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Biotechnology — Biobanking — Requirements for human mesenchymal stromal cells derived from umbilical cord tissue

Biotechnologie — Banques biologiques — Exigences relatives aux cellules stromales mésenchymateuses humaines issues des tissus du cordon ombilical

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Foreword

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This document was prepared by Technical Committee ISO/TC 276, *Biotechnology*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Mesenchymal stromal cells are a heterogeneous cell population that is characterized by multiple functional properties including the ability to secrete paracrine factors,[8] regulate immune effector cells,[9][10] maintain primitive phenotypes of other cell populations[11][12] and support tissue regeneration.[13][14] Mesenchymal stromal cells can contain a sub-population of stem or progenitor cells that demonstrate *in vitro* self-renewal and differentiation, as has been rigorously demonstrated for umbilical cord-derived progenitor cells.[15]

Mesenchymal stromal cells and mesenchymal stem cells are both abbreviated as “MSCs”.[16] For the purpose of this document, the abbreviated term “MSCs” refers to mesenchymal stromal cells.

The functional definition of MSCs has evolved over time as the biology of these cells is better understood. Despite these advances, substantial ambiguities persist regarding the nomenclature, nature, identity, function, mode of isolation and experimental handling of these cells. MSCs are not fully defined by the initial minimal criteria[17] proposed by the International Society of Cell and Gene Therapy (ISCT), and as such require careful characterization by a matrix of functional assays.[16]

MSCs have been isolated from umbilical cord[15], bone marrow[18][19] and other tissue sources, and are widely used for non-clinical research. MSCs from different tissue sources have different properties. Different institutions use different practices for isolating, processing and biobanking these MSCs, making it difficult to compare data and results across institutions. Thus, there is a need for standardized approaches to isolate, process, expand and cryopreserve these MSCs from specific tissue sources.

This document provides requirements for biobanking of human mesenchymal stromal cells derived from umbilical cord tissue (Wharton’s jelly) (hUC-MSCs) for research purposes. This document is applicable for academic centres, public and private institutions performing a biobanking service of hUC-MSCs for research and development (R&D) and preclinical studies, not for clinical use.

Importantly, this document is focused on MSCs that have been isolated, manipulated and/or propagated from umbilical cord tissue (also called “Wharton’s jelly”) in culture for research purposes. These cells are different from unmanipulated cells found in human umbilical cord tissue (Wharton’s jelly).

ISBT 128[20] provides terminology and abbreviations for all medicinal products including cell therapy, and abbreviates these as “MSC(WJ)” to denote mesenchymal stromal cells from Wharton’s jelly. This document recognizes this abbreviation, but uses the more commonly-used convention in research to denote human mesenchymal stromal cells derived from umbilical cord tissue (Warton’s jelly) (hUC-MSCs).[21]

Biotechnology — Biobanking — Requirements for human mesenchymal stromal cells derived from umbilical cord tissue

1 Scope

This document specifies requirements for the biobanking of human mesenchymal stromal cells derived from umbilical cord tissue (i.e. Wharton's jelly), further referred to as hUC-MSCs, including the collection of umbilical cord tissue and associated data, isolation, culture characterization, quality control, cryopreservation, storage, thawing, disposal, distribution and transport.

This document is applicable to all organizations performing biobanking of hUC-MSCs used for research and development.

This document does not apply to hUC-MSCs for the purpose of *in vivo* application in humans, clinical applications or therapeutic use.

NOTE International, national or regional regulations or requirements, or multiple of them, can also apply to specific topics covered in this document.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 8601-1, *Date and time — Representations for information interchange — Part 1: Basic rules*

ISO 20387:2018, *Biotechnology — Biobanking — General requirements for biobanking*

ISO 21709:2020, *Biotechnology — Biobanking — Process and quality requirements for establishment, maintenance and characterization of mammalian cell lines*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 20387:2018, ISO 21709:2020 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
authenticity
quality of being genuine or true

3.2
biobank
legal entity or part of a legal entity that performs *biobanking* (3.3)

[SOURCE: ISO 20387:2018, 3.5]

3.3
biobanking
process of acquisitioning and storing, together with some or all of the activities related to collection, preparation, preservation, testing, analysing and distributing defined biological material as well as related information and data

[SOURCE: ISO 20387:2018, 3.6]

3.4
biorisk
effect of uncertainty expressed by the combination of the consequences of an event (including changes in circumstances) and the associated “likelihood” (as defined in ISO Guide 73) of occurrence, where biological material is the source of harm

Note 1 to entry: The harm can be the consequence of an unintentional exposure, accidental release or loss, theft, misuse, diversion, unauthorized access or intentional unauthorized release.

[SOURCE: ISO 35001:2019, 3.17]

3.5
cell culture
growth of cells dissociated from the parent tissue by spontaneous migration, mechanical or enzymatic dispersal for propagation under *in vitro* conditions

3.6
cell master file
complete dossier of all procedures and records used to generate a cell

3.7
cell morphology
form and structure of the cell

Note 1 to entry: Morphology can be represented by a single parameter or a combination of two or more parameters.

[SOURCE: ISO 21709:2020, 3.3]

3.8
cell population purity
percentage of a particular cell type in a population, of which has the same specific biological characteristics, such as cell surface markers, genetic polymorphisms and biological activities

3.9
colony forming unit fibroblast
CFU-F
typical *in vitro* assay to demonstrate *self-renewal* (3.23) potential of progenitor cells plated at low frequencies that results in a formation of a colony of fibroblast-looking cells

Note 1 to entry: A count of these colonies is instructive of the colony forming potential or *in vitro* self-renewal capacity of these cells.

3.10
cryopreservation
process by which cells are maintained in an ultra-low temperature in an inactive state so that they can be revived later

[SOURCE: ISO 21709:2020/Amd 1:2021, 3.6]

3.11
differentiation
process to bring the cells into a defined cell state or fate

3.12
differentiation potential
ability that refers to the concept that stem and progenitor cells can produce daughter cells which are able to further differentiate into other cell types

3.13
flow cytometry
methodologically oriented subdiscipline of analytical cytology that measures cells in suspension in a liquid vehicle as they pass, typically one cell at a time, by a measurement station

Note 1 to entry: The measurement represents transformations of changes in the output of a detector (or detectors) due to changes in scattered light, absorbed light, light emitted (fluorescence) by the cell, or changes in electrical impedance, as the cell passes through the measuring station.

Note 2 to entry: Flow cytometry allows simultaneous evaluation of morphological characteristics of cells (size and internal complexity) with membrane or intracellular antigens.

[SOURCE: CLSI H44-A2:2004, Clause 4, modified — Note 2 to entry has been added.]

3.14
heterogeneity
<cells> non-uniformity of composition, quality or structure of a population of cells

3.15
homogeneity
<cells> uniformity of composition, quality or structure of a population of cells

3.16
human mesenchymal stromal cell derived from umbilical cord tissue
hUC-MSC
heterogeneous cellular population isolated from *umbilical cord* (3.25), which has the ability to modulate the immune response, secrete paracrine factors and undergo adipogenesis, osteogenesis and chondrogenesis *in vitro*

Note 1 to entry: Without any manipulation, "culture-adapted MSCs" is an alternate term used to denote cells that are different from cells that are found *in vivo*. It is increasingly clear that these cell types have different properties in terms of gene expression, functionality and phenotype.

3.17
licensing
<mesenchymal stromal cells> act of stimulating *hUC-MSCs* (3.16) using inflammatory cytokines to become more immunosuppressive

Note 1 to entry: Licensing is a biological term and not a regulatory or legal term.

3.18
passage
subculture
process of further culturing of cells in a culture vessel to provide higher surface area/volume for the cells to grow

Note 1 to entry: A passage can be performed by harvesting an aliquot from the parent vessel and reseeding it into another vessel.

3.19
passage number
number of subculturing that occurred

Note 1 to entry: For this document, P_0 is understood as the starting population of the cells.

[SOURCE: ISO 21709:2020, 3.13, modified — Note 1 to entry added.]

3.20
population doubling time
PDT
doubling time
time taken for cultured cell count to double

Note 1 to entry: The time is measured in hours.

[SOURCE: ISO 21709:2020, 3.8, modified — "population doubling time" and "PDT" added as the preferred term. Note 1 to entry added.]

3.21
primary culture
culture started from cells, tissues, or organs taken directly from an organism, and before the first subculture, propagation and consecutive *passages* (3.18) *in vitro*

[SOURCE: ISO 21709:2020, 3.16, modified — Note 1 to entry deleted.]

3.22
proliferation
cell number expansion by cell division

3.23
self-renewal
ability of *stem cells* (3.24) to divide symmetrically, forming two identical daughter stem cells

Note 1 to entry: Adult stem cells can also divide asymmetrically to form one daughter cell, which can proceed irreversibly to a differentiated cell lineage and ultimately lead to focused functional differentiated cells, while the other daughter cell still retains the characteristics of the parental stem cell.

3.24
stem cell
non-specialized cells with the capacity for *self-renewal* (3.23) and *differentiation potential* (3.12), which can differentiate into one or more different types of specialized cells

Note 1 to entry: Most adult stem cells are multipotent stem cells.

3.25
umbilical cord
umbilical cord tissue
UC
soft, gelatinous connective tissue (i.e. Wharton jelly), excluding umbilical arteries, umbilical vein and placenta

3.26
viability
attribute of being alive (e.g. metabolically active, capable of reproducing, have intact cell membrane, or have the capacity to resume these functions) as defined based on the intended use

[SOURCE: ISO 21709:2020, 3.17]

3.27
viable cells
cells within a sample that have an attribute of being alive (e.g. metabolically active, capable of reproduction, possessed of intact cell membrane, or with the capacity to resume these functions) defined based on the intended use

[SOURCE: ISO 20391-1:2018, 3.29]

4 Abbreviated terms and symbols

2D1	clone of anti-human CD45 antibody
4F2	clone of anti-human CD98 antibody
561	clone of anti-human CD34 antibody
581	clone of anti-human CD34 antibody
58XB4	clone of anti-human CD104 antibody
63D3	clone of anti-human CD14 antibody
A20	tumour necrosis factor alpha-induced protein 3 (TNFAIP3)
ACAN	aggrecan
AD2	anti-human CD-73 (Ecto-5'-nucleotidase) antibody
AHR	aryl hrdrocarbon receptor
ALP	alkaline phosphatase
ANGPT2	angiopoietin-2
AP2	adipocyte protein-2
α-SMA	alpha-smooth muscle actin
B7RP2	B7-related protein 2
BCL-2	B-cell lymphoma 2
BJ18	clone of anti-human CD44 antibody
BM	bone marrow
C44Mab-5	clone of anti-human CD44 antibody
CCL2	C-C Motif Chemokine ligand 2
CCL5	C-C Motif Chemokine ligand 5
CCL7	C-C Motif Chemokine ligand 7
CCR7	C-C Motif Chemokine receptor 7
CCR10	C-C Motif Chemokine receptor 10
CD	clusters of differentiation
CD9	clusters of differentiation 9
CD13	clusters of differentiation 13
CD14	clusters of differentiation 14
CD29	clusters of differentiation 29
CD31	clusters of differentiation 31

CD34	clusters of differentiation 34
CD44	clusters of differentiation 44
CD45	clusters of differentiation 45
CD46	clusters of differentiation 46
CD55	clusters of differentiation 55
CD73	clusters of differentiation73
CD90	clusters of differentiation 90
CD98	clusters of differentiation 98
CD104b	clusters of differentiation 104b
CD105	clusters of differentiation 105
CD 146	clusters of differentiation146
CD276	clusters of differentiation 276
CEBPα	enhancer-binding protein alpha
CFSE	carboxyfluorescein succinimidyl ester
CFU	colony forming units
CIITA	human gene which encodes a protein called the class 2, major histocompatibility complex, transactivator
CO_2	carbondioxide
COL2A1	collagen type 2 alpha 1
COX-2	prostaglandin-endoperoxide synthase 2 (cyclooxygenase-2)
CX3CR1	C-3X-C Motif Chemokine receptor 1
CXCL9	C-X-C Motif Chemokine ligand 9
CXCL10	C-X-C Motif Chemokine ligand 10
CXCL11	C-X-C Motif Chemokine ligand 11
CXCL12	C-X-C Motif Chemokine ligand 12
CXCR1	C-X-C Motif Chemokine receptor type 1
CXCR4	C-X-C Motif Chemokine receptor type 4
CXCR6	C-X-C Motif Chemokine receptor type 6
DCN.70	anti-CD276 (B7-H3) antibody
DMEM	Dulbecco's modified eagle medium
DMEM-LG	Dulbecco's modified eagle medium low glucose
DMSO	dimethyl sulfoxide

DRAP-24	clone of anti-human CD9 antibody
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
FABP4	Fatty acid-binding protein 4
FACS	fluorescence activating cell sorter
FBS	fetal bovine serum
FRP-1	frizzled-related protein
GAL-1	galactose-1
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCD14	clone of anti-human CD14 antibody
HCsAg	hepatitis C surface antigen
HCV	hepatitis C virus
HEL113	gene of vimentin
HGF	hepatocyte growth factor
HI30	clone of anti-human CD45 antibody
HI9a	clone of anti-human CD9 antibody
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLA-Class I	human leukocyte antigen – Class I
HLA-Class II	human leukocyte antigen – Class II
HLA-DR	human leukocyte antigen DR
HO-1	haem oxygenase-1
HSP70A	heat shock protein 70A
HSP70B	heat shock protein 70B
hUC-MSC	human umbilical cord mesenchymal stromal cell
ICAM-1	intercellular adhesion molecule-1
IDO	indoleamine 2,3-dioxygenase 1
IFN-γ	interferon-gamma
IFU	instructions for use
IL-1	interleukin-1