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ISCT Committee Paper

An International Society for Cell and Gene Therapy Mesenchymal Stromal Cells (MSC) Committee perspectives on International Standards Organization/Technical Committee 276 Biobanking Standards for bone marrow-MSCs and umbilical cord tissue–derived MSCs for research purposes

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ABSTRACT

The rapidly growing field of mesenchymal stromal cell (MSC) basic and translational research requires standardization of terminology and functional characterization. The International Standards Organization's (ISO) Technical Committee (TC) on Biotechnology, working with extensive input from the International Society for Cells and Gene Therapy (ISCT), has recently published ISO standardization documents that are focused on biobanking of MSCs from two tissue sources, Wharton's Jelly, MSC(WJ) and Bone Marrow, MSC(M)), for research and development purposes and development. This manuscript explains the path towards the consensus on the following two documents: the Technical Standard ISO/TS 22859 for MSC(WJ) and the full ISO Standard 24651 for MSC(M) biobanking. The ISO standardization documents are aligned with ISCT's MSC committee position and recommendations on nomenclature because there was active input and incorporation of ISCT MSC committee recommendations in the development of these standards. The ISO

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Wharton's Jelly

standardization documents contain both requirements and recommendations for functional characterization of MSC(WJ) and MSC(M) using a matrix of assays. Importantly, the ISO standardization documents have a carefully defined scope and are meant for research use of culture expanded MSC(WJ) and MSC(M). The ISO standardization documents can be updated in a revision process and will be systematically reviewed after 3–5 years as scientific insights grow. They represent international consensus on MSC identity, definition, and characterization; are rigorous in detailing multivariate characterization of MSCs and represent an evolving-but-important first step in standardization of MSC biobanking and characterization for research use and development.

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Introduction

The International Society for Cell and Gene Therapy (ISCT)'s Mesenchymal Stromal Cell (MSC) Committee has been working closely with the International Standards Organization's Technical Committee (ISO/TC) 276 on Biotechnology for the past few years to help develop and refine ISO standardization documents for biobanking and research and development of umbilical cord tissue mesenchymal stromal cells, abbreviated as MSC(WJ), or mesenchymal stromal cells (Wharton's Jelly), and bone marrow–derived mesenchymal stromal cells, abbreviated as MSC(M). These international-consensus ISO standardization documents have recently been published (https://www.iso.org/standard/74052.html; https://www.iso.org/standard/79141.html). The following details the development of these standards.

Historical Overview of Standards Development at ISO

ISO is an international standard developing organization that meets all the criteria for developing international consensus standards as outlined in Annex 4 of the World Trade Organization's Technical Barriers to Trade Agreement. ISO has several technical committees with voluntary international experts from representative national standards organization bodies who work through a standardized process to develop consensus standards. The ISO/TC 276 was created in 2013, has voting experts from 31 participating countries and non-voting experts from 19 observing countries and has published 27 ISO standardization documents to date. Standards are copyrighted and need to be purchased through the ISO website; this has been the ISO model for developing and implementing standards in all technical committees. The ISO experts are either members of national standards organization or liaison organizations/committees and possess a broad range of expertise, including biobanking, expertise in cell and gene therapy manufacturing, as well as developing quantitative analytical measurement tools for nucleic acids, proteins, metabolites, infection contaminants and cell systems (within the biotechnology technical committee) that provide measurement assurance for the biotechnology industry.

Typically, a proposal for an ISO standard can be put forth by any member country or liaison representative. This *New Work Item Proposal* must include detailed justification for the need for such a standard. If the rationale and scope of the standard are sufficiently strong, it will be voted on for approval to be listed in the ISO technical committee's work program. If approved, the standardization project is listed as an *Approved Work Item* (AWI). After the completion of the first full text draft of the standardization project within the relevant ISO Working Group (WG), it can be commented on by the members of the WG during a W*orking Draft* (WD) consultation. All comments are handled in a consensus driven process within the respective WG and the WD is updated accordingly. The next optional step is the circulation of a *Committee Draft* (CD) to the members of the ISO technical committee for commenting to receive their input. The received comments are again handled in a consensus-driven process within the respective WG and the CD is updated accordingly to move further to the inquiry stage where the *Draft International Standard* (DIS) is circulated to the ISO technical committee members for approval and to gather additional comments and input. At this stage, the public can also comment on the DIS via the relevant national standardization organizations that are the representing members in ISO.

If there are significant technical comments or concerns that result in a technical revision of the DIS by the WG, a *Final DIS* will be circulated to the ISO technical committee members for an approval voting and editorial commenting. Once the final vote is in, and the standard is approved, it is editorially formatted by ISO editors and published.

For the development of an ISO Technical Specification (ISO/TS), standardization projects are only circulated for WD and mandatory CD commenting. If the CD receives significant technical comments or concerns that result in a technical revision of the CD, a second CD ballot or an additional approval ballot is performed within the ISO technical committee. The ISO standard development process (see Figure 1A) is robust and stringent to ensure that high-quality consensus ISO standards are developed.

Specific Process for Development of the MSC(M) and MSC(WJ) Biobanking Standards

During the WD, CD drafts and DIS and *Final DIS* stages, the drafts are often shared with third parties such as ISCT through an official, elected liaison, as was the case with the MSC(WJ) and MSC(M) ISO standardization documents. Notably the ISO TC committee has an ISCT MSC committee member serving in this liaison role. ISO TC committees often have such liaisons with research societies and other expert groups as a conduit to solicit and vet important information that ends up in the consensus standards. Importantly, the WD, CD and DIS documents each went through multiple rounds of iteration and revisions, with extensive written input from ISCT's MSC and Executive Management Committee (Figure 1A). The drafts were reviewed between December 2017 and January 2022 for ISO/TS 22859 and between July 2019 and January 2022 for ISO 24651; they were led by project leads representing the Standardization Administration of China for ISO/TS 22859 and the Colombian Institute of Technical Standards and Certification for ISO 24651. Other experts in the ISO/TC 276/WG 2 "Biobanking and bioresources" who represented various national standards organizations include, for example, the US Food and Drug Administration (FDA), various academic institutes (University Health Network, Canada; Crick, United Kingdom; INSERM, France; Instituto Superiore di Sanità, Italy) and industry representatives.

Why Was This Standard Developed?

Typically, a standard is developed when the field has matured enough for there to be consensus for standards. An example of this is the widely used ISO standard to qualify and standardize manufacturing processes, ISO 9001; this qualification process is used by many manufacturers including medical device manufacturers across the world to show compliance of their process, which in turn leads to an assurance of good-quality products for regulatory compliance. In the MSC field, different approaches and non-standardized practices abound in isolating, manufacturing and characterizing MSCs, and

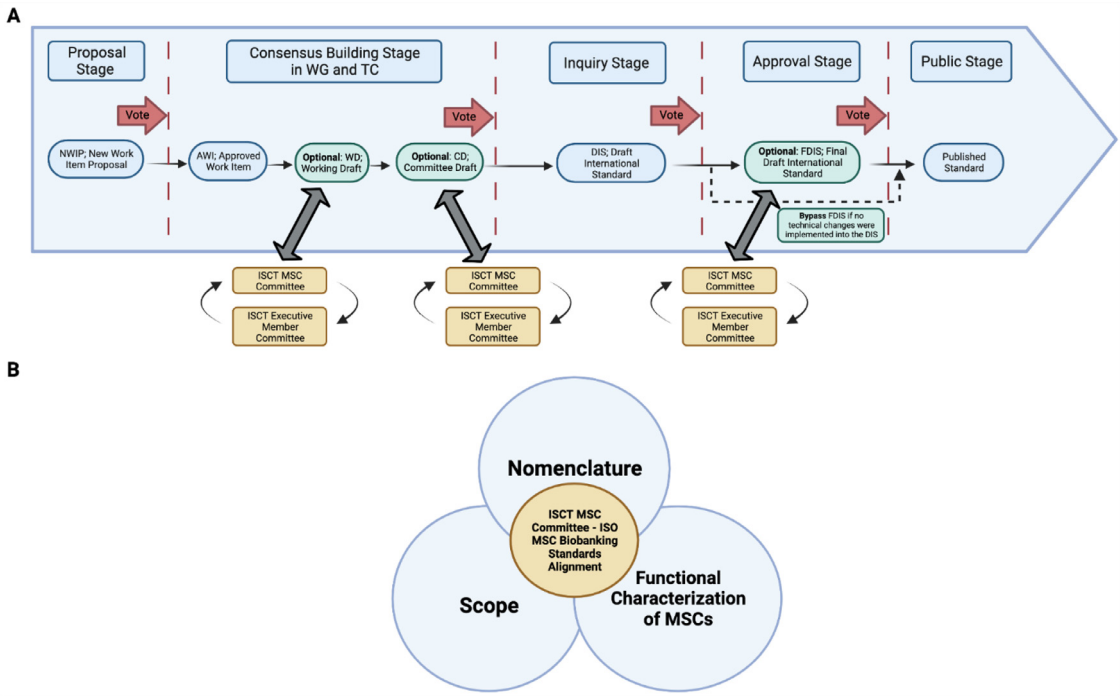

Figure 1. Historical ISO standard development process. (A) Interaction with ISCT's MSC and Executive Management Committees. (B) Alignment between ISCT and ISO Biobanking Documentary Standards.

there is little-to-no consensus on any of these aspects, including nomenclature [1,2]. However, the field is rapidly moving, with approximately 1616 clinical trials listed under the search string "mesenchymal stem cells OR mesenchymal stromal cells" on clinicaltrials.gov in 2023. To provide additional context for the maturity of the MSC research and development field, we are citing some examples of a handful of approved MSC products globally. These include darvadstrocel as the first allogeneic adipose tissue-derived MSC therapy approved in the European Union, Israel and Switzerland for the treatment of complex perianal fistulas in non-active/mildly active luminal Crohn's disease [3,4]; Stempeutics has an approved MSC product for critical limb ischemic in India [5], and Mesoblast has an approved MSC product for steroid-refractory adult and pediatric graft-versus-host disease in Japan [6]. There are no approved MSC products in the United States [7], and recent trials using MSCs in coronavirus disease 2019 acute respiratory distress syndrome failed to meet their primary endpoint [8]. Thus, although the field is mature with advanced clinical trials and emerging authorized MSC products, it is also plagued by absence of significant commercial success or by consistent demonstration of clinical utility in any disease indication. Lack of consensus on nomenclature and functional characterization of MSCs in the research and development stages has likely contributed to these issues. A standard that provides consensus-based recommendations for nomenclature and functional characterization of MSCs in the research and development stage can thus contribute to harmonization of research findings and will set the stage for future commercial and clinical success.

The minimal criteria to define MSCs were developed by the ISCT MSC committee in 2006 [9] and continue to serve as a de facto standard for the research and development field [10], although they were never intended as a standard. However, the ISCT recognizes that these criteria are inadequate for functionally defining MSCs [1,2]. Thus, there is an overwhelming need for consensus-based, broad and evolving standards that provide guidance on terminology, identity and functional definitions of MSCs which included functional characterization of their properties.

Such a gap is filled by the release of these two ISO standardization documents. Importantly, ISO/TS 22859 for MSC (WJ) is a Technical Standard (TS) whereas ISO 24651 for MSC(M) is a full ISO standard. Systematic reviews within the related ISO technical committee to check the content of an ISO standardization document against the state of the art and science will be automatically initiated by ISO. The systematic review will take place 3 years after publication for ISO/TS documents and 5 years after publication for ISO Standards. ISO/TS documents need to be revised, withdrawn or taken over as an ISO standard project after latest 6 years after their publication. Aside from that, a revision can be triggered at any time, if there is the justified need to change technical content according to the state of the art and science.

ISCT's MSC committee would like to draw attention to three main aspects of the ISO standards (Figure 1B):

- Use of MSC terminology and accompanying definitions, specifications of tissue of origin and delineation between functional definitions for stem cells and stromal cells as per the ISCT MSC position papers [1,2].
- Carefully defined scope of both ISO standardization documents to apply to MSC(WJ) or MSC(M) that are culture-expanded and used only for research and development purposes.
- Recommendations to use a suite of *in vitro* characterization assays of MSCs including a matrix of functional assays under both licensed (stimulated with pro-inflammatory cytokines) and unlicensed conditions.
- *MSC Terminology* – There have been many years of heated debate around MSC terminology, as recently outlined in the MSC committee papers [1,2] and other community-based efforts to achieve consensus on reporting guidelines [11]. ISO/TS 22859 for MSC (WJ) and ISO 24651 for MSC(M) consistently define and abbreviate MSC as per ISCT committee position papers. Specifically, both the ISO/TS and ISO standard note that "mesenchymal stromal cells and mesenchymal stem cells are both abbreviated as "MSCs" ... (but) for the purpose of this document (i.e., the standards), the abbreviated term "MSCs" refers to mesenchymal stromal cells. "

ISO/TS 22859 and ISO 24651 further acknowledge that MSCs should be denoted by tissue of origin and the recommended suffix abbreviation as put forth by the ISCT MSC committee as MSC(WJ) for MSCs from Wharton Jelly and MSC(M) for MSCs from bone marrow [2]. These abbreviations are aligned with recommendations from International Society of Blood Transfusion 128 [12], which are global standards for identification and labeling of human medical products including blood, cells, tissues and organ products. However, both ISO/TS 22859 and ISO 24651 continue to use the abbreviation more commonly used in basic research, denoting them as (hUC-MSCS) and (hBM-MSCS) respectively. Uptake of standardized abbreviation in basic research will take some time, as we previously outlined in the ISCT position paper [2], but this acknowledgement is an important step in the right direction.

In addition, both ISO/TS 22859 and ISO 24651 delineate functional definitions of mesenchymal stromal cells versus mesenchymal stem cells, requiring a robust matrix of *in vitro* assays for the former, and evidence of self-renewal and differentiation *in vivo* and *in vitro* for the latter. This is again consistent with the ISCT MSC committee position paper [1].

- *Scope* – Both the ISO/TS 22859 and ISO 24651 focus only on culture-expanded mesenchymal stromal cells. The definition clarifies that these are often referred to as “culture-adapted MSCs” to denote cells that are different from those are found *in vivo*, in terms of gene expression, functionality and phenotype.

Importantly, ISO/TS 22859 and ISO 24651 are *biobanking* standards intended to provide guidance and minimum requirements for the isolation of MSCs from their respective tissues of origin, expansion, characterization and biobanking for research and development purposes. The scope is intentionally narrowly defined after careful deliberation and is aimed at target audiences in academic centers, public and private institutions using MSC(WJ) or MSC(M) for research and development pre-clinical studies. These ISO standardization documents are not intended to standardize MSCs for investigational clinical use as different commercial entities and national regulatory bodies may have differing goals and requirements.

- *Detailed characterization* - Importantly, although the standards are biobanking standards, they have included detailed sections with requirements and recommendations on multivariate characterization of MSCs including morphology; assessment of cell viability; measurements of proliferation and population doubling times; *in vitro* surrogate assessments of self-renewal and differentiation; immunophenotyping with specifications for threshold levels of cell surface antigens and recommendations for multiple antibody clones; assessment of multiple expressed/secreted factors by quantitative methods both at the gene and protein level under conditions of pro-inflammatory cytokine stimulation (licensing) and unlicensed (control) conditions and functional evaluation of immunoregulation by co-culture with peripheral blood mononuclear cells, T cells, monocytes/macrophages or other immune cell subsets. In addition, the biobanking ISO standardization documents include requirements and recommendations on the isolation of MSCs from the tissue of origin, cell expansion and subculturing; cryopreservation, storage, thawing and distribution of MSCs. The biobanking ISO standardization documents also include quality requirements and recommendations, microbial testing requirements and recommendations as well as requirements and recommendations on personnel training, reagents and consumables. The detailed characterization section is included with extensive input from the ISCT MSC committee and reflects the ISCT MSC committee’s previous position papers on multimodal matrix-based MSC characterization [13,14].

Implementation of ISO Biobanking Standards From an ISCT Perspective

The dissemination of the ISO standards follows the ISO business model of providing standards that are copyrighted by ISO and available for purchase; requests for permission for use can also be directed to the ISO Central Secretariart or to specific ISO members in any given country (for example, Standards Coordination Council in Canada or American National Standards Institute in the United States). The copyright and purchasing of standards have not previously posed an undue burden on the adoption of these standards. For instance, the ISO 9000 standards are arguably the most influential management standard provides guidance [15] on management systems and processes that are used to produce various products and services. These voluntary consensus standards have been adopted by industry, and institutions including European Commission [16], several US government agencies [17] and indeed, promulgated as a global standard to such an extent that they have transformed to de facto obligations for conducting international trade and business [18]. Conformance with these standards is certified by third-party organizations, accredited for this purpose [18].

ISO/TS 22859 and ISO 24651 biobanking standards are similar voluntary standards, and the ISCT MSC committee envisions a roadmap for their adoption, similar to the organic uptake of a previous ISCT MSC committee position paper that was published in 2006 and spelled out minimal criteria to define MSCs [9]. This paper has more than 11 000 citations and is used not just in research and development but also during clinical MSC investigational product development [19,20]. ISCT does not envision that compliance with these ISO biobanking standards will be regulated or enforced by any single organization, at least not initially. However, significant uptake could lend de facto status to these ISO biobanking standards, as a requirement for example, by scientific journals for consideration of manuscripts describing MSC research or by granting agencies funding basic or translational research involving MSCs.

Since there are no formal requirements that are levied by journals or funding agencies to follow ISO biobanking standards or any standards for MSC research and development, instruments to measure their uptake do not exist. However, the ISCT’s MSC committee is involved directly [21] or indirectly [22] in conducting several surveys and can periodically assess uptake of these voluntary ISO biobanking standards using these survey instruments. These surveys could provide assessments of the impact of these ISO biobanking standards and the extent to which they have or have not been adopted by global MSC researchers.

Importantly, although these ISO biobanking standards are intended for use by researchers during the research and development stage, the use of a matrix of MSC characterization assays is well-aligned with FDA recommendations for multivariate readouts describing investigational products, [23] and could pave the way for potency assays that are acceptable to the FDA and/or other regulators. Indeed, FDA are expert members sat on this ISO TC 276 working group and contributed to the development of these ISO biobanking standards. FDA has expressed interest in standards development in the cell and gene therapy field and has awarded funding to the Standards Coordinating Body and Nexight Group to engage with experts to accelerate standards development in regenerative medicine and advances therapies [24]. The development of standards is aligned with the mandate of the 21st Century Cures Act of 2016.

Limitations of the ISO Biobanking Standards

As with all voluntary standards, the ISO Biobanking Standards come with their own set of restrictions, including the requirement to purchase these copyrighted standards. However, as noted previously, this is how all ISO standards are disseminated, which has not posed a

significant barrier in adoption of previous ISO standards. In addition, the standards are carefully limited in scope to research and development use. This was done after several rounds of debate and discussion as well as considerable deliberation. It was strongly argued that the imposition of prescriptive standards of MSC characterization for investigational clinical product development falls in the purview of regulators and the sponsors, varies from jurisdiction to jurisdiction and may have proprietary elements. Thus, it was argued the scope of the ISO MSC standards should not be extended to include MSC products at the investigational or commercial stages. Although this might arguably limit impact of the current standards, as we have outlined, there is a potential roadmap for adoption by researchers, industry, sponsors, regulators, journal editors, granting agencies and the like that could eventually broaden the impact of the ISO/TS 22859 and ISO 24651 standards.

Summary

ISO/TS 22859 and ISO 24651 are international consensus standardization documents, developed with iterative, rigorous input from international experts and the ISCT MSC and Executive Management Committee committees. As an ISO technical specification or an ISO standard, they should be treated as evolving documents with iterations to amend various sections during revisions as the science progresses and there is deeper understanding of MSC biology and functionality. As a first step in developing such progressive ISO standardization documents, it represents a significant consensus position. By including standardized terminology, carefully defined scopes, as well as requirements and recommendations for multivariate functional characterization, it represents rigorous standards. The ISCT MSC committee urges researchers to avail themselves of these standards in their research and development activities.

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

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Author Contributions

Conception and design of the study: SV. Acquisition of data: SV, GD, LK, VRP. Analysis and interpretation of data: SV, JG, IM. Drafting or revising the manuscript: SV, KLB, RC, GD, AJF, JG, MK, LK, MML, JN, VMRP, YS, KT, DJW, IM. All authors have approved the final article.

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