

Annals of Stem Cell Research

Review Article

Off-the-Shelf Allogeneic Mesenchymal Stromal Cell Products: Potency Assays and Batch Consistency

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Received: 7 March 2026; Accepted: 25 May 2026; Published: 30 August 2026; DOI: 10.5281/zenodo.22274838

Citation of this article: Wozniak T, Peeters E, Norkus G (2026) Off-the-Shelf Allogeneic Mesenchymal Stromal Cell Products: Potency Assays and Batch Consistency. Ann Stem Cell Res, 9(1): 01-08.

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Abstract

Background: Off-the-shelf allogeneic mesenchymal stromal cell products must be released lot by lot against a specification anchored by a potency assay, and many candidate assays exist.

Objective: To ask whether any candidate potency assay has been shown to predict clinical response, and what follows for batch consistency.

Methods: Narrative review of potency assay studies, regulatory guidance and approval records for licensed products.

Findings: No assay reviewed has been shown to correlate with clinical response. In a ten-donor panel, interferon-gamma-induced IDO1 expression ranged from 12% to 91% of cells among preparations meeting identity criteria, and correlated with T-cell proliferation at $r = -0.9$. Reviewers of the first licensed product recorded that its release assays may not support comparability across manufacturing changes.

Conclusions: The evidence supports demonstrating batch consistency against a specification; it does not support any claim that a release value predicts patient benefit, which requires lot-linked outcome data.

Keywords: Mesenchymal stromal cells; Potency assay; Batch consistency; Allogeneic cell therapy; Donor variability

Introduction

An off-the-shelf allogeneic mesenchymal stromal cell (MSC) product is a manufactured biologic that must be released lot by lot against a specification, and a specification is only as good as the potency assay that anchors it. Two decades of work have produced an abundance of candidate assays: tryptophan catabolism through indoleamine 2,3-dioxygenase, co-culture suppression of T-cell proliferation, prostaglandin E2 and TSG-6 secretion, interferon-gamma licensing competence read through phosphorylated STAT proteins, machine-learned morphological signatures, susceptibility to recipient-mediated apoptosis, and multi-analyte matrices combining several of these. Each has a mechanistic warrant drawn from a preclinical model. None, in the literature assembled for this review, has been shown to predict whether a patient responds.

That absence is the subject of this article, not an aside within it. It is easy to read the potency literature as a menu of maturing options among which manufacturers may reasonably choose. Read against the question a release assay exists to answer, the same literature reads differently: the field has a well-populated column for mechanism and an empty column for clinical correlation, and the emptiness has survived the licensure of products on both sides of the Atlantic. The regulatory documents are unusually explicit about this, and one of them, the United States Food and Drug Administration's own assessment of the first approved MSC product, records doubt about whether its licensed potency assays can do the job a potency assay is licensed to do.

The argument proceeds from identity criteria to assays, from assays to the regulatory texts that govern them, from those texts to the two products whose specifications are on the public record, and finally to the sources of lot-to-lot variability that a potency assay would have to track if it were fit for purpose. Numbers are given with the N behind them; where the underlying work is qualitative or reported

at second hand, it is described as such.

Identity is not potency

The International Society for Cellular Therapy's minimal criteria define an MSC by plastic adherence, expression of CD73, CD90 and CD105, absence of CD45, CD34, CD14, CD11b, CD79a and HLA-DR, and tri-lineage differentiation in vitro [1]. These criteria settled a nomenclature problem and were never intended to measure therapeutic activity, a point the same committee later made explicit in separating stem from stromal cell claims [2] and in proposing a separate immunological characterisation framework [3].

The gap between passing identity and having function is large and measurable. In a ten-donor panel of bone-marrow MSC characterised under a defined potency assay matrix, interferon-gamma-induced IDO1 expression ranged from 12% to 91% of cells, a near eightfold spread across preparations that met identity release criteria [4]. Within the same panel, two individual donor lots differed by 2.6-fold in the half-maximal inhibitory concentration for CD4+ proliferation and 2-fold for CD8+, measured head to head [4]. That functional readout was tightly coupled to the licensing marker: IDO1 expression correlated with both CD4+ and CD8+ T-cell proliferation at $r = -0.9$, $P < 0.001$, across ten MSC donors tested against peripheral blood mononuclear cells from 22 blood donors [4].

This is the shape of the problem in miniature. Identity is uninformative about a variable that moves nearly an order of magnitude between donors; a functional assay resolves that variable well and correlates internally with another in-vitro readout. What no source examined here supplies is the third link, from either number to a patient.

The assays on offer and what each measures

The mechanistic case for IDO is the oldest and the cleanest. Human bone-marrow stromal cells inhibit allogeneic T-cell responses through IDO-mediated

tryptophan degradation [5], and interferon-gamma is required to induce the immunomodulatory phenotype at all, which makes licensing a precondition rather than an enhancement [6]. Prostaglandin E2 has its own lineage: MSC attenuate murine sepsis by reprogramming host macrophages to produce interleukin-10 in a PGE2-dependent manner [7]. TSG-6 has another: intravenously infused human MSC embolised in the lung secrete this anti-inflammatory protein and improve murine myocardial infarction [8]. Each mechanism is real in its model system, and each supports a different release assay.

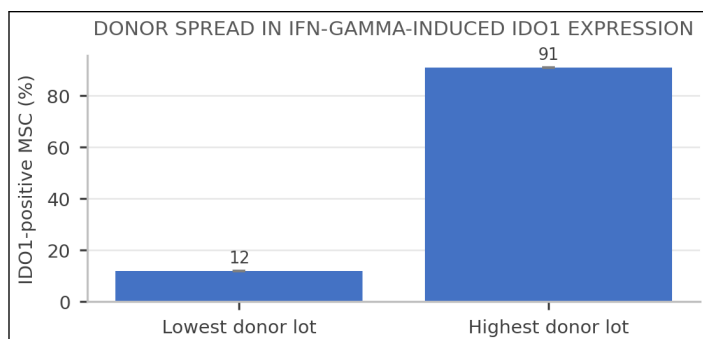


Figure 1: Confirmed range of interferon-gamma-induced IDO1 expression across identity-qualified bone-marrow MSC lots, 12% to 91% IDO1-positive cells; N = 10 MSC donors, with IDO1 correlating with CD4+ and CD8+ T-cell proliferation at $r = -0.9$, $P < 0.001$, against PBMC from 22 blood donors [4].

Direct functional co-culture is the most obvious candidate because it reads the proposed action rather than a proxy. A reproducible immunopotency assay measuring MSC-mediated T-cell suppression has been described in standardised form [9], and a robust variant tested 15 donors across three tissue sources at MSC:PBMC ratios from 1:1 to 1:30, reporting significant individual variability and profound variation in potency between donors [10]. That assay's own responder cells vary: across 35 experiments with pooled PBMC, mitogen-driven proliferation was $66.05 \pm 11.38\%$ and mixed-lymphocyte-reaction-driven proliferation $73.04 \pm 5.44\%$ [10]. A release assay whose denominator moves by that much needs careful control before its numerator means anything.

The remaining candidates move upstream or sideways. Phospho-STAT matrix loop analysis reads licensing competence rather than any single effector [11]. Morphological profiling by machine learning of interferon-gamma-stimulated cells proposes cell shape as a surrogate for overall immunosuppressive capacity [12]. A distinct line of work relocates the mechanism to the recipient: apoptosis of infused MSC induces recipient-mediated immunomodulation [13], and phagocytosis of MSC by monocytic cells triggers the immunomodulatory response [14], implying that a potency assay might have to measure the host as well as the product. Two influential syntheses have argued for combining assays rather than choosing between them [15,16], and for reading the whole enterprise as a manufacturing problem [17].

Set these candidates side by side and the asymmetry is stark. Every one of them can be given a measurand, and every one can be given a mechanistic rationale traceable to a specific experiment. The column recording whether the assay value has been shown to track clinical response is empty for all of them, and it is empty in the same way each time: not contested, not weakly positive, simply never populated by a study that measured a release value and a patient outcome in the same lots. The honest presentation of the field is therefore a table with one blank column, and the blank is the finding.

What the regulators ask, and what they concede

The governing United States text is the Food and Drug Administration's January 2011 final guidance on potency tests for cellular and gene therapy products, docket FDA-2008-D-0520. It states that "Ideally, the potency assay will represent the product's mechanism of action (i.e., relevant therapeutic activity or intended biological effect)" (section III.A.2), and, in section III.B.3, that "a single biological or analytical assay may not provide an adequate measure of potency" where a "Product has complex and/or not fully characterized mechanism of

action" or has "multiple active ingredients and/or multiple biological activities" [18]. That second passage is the licence for the assay-matrix approach, and it is a concession rather than an endorsement: the matrix is what regulators accept when the ideal is unavailable. The agency's own scientists made the application to MSC explicit [19], and the combinatorial matrix was subsequently built and tested on 10 clinical-grade MSC lots plus 3 independent healthy bone-marrow donors against 3 PBMC responder donors, retaining analytes with $R^2 \geq 0.5$ against T-cell suppression [20].

Table 1: Candidate MSC potency assays, what each measures, the mechanistic link claimed for it, and whether a correlation with clinical response has been demonstrated; the final column is left empty where no verified source reports such a correlation [5,6,7,8,9,10,20,11,12,13,14,24,4].			
Assay	What it measures	Stated mechanistic link	Clinical correlation shown
IDO induction	Tryptophan catabolism after licensing	IDO-mediated tryptophan degradation inhibits T-cell responses	
T-cell suppression co-culture	Inhibition of mitogen- or MLR-driven proliferation	Direct readout of the proposed immunosuppressive action	
PGE2 secretion	A soluble mediator in conditioned medium	PGE2-dependent macrophage reprogramming to IL-10	
TSG-6 secretion	A soluble anti-inflammatory protein	Lung-embolised MSC secrete TSG-6 in murine infarction	
Phospho-STAT matrix loop	Licensing signalling competence	Licensing lies upstream of IDO and the wider programme	
TNFR1 plus IL-2Ralpha inhibition	Surface receptor level and functional inhibition	Adopted as the licensed release pair for remestemcel-L	

The position was extended, not resolved, by the draft guidance on potency assurance for cellular and gene therapy products issued on 28 December 2023 under docket FDA-2023-D-4299, which remains labelled "Not for implementation. Contains non-binding recommendations." [21]. In Europe the Committee for

Medicinal Products for Human Use guideline on human cell-based medicinal products, EMEA/CHMP/410869/2006, was published on 21 May 2008 and took legal effect on 1 September 2008 [22]; a regulatory perspective from a national competent authority sets out what assessors in practice expect of in-vitro MSC potency assays and where submissions fall short [23].

What no regulator has done is require the demonstration this review finds missing. The texts ask that potency be quantitative, lot-specific, stability-indicating and, ideally, mechanism-linked; they do not ask that the assay value be shown to predict benefit, because for most biologics a mechanism-linked assay makes that demonstration redundant. For a product whose mechanism is contested, distributed across several mediators and possibly resident partly in the recipient, the redundancy fails, and the regulatory standard as written can be met in full by a specification that carries no demonstrated relationship to outcome.

Two products and their release specifications

Remestemcel-L was approved as RYONCIL on 18 December 2024. The Summary Basis for Regulatory Action records lot-release potency testing as "TNFR1 Expression, and IL-2Ralpha Inhibition", a drug product target concentration of 6.68×10^6 MSC/mL, a target dose of 2×10^6 MSC/kg, and cryopreservation in Plasma-Lyte A with human serum albumin and 10% DMSO [24]. The same document records the reviewers' judgement that the two assays "may not be able to support product or process comparability for any future manufacturing changes" [24]. A licensed product therefore carries, in its own approval record, an explicit statement that its release assays may not survive a process change, which is the specific function a mechanism-linked potency assay is supposed to perform. A review by the Le Blanc group states further that these two markers have failed to predict patient responsiveness; that is a secondary assertion within a

review rather than an independent measurement, and is reported here as such [25]. The pivotal trial supporting the product was a single-arm phase 3 study in steroid-refractory paediatric acute graft-versus-host disease [26], a setting first opened by a European phase II collaborative study [27] and pursued with a deliberately pooled multi-donor preparation intended to damp donor variability [28].

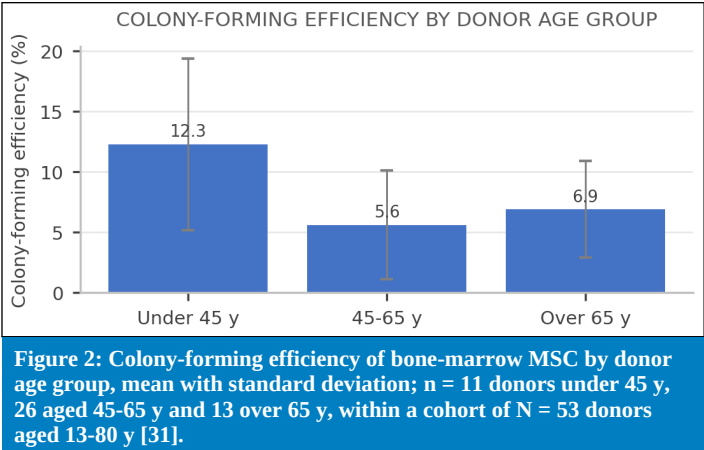
Table 2: Authorised allogeneic MSC products and the specification content on the public regulatory record, with a pooled-donor investigational preparation for contrast [24,30,28].			
Product	Status	Presentation	Documented release potency
RYONCIL (reme stemcel-L-rknd)	US BLA approved 18 December 2024	6.68 x 10 ⁶ MSC/mL; 2 x 10 ⁶ MSC/kg	TNFR1 expression and IL-2/Ralpha inhibition
Alofisel (darvadstrocel)	EU authorised 23 March 2018; withdrawn 13 December 2024	5 x 10 ⁶ cells/mL; 120 x 10 ⁶ cells in 24 mL	Potency specification accepted; assay not named publicly
MSC-FFM (pooled donor)	Investigational or hospital-exemption use in the EU	Pooled from multiple bone-marrow donors	Not publicly specified

Darvadstrocel, authorised in the European Union as Alofisel on 23 March 2018 following a Committee opinion of 14 December 2017, presented 5 x 10⁶ cells/mL, 120 x 10⁶ expanded adipose-derived stem cells in 24 mL across four vials, on the strength of a phase 3 randomised trial in complex perianal fistulas [29]. Its assessment report records that a major objection concerning the potency assay was raised and subsequently resolved, and that a prospective comparability exercise between pre- and post-change batches was required and accepted; the assay itself is not named in the public text, and no inference about its identity is drawn here. The marketing authorisation was withdrawn on 13 December 2024 at the holder's request for commercial reasons [30].

Donor variation, cryopreservation and lot-to-lot consistency

The variability a release assay must track begins with the

donor. In 53 bone-marrow donors aged 13 to 80, colony-forming efficiency was 12.3 +/- 7.1% below 45 years (n = 11), 5.6 +/- 4.5% at 45-65 years (n = 26) and 6.9 +/- 4.0% above 65 years (n = 13); female donors reached 9.3 +/- 6.2% against 5.9 +/- 4.8% for male, P < 0.05, and population doubling time was 3.3 +/- 1.9 days in females (n = 25) against 5.0 +/- 3.7 days in males (n = 27), P < 0.05 [31]. Function tracked demography as well: MSC from female donors (n = 18) suppressed T-cell proliferation significantly more than those from male donors (n = 16), P < 0.001, and cells from older donors produced more IL-6 in co-culture with activated T cells, P < 0.05 [31].



Processing adds a second layer. Cryopreserved MSC have been reported to display impaired immunosuppressive properties attributed to a heat-shock response and defective interferon-gamma licensing [32], and frozen-thawed MSC in the assay-matrix study were defective at inhibiting T-cell proliferation [20]; the magnitude of that loss is not resolved by any primary numeric series available here, and the broader literature on freeze-thaw effects across cellular therapeutics has been reviewed rather than settled [33]. One single-donor study found 69% viability immediately after thaw, 82% after 24 h of acclimation and 77% in continuously cultured fresh cells, with acclimated cells suppressing T-cell proliferation significantly more than freshly thawed cells [34]; with N = 1 donor that is a hypothesis, not a specification. Extracellular vesicle readouts add a further

candidate axis, with monocyte uptake rising from under 10% of cells at 6 h to 87% at 24 h and 98% at 48 h, and CD63 content correlating with vesicle number at $r = 0.86$, $P < 0.001$ [4].

Conclusion

The candidate potency assays for allogeneic MSC products are numerous, mechanistically motivated, and reproducible in the hands that built them. Not one of them has been shown, in the sources verified for this review, to correlate with clinical response. The regulatory framework accommodates this by permitting assay matrices where mechanism is incompletely characterised [18], and the accommodation has held through a draft revision [21] and across jurisdictions [22]. It is not a solution. The clearest evidence that it is not comes from the approval record of the one licensed United States product, where the reviewers wrote down that the release assays may not support comparability across a process change [24].

What follows for the field is narrow and unglamorous. The missing datum is not another assay but a prospectively collected, lot-linked pairing of a release potency value with a patient outcome, at a sample size that can support a correlation. Until such a dataset exists, batch consistency can be demonstrated against a specification and cannot be demonstrated against a benefit, and the near-eightfold donor spread in a single licensing-dependent marker among identity-qualified preparations [4] should be read as an unquantified clinical risk rather than a manufacturing curiosity.

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