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PERSPECTIVE

International Society for Cellular Therapy perspective on immune functional assays for mesenchymal stromal cells as potency release criterion for advanced phase clinical trials

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Abstract

Mesenchymal stromal cells (MSCs) as a pharmaceutical for ailments characterized by pathogenic autoimmune, alloimmune and inflammatory processes now cover the spectrum of early- to late-phase clinical trials in both industry and academic sponsored studies. There is a broad consensus that despite different tissue sourcing and varied culture expansion protocols, human MSC-like cell products likely share fundamental mechanisms of action mediating their anti-inflammatory and tissue repair functionalities. Identification of functional markers of potency and reduction to practice of standardized, easily deployable methods of measurements of such would benefit the field. This would satisfy both mechanistic research as well as development of release potency assays to meet Regulatory Authority requirements for conduct of advanced clinical studies and their eventual registration. In response to this unmet need, the International Society for Cellular Therapy (ISCT) addressed the issue at an international workshop in May 2015 as part of the 21st ISCT annual meeting in Las Vegas. The scope of the workshop was focused on discussing potency assays germane to immunomodulation by MSC-like products in clinical indications targeting immune disorders. We here provide consensus perspective arising from this forum. We propose that focused analysis of selected MSC markers robustly deployed by in vitro licensing and metricized with a matrix of assays should be responsive to requirements from Regulatory Authorities. Workshop participants identified three preferred analytic methods that could inform a matrix assay approach: quantitative RNA analysis of selected gene products; flow cytometry analysis of functionally relevant surface markers and protein-based assay of secretome. We also advocate that potency assays acceptable to the Regulatory Authorities be rendered publicly accessible in an "open-access" manner, such as through publication or database collection.

Key Words: *Mesenchymal Stromal cells, potency assays, release assays, matrix assays, immune functional testing, clinical trials, ISCT*

Culture-expanded mesenchymal stromal cells (MSCs) meeting minimal core identity for MSCs as defined by International Society for Cellular Therapy (ISCT) in 2006 [1] derived from marrow, adipose tissue, umbilical cord tissue and other sources from either autologous or allogeneic donor sources are being studied in clinical trials across numerous regulatory jurisdictions worldwide. The ailments targeted with this cell pharmaceutical platform fall roughly within two pathophysiological categories: immune/inflammatory and tissue repair/restoration [2]. It is now widely accepted that the pharmaceutical effect of MSC-like cells is predominantly mediated by paracrine and contact factors arising from intrinsic MSC physiological processes that are maintained after culture expansion. It is further accepted that following in vivo delivery, MSCs are further responsive to environmental cues encountered in situ leading to additional cellular functionalities [3]. Culture expanded MSC-like cells are unambiguously classified as a more-than-minimal-manipulated cellular and gene therapy (CGT) product regulated in the United States under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262). As a type of CGT product, MSC-like cells require an Investigational New Drug Application (IND) from the Food & Drug Administration (FDA) for conduct of clinical trials in the USA. The FDA further requires development of tests to measure potency as part of release criteria of advanced clinical trials designed to support marketing approval and registration. Similar requirements are made by the European Medicines Agency (EMA) for Advanced Therapy Medicinal Products (ATMPs), which include cell therapies, as defined by the European Regulation (European Commission [EC]) No. 1394 / 2007,[1] further strengthened on December 30, 2008, and directly enclosed in the legislation of each EU member nation with no need of other implementation. The EU Regulation is in compliance with the 2004/23/EC directive on donation, supply and testing of human cells and tissues and with directive 2002/98/EC on human blood and blood components.[2] The tripartite components of release criteria for MSC-like cellular products in early phase clinical trials—identity, viability and sterility—raise little practical controversy and the consensus on markers for identity of MSC-like cells, considering their intrinsic heterogeneity and phenotype plasticity, is also reasonably well defined [1,4]. However, the issue of potency testing remains largely open-ended and is informed by the putative mechanism of action (MOA) of MSC-like cells in a given indication. Care must be made in distinguishing curiosity-driven research as part of ancillary studies on cell products and release potency assays required to satisfy the Regulatory Authorities. Although pre-clinical MOA studies will necessarily inform the methods and reduction to practice of deployable potency assays, the latter have specific requirements for the following as part of assay validation: accuracy, precision, specificity, linearity and range, system suitability, and robustness.

International regulatory authority guidance on potency tests for cellular therapy products

The FDA has published guidance with recommendations for developing tests to measure potency for CGT products.[3] These recommendations are intended to clarify the potency information that could support

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:EN:PDF.

[2] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF.

[3] http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM243392.pdf.