended for hPSC-based product manufacturing including consideration of the following questions:

- What are the considerations for sensitivity, specificity, reproducibility of genetic testing techniques e.g., karyology, WGS, adventitious agents detection?
- What standards are applicable or needed for testing?
- What criteria should hPSC banks use for selection of external service providers?

Dr Steve Oh (AStar, Singapore) reported that it was common to use IVF clinic karyology services but it was not always clear how to validate the analytical data reported by the clinic. In response Dr Kapil Bharti advised that Cell Line Genetics in Wisconsin had been providing karyology testing for cell lines as a service for ten years and were able to provide quality assurance although validation data was not available. Dr Jung Hyun Kim confirmed that the absence of validation data was also and issue for karyological services in Korea. The ISCBI had evaluated international standards for clinical karyological testing and published best practice recommendations to assure adequate sensitivity of karyological testing specifically for hPSC lines (Andrews et al., 2010 & 2015). Delegates considered that formal regulated accreditation would be important for services provided to stem cell banks supplying cell lines for product development. In the UK Clinical Pathology Accreditation (CPA) accreditation was

applied in many testing laboratories including cytogenetics laboratories and in the USA the Clinical Laboratory Improvement Amendments (CLIA) guidelines and accreditation is also applied to karyology[7]. Dr Jusaku Minari (CiRA, Japan) highlighted the increasing international adoption of the ISO standard 15189 for accreditation of medical laboratories (Guzel and Guner, 2008) which had been adopted for molecular genetic testing (Berwouts *et al*., 2010).

Delegates went on to consider the demands of validating service provider data for complex molecular genetic testing such as WGS, Copy Number Variation, CHIP, RNAseq etc. Division of single test samples for all assays used was considered an important step. Dr Kapil Bharti reported that in the US there were genomics service providers accredited to CLIA standards already mentioned. Also in the USA CLSI had produced guidelines for validation of copy number variation microarray genetic analysis[8] and multiplex nucleic acid testing[9] and ISO standards for various aspects of omic analysis were under development. It was also noted that it was vital to have a clear strategy for managing complex nucleic acid data for cells used in the manufacture of cell-based medicines, particularly for genetic stability testing where the data could raise questions relating to safety which could not be immediately understood and could thus cause problems for product developers. Prof Glyn Stacey reported that the need for understanding of genetic stability in hPSC lines was being taken up by the International Stem Cell Initiative (Andrews *et al.,* 2017) which would be updating the ISCBI community at future workshops

Session III: Cost of Goods considerations for production of hPSC for clinical use

Chairs: Jung-Hyun Kim, KNIH, Osong, Korea and Steve Oh BTI A*Star

Ohad Karnielli (Adva Biotechnology Ltd, Israel)

Ohad Karnielli (OK) described attempts to make MSC cells manufacture more efficient using a semi-automated bioreactor (Karnielli, 2015) and a new automated and controlled CAR T platform to address autologous manufacturing challenges. He presented a case study for very large scale dose manufacturing capable of performing hundreds of manipulations per day under clean room conditions.

Dr Karnieli described Adva experiences in the costs of translation from R&D to GMP manufacturing. GMP manufacturing had taken around 3x longer so costs for developing a GMP process could cost multi-millions of dollars. Translation of the process for GMP manufacture to a Contract Manufacturing Organization could be difficult to predict and increases costs. Dr Karnieli also stated that cleanroom consumables could be a major cost element for cell culture process.

Korean National Institutes for Health (KNIH) experiences in cost of goods considerations for production/quality tests of hPSCs for clinical applications. Jung-Hyun Kim (National Stem Cell Bank of Korea, KNIH, Korea)

In 2016 the KNIH established a facility for manufacturing hPSCs under GMP license for a number of clinical applications and supporting other researchers by partnering with contract manufacturing organizations (CMOs). The total area of clean rooms and the QC area of production facilities are approximately 500m^2, and Dr Kim reported that the maintenance cost of facilities was in excess of $2 million/year which did not include materials/QC costs. Dr Kim's experience was that the facility

[7] https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia

[8] https://clsi.org/media/1472/mm21ed1_sample.pdf

[9] https://clsi.org/standards/products/molecular-diagnostics/documents/mm17/

maintenance costs are much higher than any other manufacturing costs and that reducing GMP down time is important to reduce costs and considered that facility rental or use of a CMO may present a more cost effective solution. Dr Kim went on to emphasise that there could be unanticipated hurdles in his manufacture which can significantly impact on CoGs and these are discussed in the following paragraphs.

Key areas for reducing costs were a well-controlled manufacturing process, minimising differences between the lab-scale process and the GMP operation and the need to ensure that scale up system is sufficiently robust at lab-scale to enable manufacture of clinically relevant cell numbers and quality. Dr Kim also reflected on the challenge of the cost of the technology transfer process into a GMP manufacturing quality management system that may also involve a Contract Manufacturing Organisation (CMO) bringing additional expense including training in the cell culture process.

Donor selection had also caused unexpected delays in manufacturing at KNIH and Dr Kim recommended that formal donor selection criteria can help to avoid such problems (Andrews *et al*., 2015).

In the manufacturing process human error had also been recognised at KNIH as a potentially significant costs. Dr Kim proposed mechanisms to control this within the quality management system. Dr Kim also emphasised that local weather extremes and power supply reliability could cause significant losses or extra costs and that risk assessment and disaster planning were very important procedures for GMP facilities.

Dr Kim also reflected on important efficiency and cost benefits that could be obtained from early discussion with regulators since in particular this can help to avoid unacceptable traceability of raw materials and manufacturing and testing requirements. Dr Kim emphasised the importance of thorough testing of master cell banks to mitigate the risk insurmountable issues of microbial contamination or incorrect cell identity are not revealed until later in manufacturing

Eihachiro Kawase (University of Kyoto, Japan)

Eihachiro Kawase pointed out that it was important to consider the number of vials and cells/vial required, labelling and costs of validation including preservation and storage as the need to repeat banking campaigns caused delay and additional production and testing costs.

At the stage of clinical studies, the costs of the implantation method development and also patient monitoring and warranty could be very significant and need to be considered.

Most significant costs experienced in Dr Kawase's hESC manufacturing facility in Kyoto had been cell culture materials, cell line safety testing and staff costs including training. The full costs of QC and validation were difficult to assess and another significant cost in Japan was the requirement for renewal of manufacturing facilities every at least ever ten years.

Commentary on CoGs for treatment of age-related macula degeneration using autologous hiPSCs. Kapil Bharti (NIH, USA).

Dr Kapil Bharti had found that the largest cost in hPSC-derived RPE was the time in GMP manufacturing and anything to reduce that would improve COGs. Contracting out GMP manufacture had proven more costly than in-house provision. Validation was also a major part of the cost but QC, whilst not cheap, was not their major cost. Dr Bharti summarized key costs in the RPE manufacturing and some possible cost reductions.

He reflected on certain costs of patient bespoke iPSCs that were difficult to calculate including manufacturing cell lines at a rate of only one or two at a time in early trial phases which was inefficient on staff and facility resources.

Dr Bharti stated that NIH experiences indicated that cleanroom maintenance time caused increased cost and alternative approaches to manufacturing in parallel or renting cleanroom facilities and streamlining SOP numbers may help to control costs.

CoGs Experiences at CiRA. Yuiji Arakawa, Centre for iPSC Research and Application, Kyoto, Japan

Dr Yuji Arakawa reported that manpower costs were a substantial proortion of total cost in their facility and other significant costs were due to QA, maintenance and servicing. These can be high per banking activity if outsourced but in-house provision meant ongoing continuous costs. CiRA also found that outsourced virus testing and whole genome sequencing were costly. Cell banks were produced at 100s of vials per bank which took one month to produce and could cost several million dollars per batch. Dr Arakawa reported that different sources of iPSCs varied in charge per vial and some charges varied depending on the intended use. CiRA planned to sell iPSC stocks at $10,000K/vial.

Dr Arakawa thought that sharing information on cost efficiencies and on procedures (SOPs) would be really helpful in reducing individual bank costs and Prof Shin Kawamata (FBRI) proposed that sharing manufacturing protocols used at CiRA and invite industry involvement would also add value.

Session III Workshop Discussion.

Delegates concluded that a key challenge was to find ways to avoid the cost and space required for cleanroom cell culture operations and that automation involving use of automated cell culture bioreactors was the most likely strategy to achieve this goal. Automation was felt offer the key benefits of reducing facility footprint, avoiding down-time and enabling the operation of multiple manufacturing processes in parallel. One challenging issue was assuring new automated bioreactors would be acceptable in GMP manufacturing and in particular from the perspective of the potential for contamination. It was agreed that experience indicated that supplier claims of “closed” culture systems needed to be validated carefully. It was noted that importance of validation not only related to facilities and equipment, but also to implementation of new analytical methods, such as multiplexed PCR primer systems which often required method adaptation and thus additional validation.

Use of sealed bioreactors that could operate in class D environments would be a significant benefit for streamlined cell banking and the EBiSC iPSC bank for disease modelling had been experimenting with such systems to improve cell banking efficiency for almost 1000 iPSC lines[10] and Dr Sheng Cao (Miltenyi Biotec) reported that Miltenyi semi-automated culture systems were being validated for manufacture in a Class D air quality background. Dr Hashimoto (DS Pharma, Kobe) also reported that for this system the balance of cost of validation was as follows: 45% staff, 23-25% testing and 25% materials. Many delegates agreed that validation was a significant burden in both time and resource.

The discussion also turned to the issue that some manufacturers falsely claim “GMP” quality of equipment. This had also been covered in the discussion at previous ISCBI meetings and had been a clear concern for regulators (see notes from ISCBI Los Angeles June 2020 available on request to admin@iscbi.org).

[10] https://www.myeventflo.com/event-lecture.asp?lectID=13203

Delegates reflected on the fact that molecular interventions in manufacturing can also raise complexities regarding safety and quality control. This had been a challenge for CART manufacturing where in addition, the viral load may need to be monitored in patients post treatment. The development of gene-edited hPSCs also introduced additional quality control costs which may include as yet to be determined safety testing (ISCBI workshop proceedings, Melbourne June 2018, available on request to admin@iscbi.org).

Costs for vials of cells for use in manufacture were discussed for different centres and it was clear that there was significant variation from $1000-10.000 per vial and in some cases special contract condition were understood to apply additional charges.

A full published report of session I & III are in preparation and will include further discussion of the issues raised.

References

Andrews, P.W., Arias-Diaz, J., Auerbach, J., Alvarez, M., Ahrlund-Richter, L., Baker, D., Benvenisty, N., Ben-Josef, D., Blin, G., Borghese, L., Borstlap, J., Bruce, K., Brüstle, O., Buckle, R., Camby, C., Choo, A.B., Chen, W., Collins, D., Colman, A., Crombie, C., Crook, J.M., Cypess, R., De Sousa, P., Dhawan, J., Douay, L., Dvorak, P., Dyke, T., Eriksson, L., Firpo, M., Fitzgerald, C., Glover, C., Gokhale, P., Greene, M., Ha, H-Y., Hampl, A., Healy, L., Hei, D., Holm, F., Hovatta, O., Hunt, C., Hwang, S-M., Inamdar, M., Isasi, R., Itskovitz-Eldor, J., Jessie, N., Kim, D-W, Kirzner, R., Kiatpongsan, S., Knowles, B.B., Kuo, H-C., Laughlin, M., Lavon, N., Ludwig, T., Lakov, M., Lee, D-R., Macauley, J., McKay, R., Menasche, P., Menendez, P-M., Michalska, A., Mileikovskaia, M., Minger, S., Mishra, G., Moody, J., Montgomery, K., Morris, C., Mummery, C., Nagy, A., Nakamura, Y., Nakatsuji, N., Nishikawa, S-I, Oh, S., Oh, S-K, Olson, P., Otonkoski, T., M., Patole, M., Park, H-S., Pei, X., Pera, M., Rajala, K., Reubinoff, B., Robins, A., Rooke, H., Rumayor, V., Scotmann, H., Sherlock, J., Simon, C., Sipp, D., Skinner, R., Smith, D., Stacey, G.N., Stefanovic, S., Strehl, R., Taft, R, Takahashi, T., Talib, S., Terstegge, S., Turner, R., Tuuri, T., Yu, J., Zandstra, P., Zapata, A., Zeng, F., Zhou Q.,, Tannenbaum, S. (2010). Consensus guidance for banking and supply of human embryonic stem cell lines for research purposes. *Stem Cell Reviews and Reports* 5, pp301-314.

Andrews PW, Baker D, Benvinisty N, Miranda B, Bruce K, Brüstle O, Choi M, Choi YM, Crook JM, De Sousa PA, Dvorak P, Freund C, Firpo M, Furue MK, Gokhale P, Ha HY, Han E, Haupt S, Healy L, Hei DJ, Hovatta O, Hunt C, Hwang SM, Inamdar MS, Isasi RM, Jaconi M, Jekerle V, Kamthorn P, Kibbey MC, Knezevic I, Knowles BB, Koo SK, Laabi Y, Leopoldo L, Liu P, Lomax GP, Loring JF, Ludwig TE, Montgomery K, Mummery C, Nagy A, Nakamura Y, Nakatsuji N, Oh S, Oh SK, Otonkoski T, Pera M, Peschanski M, Pranke P, Rajala KM, Rao M, Ruttachuk R, Reubinoff B, Ricco L, Rooke H, Sipp D, Stacey GN, Suemori H, Takahashi TA, Takada K, Talib S, Tannenbaum S, Yuan BZ, Zeng F, Zhou Q. (2015) Points to consider in the development of seed stocks of pluripotent stem cells for clinical applications. Regenerative Medicine. 10 (02s) doi: 10.2217/RME.14.93

Andrews PW, Ben-David U, Benvenisty N, Coffey P, Eggan K, Knowles BB, Nagy A, Pera M, Reubinoff B, Rugg-Gunn PJ, Stacey GN (2017) Assessing the safety of human pluripotent stem cells (PSCs) and their derivatives for clinical applications. Stem Cell Reports.11, 9(1); 1-4. DOI: 10.1016/j.stemcr.2017.05.029

Berwouts, S., Morris, M. & Dequeker, E. Approaches to quality management and accreditation in a genetic testing laboratory. *Eur J Hum Genet* **18,** S1–S19 (2010). https://doi.org/10.1038/ejhg.2010.104

Cho SY, Hong EJ, Nam NM, Han B, Chu C and Park O (2012) Opening of the National Biobank of Korea as the Infrastructure of Future Biomedical Science in Korea. Osong Public Health Res. Perspect. 3(3): 177–184. doi: 10.1016/j.phrp.2012.07.004

GDPR (2016) Regulation (EU) 2016/679 of the European Parliament and of the Council (26th April 2016) on the protection of natural persons with regard to the processing of personal data and of the free movement of such data and repealing Directive 95/46/EC(general data protection regulations). Official Jpourtnal of the European Union, L119/1, 4th May 2016.

Guzel O, Guner EI. ISO 15189 accreditation: Requirements for quality and competence of medical laboratories, experience of a laboratory I. Clin Biochem. 2009 Mar;42(4-5):274-8. doi: 10.1016/j.clinbiochem.2008.09.011. PMID: 19863920. (for further information from ISO see www.iso.org)

Isasi, R, Peter W. Andrews, PW, Baltz, JM, Bredenoord, AL, Burton, P, Chiu, I-M, Hull, SC, Jung, J-W, Kurtz, A, Lomax, G, Ludwig, T, McDonald, M, Morris, C, Ng, HH, Rooke, H, Sharma, A, Stacey, GN, Williams, C, Zeng, F and Knoppers BM. (2014) Identifiability and Privacy in Pluripotent Stem Cell Research. Cell Stem Cell, 14, 428-430.

Isasi, R., Knoppers, B.M., Andrews, P.W. Bredenoord, A, Colman, A, Lee E-H, Hull, S Kim, O-J, Lomax, G, Morris, C, Sipp, D, Stacey, G, Wahlstrom, J, & Zeng F (2012) Disclosure and management of research findings in stem cell research and banking: policy statement. Regen Med ; 7 (3), 440-448.

Karnieli O. (2015) Cell Therapy: Early Process Development and Optimization of the Manufacturing Process are Critical to Ensure Viability of the Product, Quality, Consistency and Cost Efficiency. J Commercial Biotechnology, 21 (1): 83- https://doi.org/10.5912/jcb695

Kim J-H, Kurtz A, Yuan B-Z, Zeng F, Lomax G, Loring JF, Hyeon Ju Ji, Clarke L, Inamdar MS, Pera M. Firpo MT, Sheldon M, Rahman N, O'Shea O, Pranke P, Zhou Q, Isasi R, Rungsiwiwut R, Kawamata S, Oh S, Ludwig T, Masui T, Novak TJ, Takahashi T, Fujibuchi W, Koo,SK, Stacey GN, (2017) Report of the International Stem Cell Banking Initiative Workshop Activity: Current Hurdles and Progress in Seed-Stock Banking of Human Pluripotent Stem Cells. SCTM, 6; 1956-1962.

Kobold S, Guhr A, Mah N, Bultjer N, Seltmann S, Seiler-Wulczyn AEM, Stacey GN, Hao J, Wang L, Lo¨ser P and Kurtz A (2020) A Manually Curated Database on Clinical Studies Involving Cell Products Derived from Human Pluripotent Stem Cells. Pluripotent Stem Cells. Stem Cell Reports, 15; 1-10. DOI: 10.1016/j.stemcr.2020.06.014

Kurtz A, Seltmann S, Bairoch A, Bittner MS, Bruce K, Capes-Davis A, Clarke L, Crook JM, Daheron L, Dewender J, Faulconbridge A, Fujibuchi W, Gutteridge A, Hei DJ, Kim YO, Kim JH, Kokocinski AK, Lekschas F, Lomax GP, Loring JF, Ludwig T, Mah N, Matsui T, Müller R, Parkinson H, Sheldon M, Smith K, Stachelscheid H, Stacey G, Streeter I, Veiga A, Xu RH.(2018) A Standard Nomenclature for Referencing and Authentication of Pluripotent Stem Cells. Stem Cell Reports. 10(1):1-6. doi: 10.1016/j.stemcr.2017.12.002.

Lomax GP, Hull SC, Lowenthal J, Rao M, Isasi R. (2013) The DISCUSS Project: induced pluripotent stem cell lines from previously collected research biospecimens and informed consent: points to consider. Stem Cells Transl Med. 2(10):727-30. doi: 10.5966/sctm.2013-0099.

Luong MX, Auerbach J, Crook JM, Daheron L, Hei D, Lomax G, Loring JF, Ludwig T, Schlaeger TM, Smith KP, Stacey G, Xu RH, Zeng F.(2011) A call for standardized naming and reporting of human ESC and iPSC lines. Cell Stem Cell. 8(4):357-359. PMID: 21474098, DOI: 10.1016/j.stem.2011.03.002

Morrison M, Bell J, George C, Harmon S, Munsie M, Kaye J. The European General Data Protection Regulation: challenges and considerations for iPSC researchers and biobanks. Regen Med. 2017 Sep;12(6):693-703. doi: 10.2217/rme-2017-0068. Epub 2017 Oct 4. PMID: 28976812; PMCID: PMC5857917.

Panina Y, Karagiannis P, Kurtz A, Stacey GN, Fujibuchi W (2020).Human Cell Atlas and Cell Type Authentication for Regenerative Medicine. Exp Mol Med 52, 1443–1451. https://doi.org/10.1038/s12276-020-0421-1

PRC regulation 1. Measures for the Ethical Review of Biomedical Research Involving Humans, No. 14, promulgated by then- National Health and Family Planning Commission (now the NHC) Oct. 12, 2016, effective Dec. 1, 2016

PRC regulation 2. Regulation of the People's Republic of China on the Administration of Human Genetic Resources, No. 717of the State Council of the PRC, promulgated on 28 May 2019, effective Jul. 1, 2019.

Sakurai K, Kurtz A, Stacey G et al. (2016) First proposal of minimum information about a cellular assay for regenerative medicine. STEM CELLS TRANSLATIONAL MEDICINE 2016;5:1345–1361.

US regulation 4. Protection of Human Subjects, also known as the Common Rule (45 C.F.R. 46, Subpart A).

US regulation 2. FDA regulations on the Protection of Human Subjects and Institutional Review Boards (21 C.F.R. 50 and 56)

US regulation 3. HIPAA Privacy Rule (45 C.F.R. 160 and 164)

US regulation 1. Public Health Service Act Certificates of Confidentiality (301(d), 42 U.S.C. 241(d)).

Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, & Mons B. (2016) The FAIR guiding principles for scientific data management and stewardship. Scientific Data 3(2016), Article No. 160018. doi: 10.1038/sdata.2016.18.(W

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