82

THE CHANGING ETHICAL LANDSCAPE FOR SECONDARY USE OF HUMAN BIOLOGICAL MATERIAL: IMPLICATIONS FOR STEM CELL BANKING AND RESEARCH

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The use of human biological material is essential for stem cell research. There is broad consensus that such use is ethically acceptable if two key conditions are satisfied: the wishes of the original donors of the material are respected and potential harms to them are minimized, in particular by protecting their privacy. What is less clear is how best to ensure that these conditions are satisfied without unduly impeding valuable research or imposing unreasonable burdens on researchers, oversight bodies, and institutions. The policies and regulations of various countries have taken slightly different approaches and some of these have been the subject of recent review and reform. For example, a notice of proposed changes to the U.S. "Common Rule" for human subjects research contains provisions that would require informed consent for use of human biospecimens, including even secondary use of non-identified material, although this could be a "broad consent" to future unspecified uses by means of an approved form. They would also require enhanced privacy and security protections for collection, storage and use of biospecimens.

This paper examines the position in international and national ethics policies and regulations regarding when ethics committee approval is required for secondary research use of human biological material and what consent by the original donor is required for such use. This review highlights differences that may raise concerns when stem cell lines or other biological materials are shared across borders. It also critically assesses the ability of various approaches to ensure appropriate respect for the key ethical conditions while avoiding unreasonable and unnecessary impediments to research. This assessment focuses specifically on the implications of current and proposed approaches for stem cell banks, which, like other repositories of human biological material, play important roles in ensuring protection and facilitating valuable research.

83

"SAME DAY DELIVERY"—AN OPTIMIZED TRANSPORT CHAIN FOR CELLULAR PRODUCTS

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The recent success of cellular therapy and in particular of adoptive T cell immunotherapy raised a growing interest in the field. Thus far, pilot small scale clinical trials were carried out mainly by academic investors who have usually installed their manufacturing units in close proximity to the investigating clinical site. This close neighborhood avoids the need for a sophisticated transport chain and minimizes logistic efforts. However, with the gradual development of cellular therapies to phase II and even phase III trials, multiple centers become involved across country boundaries. Furthermore, a paradigm shift occurs from small academic GMP facilities towards privately owned centralized manufacturing sites. Taken together, in later-stage clinical trials exchange of material and drug products between more and more individual players has to be assured over long distances. Thus, an often neglected, but highly important aspect of initiating a clinical trial involving distant study centers and manufacturing sites is the organization, administration and execution of the logistic chain from the place, where the starting material is collected to the manufacturing site and further on to the clinical site where patients in need await the investigational drug. Our company has gained much experience in this field over the past decade by administrating, organizing and executing stem cell donations all over the world. Stem cell donation requires an exactly on time manufactured and delivered cellular product for a patient, who is already pre-conditioned to receiving the stem cell graft. Any mistake in the logistic supply chain of the stem cell graft could put patients live at risk. Having this in mind, we developed elaborated transport capacities focused and specialize for cellular products. The logistic chain includes medical trained, multiple language speaking hand-picked couriers, state of the art transport boxes for cell products at 4°c or cryopreserved, continuous temperature logger and an online tracking system for our customers. The logistic part is supported by an administrative backbone including a 24/7/365 emergency service, experts in regulatory affairs and continuous in-house quality management. Having these capacities in place, we managed to build up a "same day delivery" strategy between many locations world-wide and are ready to serve any request for cell product transports.

84

REGULATORY PERSONNEL EDUCATION AND CURRICULUM GOALS AND OBJECTIVES

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Purpose: Regulatory personnel are in a particularly tough position with regards to cellular therapy. There are two aspects, laboratory and clinical, each with regulations and guidances and their specific focus. Educational parameters are not defined in an formal manner. Development of the goals and objectives of the curriculum is essential to success.
Methods: Goals and Objectives were created as per a method described in "Curriculum Development for Medical Education" edited by Kern, DE; Thomas, PA; Hughes, MT. (2011-01-13). Johns Hopkins University Press. Broad educational goals and specific measurable objectives were compiled, written and reviewed by Quality Management Staff and the former Regulatory Manager, who are and were responsible for compliance. Using the method described, objectives were created that detail the following: 1.Who 2.Will do 3.How much/how well 4.Of what 5.By when. After review, the objectives were organized in a timeline for current and future employees.
Results: The following are examples of the objectives identified:

Potential Learner objectives, defined as *knowledge*, were identified. For example, "By the end of the educational session, the regulatory specialist will be able to list the relevant regulations and guidances that describe compliance methods and apply the systems to the cellular therapy lab."

Potential Process Objectives, defined as *participation*, were identified. For example "The regulatory specialist will participate, after verification of regulation knowledge, in a mock inspection of a cellular therapy procedure." and "The regulatory specialists will participate, after training and observation of FDA communication, (either onsite or telephonic) the proper interaction and support expected by FDA staff."

Potential Outcome Objectives were identified. For example, "After the probation period is complete, the regulatory specialist will be trained to write a response report based on a mock FDA observation report."

Conclusion: Goals and Objectives were identified in a range of topics, including Regulations and Guidances, interaction with the FDA, Management, and Cellular Product Processing.
Discussion: The list of objectives will be used to guide development of educational modules. Defined goals and objectives will allow the Regulatory Specialists to have structured training and provide a base level of knowledge and comptency.

85

CORRELATION OF STEM CELL CONTROL FROM COMMERCIAL PRODUCTION AND SELF-MADE (NON-COMMERCIAL) CONTROL FROM UCB IN FLOWCYTOMETRY

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The amount of CD34+ cells is important to predict the quality of stem cell and safety engraftment for transplantation. Flow cytometry enumeration of CD34+ are widely used to detect the number of CD34+ in blood. The CD34+ control were needed as quality control of CD34+ enumeration. However in Indonesia, the established control seems hard to delivered. As alternative we used self-made (non-commercial) control in our laboratory from Umbillical Cord Blood (UCB) that had been plasma reduced and aliquoted in 100 tubes.This study is used to compared the stability of self-made control CD34+ with stem cell CD34+ whole blood process control (BD Stem Control) from Becton Dickson Biosciences.

UCB was taken from a single subject that delivered via C-Section into a single blood bag containing anti-coagulant Citrate Phospate Dextrose Adenine-1 (CPDA-1). Total nuclear cells were isolated from UCB by adding Tetraspan containing hydroxil ethyl-starch (HES)-6%. After the erythrocytes were sedimented, the plasma were removed to plasma bag and buffy coat was removed

to storage bag. Cryoprotectant dimethylsulfoxide (DMSO) was added with 1:5 ratio. Sample were aliquoted into 100 cryovials with 200 µL sample in each vials. Cell surface protein of CD34+ marker was evaluated using flow cytometry technique using BD FACS Canto II. BD Stem Cell Enumeration Kit was used as a single platform assay for accurate, reproducible, and rapid enumeration of CD34+. BD Stem Control was used as comparison for quality control from manufacture. BD Stem Control (low and high) were run 18 times for 10 days. For self-made control CD34+, 22 aliquoted cryovials were run for 22 days.

The detection of CD34+ Enumeration using Cell Control CD34+ Whole Blood Process Controlshowed that the mean value for low dan high CD34+ Control (cell/µL)are 13.18 SD 1.51 (CV = 11.47%) and 32.53 SD 3.30 (CV = 11.47). The meanof CD34+ (cell/µL) from self-made (non-commercial) control is 70.19 SD17.15 with CV = 24.95%. Correlation test shows that correlation coefficient (r) is 0.952. There was close correlation between control manufacture and self-made (non-commercial) control.

Key Words: Correlation, Stemcell Control, Commercial Product, Self-made (Non-commercial) control, Flowcytometry.

86

STANDARDIZED TERMINOLOGY FOR CELLULAR THERAPY, REGENERATED TISSUES, AND SOURCE ORGANS

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Aims: The International Cellular Therapy Coding and Labeling Advisory Group (CTCLAG) was formed by ICCBBA with support of professional organizations including ISCT. In 2007, the output of this group, standardized cellular therapy terminology, was published and thereafter AABB, FACT, JACIE, and NMDP required use of this terminology. Cellular therapy terminology has since been updated and new terminology has been developed for regenerated products and organs used as a source of cells for regenerated products.

Methods: CTCLAG and expert advisory groups for tissues and tissue engineered products work through a consensus process to develop additional terminology. Drafts of terminology are distributed to relevant professional societies for their comments and published on the ICCBBA website for public comment.

Results: Three sets of terminology were addressed:

- CT terminology was updated in 2013 to follow a standard format for class name: Cell Type, Source (e.g., MNC, APHERESIS).
- The proposed class name of regenerated products is in the format "REGENERATED" followed by the tissue type (e.g., REGENERATED EPIDERMIS). Additional details such as cell type, delivery mechanism, ancillary substances, excipients, and storage temperature, are added as attributes (e.g., REGENERATED EPIDERMIS, from keratinocytes, in the form of a sheet, with ancillary substances present).
- The proposed class name of organs used as a cell source for production of cell and tissue products is in the format of organ name followed by the word "Tissue" in parentheses [e.g., HEART (Tissue)]. "(Tissue)" was added to distinguish organs intended for transplant from those intended for further processing. Organs for transplant have only the organ name (e.g., HEART).

Conclusion: Through the efforts of advisory groups comprising experts in the fields of cellular therapy, tissues, and regenerated products, terminology has been developed for CT, tissue, and regenerated products. This terminology is made publicly available through the ICCBBA website (www.iccbba.org) and its use for communication and labeling is encouraged.

87

THE EFFECT OF STORAGE TEMPERATURE AND REPETITIVE TEMPERATURE CYCLING ON THE POST THAW FUNCTIONALITY OF HUMAN MESENCHYMAL STEM CELLS

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Stem cells are normally transported and stored at either –80°C or below –150°C in LN2 vapor. Best practices typically recommend storing below the glass transition (Tg) f water, approx –135°C. In industry however, there is discussion about, but limited experimental research surrounding duration of storage at –80°C and its effects on cell viability. Additionally, at either storage temperature samples are repeatedly exposed to the ambient environment when adjacent samples are accessed. This temperature cycling is believed to decrease cell viability as it induces thermal cycling stresses on the cells. Due to many variables affecting post thaw functionality, standardization should be used where possible, such as cells should be processed and stored in a closed system and have their temperature, transient exposures and access controlled and monitored.

This paper's objective is to demonstrate the impact of both storage temperature and thermal cycling on the post thaw viability and functionality of human mesenchymal stem cells (hMSCs). It will also demonstrate best practices for consumables and cold chain management.

In order to carry out these experiments, a system was evaluated utilizing a closed-system cryogenic vial (CellSeal), –190°C cryogenic automated storage (BioStore III Cryo) and –80°C ULT freezer.

In this ongoing study, hMSCs from Cook Regentec (Bloomington, IN) are tested for viability via dye exclusion, phenotypic assessment and functional growth characteristics for a base line. They then are cryopreserved with 10% DMSO and –1°C/min cooling to –80°C prior to storage in vapor LN2. The hMSC are then shipped to Brooks Life Science Systems (Chelmsford, MA) and stored at both –80°C and –190°C. Once in storage, a portion of these samples are exposed (but not touched) weekly to the ambient environment for 90 seconds (cycled) whereas the other half of the samples are held at constant temperature (control). After four months of storage the samples are packed and shipped back at their respective temperatures to Cook Regentec. There they are thawed and subjected to the same tests as prior to freezing.

The viability and functionality of the baseline vs. control vs. cycled and –80°C vs. –190°C hMSCs are analyzed and compared. The results of all five sets of samples are discussed and best practices for storage and handling of hMSC to maximize post-thaw viability and functionality is recommended.

88

NEXT GENERATION TECHNOLOGY PROCEDURES AND PRODUCTS FACILITATE BIOPRESERVATION BEST PRACTICES AND INCREASED VIABILITY FOR CELLULAR THERAPY

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The quality of procedures and products used for preparing, transporting and storage of cells at cryogenic temperatures have a direct impact on the post-thaw viability and functionality of the cells. Sub-standard preparation, handling, storage, and products may subject cells to improper cryoprotectant exposure, poorly controlled shipping conditions, variable storage temperatures and unknown transient warming events.

The objective of this study is to compare two methods of preparing, transporting and storing living cells to achieve the highest post-thaw viability. The outcome of this study recommends best practices for procedures and products to ensure consistency and control of the cold chain.

Jurkat cells, a human T-cell line from ATCC (Manassas, VA), were cultured, analyzed for viability (membrane dye exclusion) and functionality (alamarBlue metabolic indicator) and prepared for cryopreservation via identical protocols.

One group was prepared with CryoStor CS5® (BioLife Solutions, Bothell, WA) containing 5% w/v dimethyl sulfoxide (DMSO) and was frozen to –80°C using an isopropyl alcohol freezing device. The frozen cells were shipped using an evo® –80°C Smart Shipper which includes embedded monitoring, GPS and cellular communication to Brooks Life Science Systems (Chelmsford, MA). Upon arrival, the cryovials containing Jurkat cells were stored at –190°C in the BioStore III Cryo automated LN2 vapor storage system.

A second group of Jurkat cells were prepared with a traditional home-brew cryoprotective media consisting of 95% fetal bovine serum and 5% w/v DMSO and was frozen to –80°C using an isopropyl alcohol freezing device and shipped, unmononitored, using a conventional Expanded Polystyrene dry ice shipping container to Brooks. Upon arrival, the cryovials containing Jurkat cells were stored in a –80°C ULT freezer.

After frozen storage, the cryovials were packed and shipped back to BioLife in the same containers and using the same methods as used previously. Both groups of cells were then thawed and analyzed for viability and functionality immediately and after one day using the identical pre-freeze assays. The thawed cell's results were compared to each other and to the pre-freeze baseline. The procedures and products used for preparing, transporting and shipping were also compared. Best practices were recommended for preservation, control, moni-