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Short Report

Consensus International Council for Commonality in Blood Banking Automation–International Society for Cell & Gene Therapy statement on standard nomenclature abbreviations for the tissue of origin of mesenchymal stromal cells

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ABSTRACT

The Cellular Therapy Coding and Labeling Advisory Group of the International Council for Commonality in Blood Banking Automation and the International Society for Cell & Gene Therapy mesenchymal stromal cell (MSC) committee are providing specific recommendations on abbreviating tissue sources of culture-adapted MSCs. These recommendations include using abbreviations based on the ISBT 128 terminology model that specifies standard class names to distinguish cell types and tissue sources for culture-adapted MSCs. Thus, MSCs from bone marrow are MSC(M), MSCs from cord blood are MSC(CB), MSCs from adipose tissue are MSC(AT) and MSCs from Wharton's jelly are MSC(WJ). Additional recommendations include using these abbreviations through the full spectrum of pre-clinical, translational and clinical research for the development of culture-adapted MSC products. This does not apply to basic research focused on investigating the developmental origins, identity or functionalities of endogenous progenitor cells in different tissues. These recommendations will serve to harmonize nomenclature in describing research and development surrounding culture-adapted MSCs, many of which are destined for clinical and/or commercial translation. These recommendations will also serve to align research and development efforts on culture-adapted MSCs with other cell therapy products.

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Introduction

The need for standardization of terminology, coding and labeling for cellular therapy products was recognized early in the millennium, and a broad consensus has led to the international adoption of the ISBT 128 Standard. ISBT 128 terminology in particular is recognized beyond product labeling and has become the accepted standard for describing cell therapy (CT) products in documentation and publications. The mesenchymal stromal cell (MSC) committee at the International Society for Cell & Gene Therapy (ISCT) has issued several position papers [1–4] describing minimal criteria to define MSCs, the use of matrix assays to functionally characterize MSCs and the use of the abbreviation "MSC" to denote culture-adapted MSCs in conjunction with an array of functional characterization readouts. Recognizing the importance of identifying the tissue source of MSCs and the need for a standardized approach to conveying this information, the ISCT MSC committee and the Cellular Therapy Coding and Labeling Advisory Group (CTCLAG) of the International Council for Commonality in Blood Banking Automation (ICCBBA) have collaborated to develop this recommendation.

Background to ISBT 128 Terminology

In 2005, the Foundation for the Accreditation of Cellular Therapy (FACT), the Joint Accreditation Committee of the ISCT and European Society for Blood and Marrow Transplantation (JACIE) and ICCBBA met to discuss how to achieve standardized terminology, coding and labeling of CT products. The organizations recognized the benefit of using ISBT 128 and proposed its adoption as the global standard for the labeling of CT products during the ISCT meeting (Vancouver, 2005). This proposal received strong support from meeting participants, and a decision was made to form an international steering committee with representation from major scientific and professional societies in the field of CT. ICCBBA established the CTCLAG with representation from AABB, the American Society for Transplantation and Cellular Therapy (formerly American Society for Blood and Marrow Transplantation), European Society for Blood and Marrow Transplantation, FACT, International Society of Blood Transfusion (ISBT), ISCT, JACIE, National Marrow Donor Program/Be the Match and World Marrow Donor Association.

The boards of all the participating organizations issued a joint statement, confirming support for the international use of ISBT 128 and tasking CTCLAG to (i) review existing regulation regarding labeling, (ii) design product label templates that satisfy regulatory requirements, (iii) provide a focus for the standardization of terminology and product naming, (iv) promote the adoption of the ISBT 128 standard in CT facilities around the world, (v) provide advice and support to facilities introducing the standard and (vi) advise on the ongoing development of the ISBT 128 standard to support new developments in CT.

CTCLAG developed standard terminology for CT products based on the ISBT 128 terminology model using classes and attributes. Class names were structured to identify the type of cell and the source; for example, hematopoietic progenitor cells, apheresis, or hematopoietic progenitor cells, cord blood. This terminology was published in 2007 concurrently in *Bone Marrow Transplantation, Journal of Clinical Apheresis* and *Transfusion* [5] and was subsequently incorporated into the ISBT 128 Standard Terminology. Since that time, CTCLAG has managed and updated the terminology to reflect changes in CT practice, and the most current version is maintained in the ISBT 128 Standard Terminology document, which is publicly available on the ICCBBA website (www.iccbba.org) [6].

It was noted that class names could be long and that there would be a need to abbreviate these in publications and procedures. The benefit of encouraging the use of a standard set of abbreviations was recognized, and in 2008 CTCLAG introduced a table of standard abbreviations into the terminology to identify the cell type and source. These abbreviations have been widely adopted and are recognized by AABB and FACT/JACIE. As the range of CT products has increased, the table of abbreviations has been expanded to accommodate new entries in a consistent manner.

The use of ISBT 128 for the coding and labeling of CT products is both widespread and growing. At the time of writing, there are 945 CT facilities in 65 countries registered to use ISBT 128.

ISBT 128 terminology is designed to provide generic product descriptions that can be used by different CT facilities to describe their products. Such generalization is widely used in the medical products of human origin field and facilitates effectiveness and biovigilance activities.

A distinct naming system is operated by the World Health Organization (International Nonproprietary Names [INN]) [7] and the American Pharmacists Association (United States Adopted Names [USAN]). INN and USAN are aligned and provide a non-proprietary name for a specific product manufactured by one manufacturer. The INN/USAN is a structured name designed to facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. The ISBT 128 labeling system is able to accommodate INN/USAN names, and manufacturers can request an ISBT 128 Product Description Code specific to their INN/USAN.

The Development of Standard Terminology for MSCs

The growing adoption of ISBT 128 coding and labeling practices mirrors the growing number of CT products that are approved in various jurisdictions [8], and this includes culture-adapted MSCs [9]. Culture-adapted MSCs from multiple tissue sources have received market authorization in different jurisdictions worldwide. For example, culture-adapted MSCs from adipose tissue have been approved for treatment of complex perianal fistulas in Crohn disease in Europe [10], culture-adapted MSCs from bone marrow have been approved for treatment of critical limb ischemia in Malaysia and India [11,12], culture-adapted MSCs from bone marrow have been approved for treatment of steroid-refractory acute graft-versus-host disease in pediatric patients in Canada and New Zealand [13,14] and in adult and pediatric patients in Japan [15], culture-adapted MSCs from bone marrow have been approved for treatment of spinal cord injury as part of a controversial conditional approval [16] and culture-adapted MSCs from umbilical cord blood have been approved for treatment of degenerative arthritis in South Korea [17].

The growing number of culture-adapted MSC products from various tissue sources underscores advances in basic science, an increasing understanding of MSC mechanisms of action and a mounting track record of clinical safety. However, the development of MSC products has also seen numerous setbacks as a field, including the recent Food and Drug Administration decision requiring additional clinical studies and functional characterization to approve Remestemcel-L (bone marrow-derived MSCs) for treatment of pediatric acute steroid-refractory graft-versus-host disease [18]. This decision highlights challenges in mechanistically understanding heterogeneity in MSC clinical responses compounded by differences in tissues of origin, donor heterogeneity and heterogeneity in host immune responses against a backdrop of complex pathologies. Heterogeneity in defining and functionally characterizing MSCs further confounds rigorous scientific efforts, as we lack even a basic consensus on common parlance and nomenclature terminology.

The position papers published by the ISCT MSC committee speak specifically to heterogeneous populations of culture-adapted MSCs, which are distinct transcriptomically and functionally [19] from purported *in vivo* counterparts. Culture-adapted MSCs are widely recognized for their potent immunomodulatory properties and the ability to stimulate repair of diseased or damaged tissues. Importantly, the tissue source of MSCs has repeatedly been shown to influence the

functionality of MSCs [20–22], emphasizing the need to annotate the MSC abbreviations with their tissues of origin, as the authors previously recommended, while recognizing the controversy surrounding the use of "mesenchymal" in the abbreviations [4]. Indeed, there is growing evidence of the biological heterogeneity of MSCs based on tissue of origin, as evidenced by secretome [23], transcriptome [20], epigenome [24] and *in vitro* and *in vivo* functional analyses [25].

Discussion

In this article, the authors recommend a unified format for denoting the MSC abbreviations as well as tissues of origin following standard terminology developed by ICCBBA's CTCLAG. Specifically, the authors endorse the standard format to denote tissue of origin as a suffix using consensus-derived tissue abbreviations (Table 1). For example, under this standard terminology, MSCs derived from bone marrow would be abbreviated as MSC(M), MSCs derived from adipose tissue would be abbreviated as MSC(AT), MSCs derived from cord blood would be abbreviated as MSC(CB), MSCs derived from Wharton's jelly would be abbreviated as MSC(WJ) and MSCs derived from dental pulp would be abbreviated as MSC(DP). MSCs derived from bone marrow, adipose tissue, cord blood and Wharton's jelly are the most commonly investigated tissue sources under research and clinical investigation [26]. Abbreviations for other tissue sources are also recommended by ICCBBA's CTCLAG (Table 1) or will be developed using established consensus methods as newer sources of MSCs are tested and evaluated [27].

Although the use of ISBT 128 Standard Terminology standards remains in the purview of clinically used and/or approved products, the authors recommend the use of this standard terminology throughout the pre-clinical, translational and clinical research stages. This is particularly true as culture-adapted MSCs or their derivatives (including extracellular vesicles) [28] are investigated for their therapeutic properties. Consistency in nomenclature throughout the spectrum of research stages, particularly in the pre-clinical stage, will contribute to growing efforts to enable standardization and harmonization in defining and functionally characterizing MSCs from various tissues [29–32]. This MSC abbreviation recommendation is specifically directed to the clinical translational application of culture-adapted MSCs and is not intended to apply to basic research on the development/ontogeny of tissue-specific progenitor cells.

The authors recognize that the transition from the more commonly used prefix method to denoting culture-adapted MSCs with tissue of origin as a suffix—for example, MSC(M) versus BM-MSC, MSC(AT) versus AT-MSC, MSC(CB) versus UC-MSC—may take some getting used to. As the field of culture-adapted MSC products matures, with increasing market authorization approvals forecasted [33,34], this conversion to globally accepted standard terminology practices will align MSC products with other clinically used/approved CT products.

Table 1
Recommended abbreviations for type of cell and source tissue.

Type of cell	Source	Abbreviation
Dendritic cells	Apheresis	DC(A)
Dendritic cells	Cord blood	DC(CB)
Dendritic cells	Marrow	DC(M)
Dendritic cells	Whole blood	DC(WB)
Hematopoietic progenitor cells	Apheresis	HPC(A)
Hematopoietic progenitor cells	Cord blood	HPC(CB)
Hematopoietic progenitor cells	Marrow	HPC(M)
Hematopoietic progenitor cells	Whole blood	HPC(WB)
Malignant cells	Apheresis	MALIG(A)
Malignant cells	Marrow	MALIG(M)
Malignant cells	Tumor	MALIG(TM)
Malignant cells	Whole blood	MALIG(WB)
Mononuclear cells	Apheresis	MNC(A)
Mononuclear cells	Cord blood	MNC(CB)
Mononuclear cells	Umbilical cord tissue	MNC(UCT)
Mesenchymal stromal cells	Adipose tissue	MSC(AT)
Mesenchymal stromal cells	Cord blood	MSC(CB)
Mesenchymal stromal cells	Dental pulp	MSC(DP)
Mesenchymal stromal cells	Marrow	MSC(M)
Mesenchymal stromal cells	Wharton's jelly	MSC(WJ)
Nucleated cells	Adipose tissue	NC(AT)
Nucleated cells	Cord blood	NC(CB)
Nucleated cells	Marrow	NC(M)
Nucleated cells	Menstrual blood	NC(MB)
Nucleated cells	Whole blood	NC(WB)
Natural killer cells	Apheresis	NK(A)
Natural killer cells	Cord blood	NK(CB)
Natural killer cells	Marrow	NK(M)
Natural killer cells	Whole blood	NK(WB)
T cells	Apheresis	T CELLS(A)
T cells	Cord blood	T CELLS(CB)
T cells	Marrow	T CELLS(M)
T cells	Tumor	T CELLS(TM)
T cells	Whole blood	T CELLS(WB)

Conclusions

Focusing on standardized nomenclature is an important first step in enabling harmonization in a field that is exemplified by heterogeneity in the intrinsic biology of the cells as well as the methods and approaches to studying the cells. The authors therefore welcome this standardization of culture-adapted MSC nomenclature and see this as an important move in advancing MSC research, clinical translation and commercialization. ISCT and ICCBBA will continue to work with other scientific and professional societies to improve standardization in terminology.

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Declaration of Competing Interest

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

Author Contributions

Conception and design of the study SV, JG, IM, ZMS, PA, KM. Drafting or revising the manuscript: SV, RC, JG, MK, KL, IM, KM, JN, DGP, YS, ZMS, KT, DJW and PA. All authors have approved the final article.

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