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AN MCI WHITE PAPER

Authentic Dezawa MuseCells®: Why Source, Protocol, and Science All Matter

by Joseph Purita, MD

Authenticity is not a matter of terminology. It is a matter of biological identity, scientific rigor, and patient safety.

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A growing number of products have entered the marketplace under the name "MUSE" cells, yet many lack demonstrated provenance from the scientifically validated platform developed by Dr. Mari Dezawa at Tohoku University.

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The distinction at the center of this paper

Authentic Dezawa MuseCells® are defined by a specific, experimentally validated phenotype — a naturally occurring, non-tumorigenic, pluripotency-like cell population found within various human tissues and routinely isolated using the SSEA-3 pluripotent surface marker.

This distinction matters because the therapeutic effects of the Dezawa MuseCell® platform rest on properties that are highly specific and not interchangeable with those of other cell products. The defining value of authentic Dezawa MuseCells® lies in their capacity for broad differentiation and endogenous tissue repair, without the tumor-forming behavior that has limited the therapeutic use of embryonic and induced pluripotent stem cells. That is not a generic characteristic of any product labeled "MUSE." It is the result of a distinct cell identity, carefully defined through years of preclinical and translational research.

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Scientific foundation

The scientific foundation for Muse cells was established in the landmark work from Dr. Dezawa's group, including the original PNAS reports that identified and characterized multilineage-differentiating stress-enduring (MUSE) cells in adult human tissues and extraembryonic tissues such as umbilical cord and amnion. The 2010 PNAS paper first described unique pluripotent cells in adult human mesenchymal cell populations[1]. The 2011 PNAS paper established the SSEA-3$^+$/CD105$^+$ co-marker isolation protocol and demonstrated that iPS cells generated from human fibroblasts derive exclusively from the Muse subpopulation[2].

These studies[1,2] showed that authentic Dezawa MuseCells® possess self-renewal capacity, triploblastic differentiation potential across mesoderm, ectoderm, and endoderm lineages, and a non-tumorigenic, pluripotent-like profile. They also showed that SSEA-3 selection improves the precision of Dezawa MuseCell® isolation from the broader mesenchymal stem cell population[2].

[1] Kuroda Y, et al. Unique multipotent cells in adult human mesenchymal cell populations. Proc Natl Acad Sci USA (2010). PMID: 20421459 · [2] Wakao S, et al. Multilineage-differentiating stress-enduring (Muse) cells are a primary source of induced pluripotent stem cells in human fibroblasts. Proc Natl Acad Sci USA (2011). PMID: 21628574

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The biology that cannot be replicated without proper protocol

The non-tumorigenic pluripotency of authentic Dezawa MuseCells® is one of the most scientifically significant — and most frequently misunderstood — properties in regenerative cell therapy. Traditional pluripotent stem cells, such as iPSCs, carry an inherent risk of teratoma formation because their reprogramming introduces genomic instability and reactivates oncogenic pathways. Dezawa MuseCells® sidestep this entirely through a distinct mechanism.

Several features underpin this safety profile.

Authentic Dezawa MuseCells® are isolated through a long-term, severe cellular stress protocol involving trypsin incubation, serum deprivation, and hypoxia, due to the stress-tolerance. This process selectively enriches the Dezawa MuseCell® population while eliminating less-resilient, potentially unstable cells. This is not a cosmetic step. It is biologically determinative.

Unlike iPSCs, Dezawa MuseCells® do not require the reprogramming factors Oct4, Sox2, Klf4, or c-Myc. Their pluripotency is intrinsic rather than induced — meaning their genome remains intact and oncogenic activation is avoided. Unlike iPS and ES cells that depend on oncogenic LIN28 for the maintenance of pluripotency, Muse cells lack LIN28 but instead control their pluripotency by tumor-suppressor microRNA Let-7, enabling both pluripotency and non-tumorigenicity[3].

Following engraftment, Dezawa MuseCells® spontaneously differentiate into tissue-specific cell types. In liver injury models, they express hepatocyte markers including HepPar-1 and human albumin at rates of 71.1 percent and 54.3 percent, respectively, demonstrating highly organ-specific integration[4]. In cardiac models, engrafted cells express cardiac troponin I, alpha-actinin, and connexin 43[5]. In renal injury, they differentiate into glomerular cells[6]. This tissue-appropriate differentiation occurs spontaneously in response to local microenvironmental cues — without requiring directed differentiation protocols.

[3] Li G, et al. Tumor suppressor let-7 acts as a key regulator for pluripotency gene expression in Muse cells. Cell Mol Life Sci (2024). PMID: 38261036 · [4] Iseki M, et al. Muse Cells, Nontumorigenic Pluripotent-Like Stem Cells, Have Liver Regeneration Capacity Through Specific Homing and Cell Replacement in a Mouse Model of Liver Fibrosis. Cell Transplant (2017). PMID: 27938474 · [5] Yamada Y, et al. S1P–S1PR2 Axis Mediates Homing of Muse Cells Into Damaged Heart for Long-Lasting Tissue Repair and Functional Recovery After Acute Myocardial Infarction. Circ Res (2018). PMID: 29475983 · [6] Uchida N, et al. Beneficial Effects of Systemically Administered Human Muse Cells in Adriamycin Nephropathy. J Am Soc Nephrol (2017). PMID: 28674043

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The molecular mechanism of Dezawa MuseCell® homing

One of the most elegant and scientifically distinctive features of authentic Dezawa MuseCells® is their highly specific homing mechanism — a precision targeting system that sharply differentiates them from generic MSCs and underscores why protocol integrity is inseparable from function.

When tissue is damaged or cells undergo apoptosis, they release sphingosine-1-phosphate (S1P), a bioactive lipid mediator that acts as a molecular distress signal — creating a chemotactic gradient in the surrounding tissue and vasculature. Authentic Dezawa MuseCells® express sphingosine-1-phosphate receptor 2 (S1PR2) on their surface, conferring exquisite sensitivity to this gradient[5].

> *"A label is not a biology. A name is not a safety profile."*

The S1P–S1PR2 axis is the primary molecular engine driving Dezawa MuseCell® homing, as confirmed by two independent lines of evidence. Pharmacological blockade with the specific S1PR2 antagonist JTE-013 significantly inhibited migration to injured myocardium *in vivo*, confirming S1PR2 dependence[5]. Genetic silencing — by introducing S1PR2-targeted siRNA prior to infusion — abolished homing capacity entirely, providing molecular-level confirmation that S1PR2 is not merely associated with homing but is mechanistically required for it.

This S1PR2-driven homing is distinct from the mechanism used by monocytes and macrophages, which also migrate toward S1P gradients but via S1PR1 rather than S1PR2. This receptor-level specificity means Dezawa MuseCells® occupy a unique biological niche — responsive to the same damage signals as immune cells but governed by a separate molecular pathway that enables independent, non-redundant tissue repair.

The homing cascade proceeds through several coordinated steps.

Injured or apoptotic cells at the target site release S1P into the local tissue microenvironment and bloodstream, establishing a concentration gradient. Circulating Dezawa MuseCells® expressing S1PR2 detect the gradient and initiate directed migration toward the injury site.

They then undergo diapedesis through the vascular endothelium — a process facilitated by matrix metalloproteinases and integrin-mediated adhesion to VCAM-1 on activated endothelial cells. Upon reaching the injury site, the cells engraft into damaged tissue and

receive local microenvironmental cues that guide spontaneous differentiation into tissue-appropriate cell types — without preprogramming or directed differentiation protocols.

Recent data from ALS clinical trials also showed that serum S1P levels decreased continuously over 12 months following Dezawa MuseCell® infusion, suggesting that engrafted cells may functionally neutralize ongoing damage signals[7]. This appears to represent a built-in feedback loop that may help resolve the inflammatory milieu driving tissue destruction.

In cardiac studies, approximately 14.5 percent of intravenously injected Dezawa MuseCells® successfully engrafted into the infarcted myocardium within three days, with preferential accumulation confirmed by Nano-lantern labeling and live imaging. This is a remarkably high engraftment rate for intravenously administered cells — and it is a direct product of the S1PR2-mediated homing system. It is not a property that can be assumed in any cell population unless functional S1PR2 expression has been verified.

> *"The homing mechanism is not a downstream feature of vague stemness. It is a molecularly defined, experimentally validated property of authentic Dezawa MuseCells®."*

This homing specificity has profound implications for product authenticity. A cell product that lacks verified S1PR2 expression and functional S1P responsiveness — regardless of what label it carries — cannot be expected to home to injury sites with the precision documented in the peer-reviewed Dezawa MuseCell® literature. The homing mechanism depends entirely on correct derivation and characterization.

[7] *Yamashita T, et al. Safety and Clinical Effects of a Muse Cell-Based Product in Patients With ALS: Results of a Phase 2 Clinical Trial. Cell Transplant (2023). PMID: 38014622*

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Clinical validation: a decade of human evidence

The safety and preliminary efficacy of authentic Dezawa MuseCells® have been evaluated in a growing body of human clinical trials, primarily under the development of the CL2020 — an intravenous allogeneic Dezawa MuseCell® product derived from bone marrow. Where preclinical mechanism work appears below, it is to anchor the clinical observation that follows — not to substitute for it.

Conditions evaluated in human trials to date include ischemic stroke, amyotrophic lateral sclerosis, acute myocardial infarction, dystrophic epidermolysis bullosa, neonatal hypoxic-ischemic encephalopathy, and cervical traumatic spinal cord injury.

Ischemic stroke. A randomized placebo-controlled Phase II trial (Niizuma et al., 2023) of CL2020 versus placebo in subacute ischemic stroke demonstrated meaningful improvement in modified Rankin Scale outcomes, with a substantially higher proportion of CL2020-treated patients reaching mRS ≤2 at 12 weeks. Recovery did not require HLA matching or immunosuppression[8]. In the CL2020 group, ~70% became independent when using trains, walking, toileting, and eating, and ~30% regained their pre-stroke function and returned to work at 52 weeks, showing statistically significant recovery compared to the placebo group[8].

Amyotrophic lateral sclerosis. An open-label Phase 2 trial (Yamashita et al., 2023) of repeated monthly intravenous CL2020 dosing over six months confirmed safety, with no pulmonary embolism, anaphylactic shock, or other serious adverse events attributed to treatment. A subset of patients showed slowing of ALSFRS-R decline, and serum S1P levels decreased progressively over 12 months — consistent with active engagement of the S1P–S1PR2 homing biology *in vivo*[7].

Acute myocardial infarction. A first-in-human trial (Noda et al., 2020) administered a single intravenous dose of CL2020 to three STEMI patients with left ventricular ejection fraction ≤45 percent following successful percutaneous coronary intervention. No adverse drug reactions were observed, and left ventricular ejection fraction and wall motion score index were markedly improved over the 12-week follow-up[9]. This human result translates the preclinical S1P–S1PR2 cardiac homing axis — characterized in rabbit[5] and large-animal models — into the clinical setting.

Dystrophic epidermolysis bullosa (EB). A Phase 1/2 open-label study (Fujita et al., 2021) of intravenous allogeneic CL2020 in adults with dystrophic EB demonstrated tolerability

without major safety concerns. A subset of patients showed substantial reduction in refractory ulcers within four weeks of a single IV infusion, alongside meaningful improvement in pain scores[10].

Neonatal hypoxic-ischemic encephalopathy (HIE). The SHIELD trial (Sato et al., 2024) administered single-dose intravenous CL2020 to nine neonates with moderate-to-severe HIE receiving therapeutic hypothermia, in a single-center open-label dose-escalation design. No major treatment-related safety concerns were identified; one neonate had transient mild γ-glutamyltransferase elevation that resolved without intervention. The majority of treated infants demonstrated developmental quotients within normal ranges at follow-up — encouraging early signals in a population for which therapeutic options beyond hypothermia remain limited[11].

Cervical traumatic spinal cord injury. A multicenter prospective single-arm clinical trial (Koda et al., 2024) of single-dose intravenous CL2020 in ten patients with severe cervical SCI (modified Frankel B1–B2, levels C4–C7) demonstrated favorable safety and tolerability without treatment-related severe adverse events. Statistically significant improvements were observed in ISNCSCI motor scores, activities-of-daily-living measures, and quality-of-life measures relative to baseline[12].

Across these human clinical trials — spanning neurology, cardiology, dermatology, and neonatal medicine — no reports of tumor formation, immune rejection requiring immunosuppression, or serious adverse events attributable to the cells themselves have emerged. This safety record is the direct consequence of validated derivation. It is not a generic property of any loosely defined cell population.

[8] Niizuma K, et al. Randomized placebo-controlled trial of CL2020, an allogenic muse cell-based product, in subacute ischemic stroke. J Cereb Blood Flow Metab (2023). PMID: 37756573 · [9] Noda T, et al. Safety and Efficacy of Human Muse Cell-Based Product for Acute Myocardial Infarction in a First-in-Human Trial. Circ J (2020). PMID: 32522904 · [10] Fujita Y, et al. Intravenous allogeneic multilineage-differentiating stress-enduring cells in adults with dystrophic epidermolysis bullosa: a phase 1/2 open-label study. J Eur Acad Dermatol Venereol (2021). PMID: 33656198 · [11] Sato Y, et al. Safety and tolerability of a Muse cell-based product in neonatal hypoxic-ischemic encephalopathy with therapeutic hypothermia (SHIELD trial). Stem Cells Transl Med (2024). PMID: 39401019 · [12] Koda M, et al. Safety and feasibility of intravenous administration of a single dose of allogenic-Muse cells to treat human cervical traumatic spinal cord injury: a clinical trial. Stem Cell Res Ther (2024). PMID: 39135172

The danger of unverified “MUSE” products

Products on the market under the “MUSE” label that were not produced using Dr. Dezawa’s validated protocols are not authentic Dezawa MuseCells®. They are not referenced in the peer-reviewed literature, and their phenotypic identity, functional S1PR2 expression, genomic stability, and safety profile are entirely uncharacterized.

This creates several layers of serious risk.

Tumorigenicity risk, unstudied. Without the stress-selection protocol and verification of SSEA-3-positive phenotypes, there is no scientific basis to assume non-tumorigenic behavior. Administering such cells to patients carries a theoretically serious oncogenic risk that has never been studied.

Homing failure. Without verified S1PR2 expression, cells cannot be expected to home to injury sites with the precision that is fundamental to the Dezawa MuseCell® therapeutic action. They may circulate, accumulate nonspecifically, or fail to engraft entirely.

Inappropriate engraftment. Cells not verified for controlled trilineage differentiation may fail to differentiate into tissue-compatible cells to integrate functionally — leading to unpredictable tissue responses.

Immune response, uncharacterized. Authentic Dezawa MuseCells® have a well-characterized low immunogenicity profile, as demonstrated in allogeneic studies without immunosuppression. Unverified products lack such an established profile and may provoke inflammatory or rejection responses.

> *Clinicians using unverified products inherit the uncertainty of those products — a risk that patients have not knowingly accepted.*

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What authentic characterization requires

For a product to legitimately claim Dezawa MuseCell® identity, it must meet the following scientifically established criteria — derived from Dr. Dezawa’s published protocols:

1. Expression of SSEA-3 confirmed by flow cytometry. **2.** Derivation through validated stress-selection methodology, including long-term trypsin exposure, hypoxia, and serum starvation. **3.** Demonstrated trilineage differentiation capacity *in vitro* across mesoderm, ectoderm, and endoderm lineages. **4.** Confirmed S1PR2 expression and functional S1P-mediated homing verified in appropriate assays. **5.** Confirmed non-tumorigenic behavior in animal xenograft models, with absence of teratoma formation in immunocompromised mouse assays. **6.** Validated genomic stability — no evidence of chromosomal abnormality or oncogene activation. **7.** Manufacturing under GMP-compliant conditions — including US cGMP per 21 CFR Parts 210/211 for clinical-grade product — with full lot-release testing.

These are not optional quality benchmarks. They are the minimum scientific requirements for a product to be legitimately associated with the Dezawa MuseCell® platform.

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An inflection point

Disclosure. I serve on the Science Advisory Board of MuseCell Innovations® PTE Ltd. (MCI) and have a direct professional interest in the accurate representation of the Dezawa MuseCell® science.

As a physician deeply engaged in regenerative medicine — and a board member of MCI — I believe our field stands at an inflection point. The science behind authentic Dezawa MuseCells® represents one of the most compelling and rigorously developed platforms in cellular therapy today: grounded in a precisely characterized molecular biology, a unique damage-sensing homing system, and a clinical safety record earned through multiyear investigation. That science — and the patients who stand to benefit from it — deserve vigorous protection.

The regenerative medicine community must hold itself to the same evidentiary standards expected of any serious therapeutic platform. A label is not a biology. A name is not a safety profile. The S1PR2-mediated homing precision, the intrinsic non-tumorigenic pluripotency, and the validated trilineage differentiation of authentic Dezawa MuseCells® do not transfer by nomenclature alone.

> *"Authentic Dezawa MuseCells® earned their scientific credibility through decades of rigorous investigation. Products that appropriate that name*

without earning it do not share that credibility — and must not be permitted to trade on it at the expense of patient safety."

When the field protects the integrity of scientifically validated platforms, it safeguards not only the credibility of regenerative medicine — but also the opportunity for transformative therapies to reach the patients who need them most.

— Joseph Purita, MD

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DISCLOSURE & ATTRIBUTION

Claims are based on published studies of Dezawa MuseCells® produced using the licensed intellectual property and exact methodologies of MuseCell Innovations®. Only Dezawa MuseCells® originating from MCI's manufacturing ecosystem and distributed through MCI-designated, licensed partners have the safety and clinical characteristics reported in the research.

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