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Critical evaluation of compositions and clinical relevance of Wharton's jelly-derived biologics

Annette M. Marleau^{1*} , Jocelynn R. Pearl², Patricia Juarez³, Paloma Almeida², Sara Miguel², Erendira Olvera Felix³, Francesco M. Marincola², Rachel West⁴, Lee Howard⁵, Diego Guerena^{2,6} and Edward Clay^{2,6}

Abstract

Background Wharton's jelly, the mucoid connective tissue that surrounds umbilical cord vessels, contains both acellular and cellular components with recognized relevance to regenerative medicine. The acellular extracellular matrix (ECM) is composed of collagen fibers, hyaluronic acid, proteoglycans, glycosaminoglycans, that provides a scaffold for bioactive molecules such as growth factors and cytokines that support structural integrity and tissue repair. The cellular component of native Wharton's jelly consists primarily of multipotent mesenchymal stromal cells (MSCs), which are leveraged in regenerative medicine for their differentiation capacity, trophic signaling, angiogenic activity, and immune modulatory activities. There is a growing commercial market for injectable, minimally manipulated Wharton's jelly allograft products for clinical use to provide structural support or cushioning. Although these products comprise ECM, they are often presumed or represented to also contain viable MSCs capable of providing therapeutic benefit.

Methods A comprehensive literature review was performed, examining published data on the biologic components of Wharton's jelly and common methods of processing and utilizing this tissue as a source of ECM or MSC-based therapeutics. Empirical laboratory analyses were also conducted on minimally manipulated Wharton's jelly tissue products to microscopically quantify total cell content, viable cell counts, and to assess the percentages of MSCs by flow cytometry.

Results Published literature shows that ECM-based preparations can support endogenous repair processes or serve as scaffolds in tissue engineering, but they do not contain therapeutically meaningful quantities of viable primary MSCs. To achieve any measurable biological or clinical effect using MSCs, administration of MSCs at defined therapeutic doses is required, typically ≥ 10 million MSCs for local delivery and 70–190 million cells for systemic infusion. These doses can only be obtained by intentionally isolating MSCs from fresh Wharton's jelly tissue and subsequently expanding them *in vitro*. Indeed, our analyses of minimally manipulated Wharton's jelly product samples show that these materials contain ECM with only trace levels of residual cells. Total cell counts in Wharton's jelly tissue preparations ranged from 3,369 to 111,170 cells per cubic centimeter, with 0–19.1% viability, and only rare viable MSCs.

Conclusions Minimally manipulated Wharton's jelly products should be viewed as acellular ECM preparations, comprising negligible MSCs and lacking the capacity to provide cell-mediated therapeutic benefits. An

*Correspondence:
Annette M. Marleau
annette.marleau@gmail.com

Full list of author information is available at the end of the article



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understanding of the compositions of ECM products and true MSC-based therapies is essential to ensure appropriate clinical use and responsible integration into regenerative medicine practices.

Keywords Wharton's jelly, Mesenchymal stem cells, Extracellular matrix, Regenerative medicine, Cell therapy

Therapeutically relevant cellular and Acellular materials in Wharton's jelly

The field of regenerative medicine seeks to restore or replace damaged tissues using biologic materials that recapitulate the biological processes of tissue or cellular repair. Perinatal tissues, such as the human umbilical cord, have been the focus of considerable research due to their accessibility, ethical acceptability, and abundance of bioactive molecules. The human umbilical cord is a vital structure that connects the developing fetus to the placenta, serving as a lifeline for exchange of oxygen, nutrients, and waste products between the mother and the developing fetus. At term, in humans, the umbilical cord is 40–60 cm long, with a girth of 1–2 cm [1]. The structure has outer covering comprising a layer of amniotic epithelium that encloses a mucoid connective tissue through which three vessels, a vein and two arteries, carry the oxygenated and deoxygenated blood between the placenta and fetus, respectively [1].

Wharton's jelly, the gelatinous connective tissue that supports the two umbilical arteries, has the function of resisting torsional and compressive stresses imposed on the umbilical vessels throughout gestation [2]. Wharton's jelly is rich in extracellular matrix (ECM) components, including collagen, chondroitin sulfate, hyaluronic acid, and sulfated proteoglycans. Additionally, this tissue harbors growth factors, cytokines, and extracellular vesicles, which may have therapeutic properties [1]. In Wharton's jelly, MSCs actively secrete bioactive factors that contribute to the structural integrity and biochemical milieu of the ECM [3]. While Wharton's jelly was once viewed as a waste product to be discarded after birth, it has more recently been explored as a source of cellular and extracellular material for regenerative medicine applications. Wharton's jelly is easily accessible and available since every birth presents an opportunity to harvest regenerative substances, offering advantages over other sources of therapeutic cells such as bone marrow or adipose tissue [1].

Wharton's jelly-derived products derive from the biologically distinct but complementary components, ECM and MSCs, which have each been investigated in the scientific and medical literature for their therapeutic potential [4]. ECM provides the structural and biochemical scaffold of the tissue, rich in collagen, glycosaminoglycans, and proteoglycans that maintain tissue hydration, facilitate cell adhesion, and retain growth factors that influence tissue repair [5–7]. Depending on how the ECM is processed, specific structural or functional

components can be selectively preserved, leveraged, or enhanced. Processing methods may enrich certain matrix elements, modify their bioactivity, or alter their mechanical properties, thereby influencing the intended therapeutic application and the performance of the final product [8]. MSCs are present throughout the ECM of Wharton's jelly but are particularly enriched in the perivascular region, which corresponds to the connective tissue immediately surrounding the umbilical cord arteries and vein [3, 9, 10]. While MSCs can be isolated from Wharton's jelly, yields from fresh tissue are typically modest unless specific isolation methods and reagents are applied to release the cells, followed by in vitro expansion. Table 1 provides a comparison of distinctive composition and mechanisms of action of MSCs and ECM from Wharton's jelly, emphasizing their distinct biological properties [6].

The need for a scientific appraisal of claims and misconceptions regarding the composition of marketed Wharton's jelly matrix products

There is an expanding commercial market for Wharton's jelly-derived biological products in the United States, which are typically presented as ready-to-use ECM allografts for regenerative medicine applications, supplied as cryogenically preserved viscous suspensions or gels that are injectable or implantable. These products are sourced from full-term umbilical cords donated with consent and are generally marketed as “minimally manipulated” Wharton's jelly allografts, highlighting both their processing methods and their regulatory classification. Minimally manipulated Wharton's jelly products are available for clinical use in the United States without full regulatory review under the Food and Drug Administration (FDA) Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P) regulations (21 CFR Part 1271). To qualify under this pathway, the criteria for a product include manufacturing processes that do not alter the tissue's original relevant characteristics, and homologous use, defined as use consistent with the native function of Wharton's jelly as a structural, cushioning and protective connective tissue. Specifically, homologous uses for Wharton's jelly may include replacement, support, or repair of structural tissues. Such indications may include structural scaffolding for cartilage repair and for wound healing such as for chronic skin ulcers or pressure sores, or surgical wound coverage. As additional examples, these products may be applicable for other aspects of soft tissue augmentation or support, for

Table 1 Biological characteristics of Wharton’s jelly extracellular matrix and mesenchymal stem cells

Aspect	Extracellular Matrix (ECM)	Mesenchymal Stem Cells (MSCs)
Composition	Acellular network of extracellular matrix and matrix-bound growth factors.	Stromal cells of mesodermal origin; fibroblast-like morphology, multipotent differentiation potential.
Primary Function	Mechanical support, tissue elasticity, biochemical cues for cell adhesion, proliferation, and differentiation.	Tissue repair via direct differentiation, secretion of trophic factors, immune modulation.
Molecular Components	Collagens, fibronectin, laminin, decorin, biglycan, hyaluronic acid, matrix-bound cytokines and growth factors (e.g., TGF- β , VEGF, FGF).	Surface markers CD73, CD90, CD105; negative for hematopoietic markers CD34 and CD45; produce cytokines, chemokines, growth factors, extracellular vesicles.
Mechanisms of Action	Biophysical scaffold that modulates cell behavior via integrin signaling and matrix stiffness; retains and presents bioactive molecules.	Paracrine signaling (secretion of cytokines and growth factors that promote angiogenesis, suppress inflammation, stimulate tissue repair); trilineage differentiation
Immunogenicity	Minimally immunogenic when decellularized; largely inert; lacks viable donor antigens.	Low immunogenicity due to HLA-G and lack of MHC class II; can actively suppress immune responses.
Complementarity	Provides a supportive niche for MSCs.	Able to repopulate or remodel ECM scaffolds, enhancing biointegration and repair.

example as subcutaneous fillers, or as injectable hydrogels to provide localized cushioning. Conversely, using these minimally manipulated Wharton’s jelly products to treat unrelated conditions, for example, for systemic immunomodulation or cardiac repair, would be considered non-homologous since these uses are outside the scope of the functions that Wharton’s jelly naturally performs in the body.

Minimally manipulated Wharton’s jelly products are tissue matrix preparations that have been processed to retain the fundamental structural characteristics of native ECM. Minimal manipulation of tissue involves gentle, non-disruptive processing techniques such as mechanical dissociation and washing steps. These steps are often followed by cryopreservation techniques optimized to maintain the architecture of ECM tissue fragments although it is not explicitly clarified whether these tissue-focused approaches also preserve resident MSCs. The methods for minimally processing Wharton’s jelly ECM contrast with the mainstay approaches used in tissue engineering applications in which ECM is typically subjected to deliberate decellularization through chemical, enzymatic, and/or physical methods. These techniques remove or degrade bioactive constituents including cells within Wharton’s jelly, often for the purpose of also altering the tissue’s mechanical properties and to improve immunological compatibility.

In instances where manufacturers do not disclose detailed compositions of Wharton’s jelly-derived biologics, product descriptions or claims leave room for assumptions or representations that these materials contain biologically active components beyond ECM. A particularly persistent and unsupported belief is that minimally manipulated Wharton’s jelly preparations contain clinically meaningful quantities of MSCs. Therefore, to address the ongoing ambiguities and controversies surrounding Wharton’s jelly-derived products, the following sections present a comprehensive analysis of

native Wharton’s jelly and its biologic derivatives. We herein review the compositions and therapeutic applicability of Wharton’s jelly-derived biologics, including a focused assessment of whether MSCs are meaningfully present in ECM-based tissue preparations.

Biological and clinical insights into Wharton’s jelly-derived mesenchymal stem cells

Wharton’s jelly-derived MSCs are perinatal cells that retain primitive characteristics while maintaining properties typical of adult MSCs [9]. Wharton’s jelly is readily accessible compared to other tissues, offering practical advantages over bone marrow and adipose-derived stem cell sources. Its ease of collection, coupled with the robust expansion potential of Wharton’s jelly MSCs and the presence of immune modulatory molecules makes Wharton’s jelly a highly attractive MSC source for regenerative medicine applications [9, 11]. Wharton’s jelly-derived MSCs have the prototypical features of MSCs defined by the International Society for Cellular Therapy [12] including fibroblast-like adherence to plastic and expression of the surface markers CD90, CD73 and CD105 [13]. MSCs from this tissue demonstrate strong proliferative capacity, multilineage differentiation potential (osteogenic, chondrogenic, and adipogenic lineages), and paracrine activity. Like MSCs from other tissues, Wharton’s jelly MSCs are also highly immune suppressive and have low immunogenicity. They express MHC class I antigens at low levels and do not express MHC class II or costimulatory molecules CD80, CD86, and CD40 but express HLA-G [11, 14, 15]. After exposure to pro-inflammatory stimuli such as treatment with IFN- γ or TNF- α , the upregulation of HLA-DR molecules on Wharton’s jelly MSCs is less as compared to that on MSCs sourced from bone marrow [16, 17]. Moreover, exposure to pro-inflammatory stimuli strongly upregulated the synthesis of immunosuppressive molecules by MSCs from Wharton’s jelly, including TGF- β and IL-10

release, and inducing indoleamine 2,3-dioxygenase (IDO) expression [17]. In mixed lymphocyte cultures, Wharton's jelly MSCs also exerted more significant effects on *in vitro* T cell activation and proliferation compared to bone marrow-derived MSCs [17].

Recognition that MSCs exert much of their activity through the activity of secreted factors has also driven growing interest in the MSC secretome and its constituents, such as extracellular vesicles and exosomes, as therapeutic candidates [18–20]. The secretome of cultured MSCs may confer advantages over MSCs themselves from the standpoint of product manufacturing including greater scalability, fewer release criteria, longer shelf life, and easier storage. In preclinical studies, secretome derived from WJ-MSCs induced *in vitro* proliferation and migration of fibroblasts that are critical for skin repair [21], scratch closure in an *in vitro* assay [22], and accelerated wound closure when delivered in a pluronic gel in an animal model [23]. Despite encouraging early evidence, broader and much more rigorous preclinical validation is still needed to advance MSC secretome toward clinical use for many of these indications.

Preclinical studies of Wharton's jelly MSCs for a variety of indications are abundant, whereas clinical investigations, though ongoing, remain limited in scale and maturity [1, 6]. Wharton's jelly MSCs have been explored for mechanisms of action and therapeutic potential for numerous indications including myocardial repair [24], osteoarthritis [25, 26], rheumatoid arthritis [27], graft-versus-host disease [28, 29], type 1 diabetes [30, 31], multiple sclerosis [32, 33], diabetic wound healing [34, 35], and bronchopulmonary dysplasia [36, 37]. Examples of clinical studies of Wharton's jelly MSCs include a randomized study of 61 patients with type 2 Diabetes Mellitus who received two intravenous infusions of Wharton's jelly MSCs at mean doses of $6.1 \pm 2.1 \times 10^7$ (1.0×10^6 /kg; range, 5.3 – 8.9×10^7), with the number of MSCs administered calculated based on body weight [38]. Treatment with Wharton's jelly MSCs improved β cell function and reduced the incidence of diabetic complications relative to control saline over a 36-month followup with a favorable safety profile. Wharton's jelly MSCs have also been examined for orthopedic indications, including an open-label Phase I/IIa trial in patients with osteoporotic vertebral compression fractures in which patients were randomized to receive daily teriparatide (parathyroid hormone) treatment alone or combined treatment of MSCs (4×10^7 cells by intramedullary injection and 2×10^8 cells intravenously one week later) [39]. Wharton's jelly MSC treatment improved pain and disability scores, and enhanced microarchitecture at 6–12 months compared to teriparatide alone. In a small phase I study of Wharton's jelly MSCs administered intramuscularly in diabetic patients with critical limb ischemia reported

no serious adverse events, administration of the cells into the ischemic lower limbs improved painfree walking time and functional scores at six months [40]. In a pilot phase I trial in patients with acute respiratory distress syndrome (ARDS) caused by COVID-19, subjects were assigned to receive three intravenous doses of Wharton's jelly MSCs: 1 infusion of 1×10^6 WJ-MSCs/kg or placebo within 48 h of invasive ventilation followed by 2 infusions of 0.5×10^6 WJ-MSCs/kg or placebo over 5 days [41]. The data showed that treatment was safe although the study treatment did not improve the dependency on ventilation or mortality endpoints. Overall, the early phase studies report that MSCs from Wharton's jelly are safe and well-tolerated, however, robust evidence of efficacy remains preliminary and large randomized controlled trials with longterm followup are still needed.

Wharton's jelly-derived MSCs: meeting clinically relevant dose thresholds

Yields of primary MSCs isolated from various tissue sites in the body are relatively low, although the number of MSCs isolated from a tissue depends on numerous factors including the donor's age, health status, and the isolation methods applied [42]. Since MSCs are relatively scarce in primary tissues, even optimized isolation from fresh, uncultured samples yields insufficient cells for therapeutic doses. For Wharton's jelly, the MSCs yields reported in the literature are often expressed per unit cord length or per unit tissue volume. A typical umbilical cord measure an average of 40–60 cm at term [1], and while some protocols utilize the entire cord to maximize primary MSC yields [43] other groups report procurement of shorter segments [44]. Multiple reports place observed yields of primary MSCs from Wharton's jelly in the range of 10^4 to 5×10^5 MSCs per cm of cord across studies with the exception of a single outlier report claiming yields of several million MSCs per cm [14, 45–50]. Theoretically, by applying a mid-figure of 10^5 MSCs per cm from a 50-cm full length umbilical cord, approximately 5.0×10^6 MSCs could be isolated before cell culture and expansion. In practice, many protocols do not process the full cord length, balancing potential yield against workflow and manufacturing logistics, and therefore would yield even fewer MSCs.

Consequently, even when employing optimal isolation techniques using fresh Wharton's jelly, the maximum theoretical yields of primary MSCs are too low for treatment of even a single subject without first expanding the cells *in vitro*. While there is no universally accepted minimum effective dose of MSCs, empirical evidence from reported positive outcomes across clinical trials from 2004 to 2018 identified minimum effective doses ranging from 70 to 190 million MSCs/patient/dose for MSCs administered intravenously [51]. Of the clinical trials that reported

dose response data, a narrower minimum effective dose between 100 and 150 million MSCs/subject was identified [51]. For indications relying on local MSC administration, effective doses tend to fall into a lower range. For example, in a meta-analysis of osteoarthritis clinical trials, the optimal dosing window was determined to be 50–100 million cells [52]. For local administration of MSCs to treat degenerative disc disease (i.e., intradiscal injection), signals of efficacy have been demonstrated using ranges of 10–25 million MSCs [53, 54]. Accordingly, even with optimized isolation methods, the MSCs recoverable from a native, unexpanded Wharton's jelly specimen are insufficient to meet clinically effective dosing thresholds for even a single patient.

Methods for producing therapeutic MSCs from Wharton's jelly prioritize maximizing MSC release from the native tissue followed by expansion of the cells in culture, which is required to generate a bank of clinically relevant cell doses. Significant effort has been invested in optimizing both the initial isolation processes and the downstream expansion phases for clinical translation. Wharton's jelly MSCs are typically isolated using two main approaches: explant methods and/or enzymatic digestion techniques [55]. In the explant method, Wharton's jelly is first rinsed to remove blood and debris and is then mechanically cut into small fragments, typically a few mm in size. These fragments are placed in tissue culture plates with growth medium to allow MSC outgrowth. After several days, the tissue pieces are removed and the adherent MSC monolayer that has formed is cultured for further expansion. This technique is relatively simple and preserves cell viability and functions. The enzymatic digestion method involves cutting the Wharton's jelly into fragments and subsequently incubating with a solution of proteolytic enzymes to degrade ECM and liberate the MSCs. After washing the MSCs, the suspension is then cultured in growth medium to support MSC expansion. Improper control of enzyme concentration or exposure time can lead to excessive matrix degradation and cellular damage, reducing the quality of the isolated MSC population. While differences in early culture behavior and yield of MSCs are observed, expanded Wharton's jelly MSCs from either approach are comparable with respect to the desired characteristics including viability, morphology, proliferation, immunophenotype, and differentiation potential [43, 44, 46, 56–60].

Wharton's jelly extracellular matrix as a regenerative resource

Wharton's jelly ECM is a rich, hydrated scaffold composed primarily of collagens, proteoglycans, and glycosaminoglycans. Collagen types I, III, IV, and V provide structural support, while proteoglycans such as decorin, biglycan, and versican, along with hyaluronic acid and

other glycosaminoglycans, maintain tissue hydration, viscoelasticity, and facilitate cell adhesion [5, 7]. The ECM also serves as a reservoir for growth factors and bioactive molecules, contributing to the tissue's potential regenerative and trophic properties. These components create a viscoelastic matrix that supports MSCs and modulates cellular signaling. Embedded and bound to ECM components are a variety of growth factors that regulate cell behavior and contribute to the regenerative potential of the tissue including transforming growth factor-beta (TGF- β), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), insulin-like growth factor (IGF-1) and platelet-derived growth factor (PDGF) [61]. Collectively, this ECM composition, which is dense in structural proteins and enriched with trophic factors, underpins the reparative properties attributed to Wharton's jelly.

Wharton's jelly can be processed into structural allograft tissue using two general approaches, minimal manipulation and decellularization, which differ in that the former preserves the native architecture and components of the tissue, whereas the latter deliberately removes cellular material to produce a modified ECM. Minimally manipulated Wharton's jelly products preserve the native ECM, rich in collagen, glycosaminoglycans, and hyaluronic acid, although assertions that such processing also maintains viable cellular content remain largely speculative. Minimal manipulation of Wharton's jelly refers to processing steps that preserve the tissue's original structural and functional characteristics without altering its biological properties, for example, simple rinsing or cutting of tissue. In contrast, decellularization employs chemical, enzymatic, or mechanical methods specifically intended to remove cells from the tissue, resulting in a fundamentally different type of product [62–64]. Mechanical methods, such as freeze–thaw cycles or controlled agitation, physically disrupt cell membranes with minimal impact on ECM structure. Enzymatic methods use agents like DNase to degrade nucleic acids and facilitate removal of cellular debris without extensively altering matrix proteins. Chemical decellularization relies on detergents such as sodium dodecyl sulfate or Triton X-100 to solubilize cell membranes and extract intracellular components, effectively clearing cellular material while aiming to maintain the integrity of collagen, glycosaminoglycans, and other ECM constituents. Following decellularization, the remaining ECM may be lyophilized into a dry matrix or suspended to form gels, hydrogels, or injectable formulations. Some commercial preparations also incorporate stabilizers or buffers to improve handling characteristics and shelf-life. Table 2 summarizes the biological compositions, processing methods, and forms of ECM, including minimally processed and decellularized, as well as

Table 2 Overview of Processing and Formulations of Wharton’s Jelly-Derived Biologics

WJ Product Type	Composition	Prospective Clinical Applications	Physical Form(s)	Key Processing Steps	Admin- istration Method
MSCs	Living cells	Tissue repair, wound healing, autoim- munity, cardiovascular diseases, GVHD, neurological disorders, other conditions	Cell suspension	Explant culture or enzymatic treatment of WJ fragments, isolate MSCs, seed and expand MSCs in culture	Inject- able
MSC secretome	Acellular conditioned medium: extracel- lular vesicles, soluble bioactive molecules	As above for WJ-MSCs	Liquid, concentrated filtrate or lyophilized powder	Culture WJ-MSCs, collect conditioned medium, filter/centrifuge, concentrate or lyophilize	Inject- able
Decellular- ized ECM	Acellular ECM, may have lim- ited or no growth factors	Broad uses in tissue engineering as various customized scaffolds Structural support, tissue protection and cushioning (e.g., to supplement wound healing, surgical grafting, or for cartilage, ligament, muscle etc.	Gel, suspension, solid or semi-solid scaffold, tissue fragments, or dry powder	Decellularize WJ using physical, chemi- cal, and/or enzymatic methods, formu- late in gel, suspension or other form (or lyophilize or micronize for powder)	Inject- able or implant- able
Minimally manipu- lated ECM	Acellular ECM, growth factors	Structural support, tissue protection and cushioning	Gel, suspension, solid or semi-solid forms, or tissue fragments	Gentler or minimal processing of WJ, e.g., rinsing and cutting tissue, formu- late in gel, suspension or other form	Inject- able or implant- able

ECM = extracellular matrix; MSCs = mesenchymal stem cells; WJ = Wharton’s jelly

MSCs from Wharton’s jelly. These data also underscore how these products may also be deployed in different therapeutic settings.

Decellularization methods are widely employed in tissue engineering to transform the ECM components into customizable scaffolds with tailored structural, mechanical, and biochemical properties. When applied to Wharton’s jelly, these techniques enable the production of engineered extracellular matrix materials that extend far beyond simple cell removal, supporting applications that native tissue cannot achieve. Following decellularization, the ECM can be lyophilized and ground into powders, then solubilized and re-gelled to form hydrogels, freeze-dried and crosslinked to create sponges, or formulated into hydrogel-microcarrier systems for cell delivery [65–71]. Advanced fabrication methods, such as 3D molding, electrospinning, or blending with synthetic polymers, can be performed using decellularized ECM to produce scaffolds with customizable mechanical and architectural properties.

Decellularized ECM can be seeded with culture-expanded MSCs, other cell types such as fibroblasts, extracellular vesicles, and/or tissue-specific cells, supporting regeneration and functional tissue integration [72–74]. Unlike native Wharton’s jelly, which contains few MSCs, decellularized Wharton’s jelly ECM provides a dense, instructive scaffold that supports the attachment, survival, and functional differentiation of exogenously seeded MSCs. For example, in one study, decellularized Wharton’s jelly ECM was used as a scaffold to culture Wharton’s jelly MSCs and intervertebral

disc cells, which demonstrated MSC proliferation, differentiation of intervertebral disc cells, and maintenance of their viability and homeostasis [75]. In another study, an injectable hydrogel from decellularized Wharton’s jelly ECM was combined with Wharton’s jelly mesenchymal stem cells and myocardial repair was examined in ischemic rats. This composition significantly improved cardiac function recovery, reduced scar formation, and promoted cardiomyogenesis as compared to MSCs alone or ECM hydrogels alone, providing evidence for synergistic activity of MSCs seeded on the tissue scaffold [76]. In another study, decellularized Wharton’s jelly hydrogel was combined with CD56+ exosomes derived from MSCs, and the injectable composition was used in an in vivo model of meniscal tear. The Wharton’s jelly hydrogel/exosomes promoted meniscal chondrogenesis, improved meniscal ECM remodeling, and prevented articular cartilage degeneration, which accelerated meniscus healing [72]. Decellularized Wharton’s jelly ECM has also been found to serve as a chemoattractive scaffold in vivo in a calvarial defect model [64]. A matrix comprising bone marrow MSCs cultured on Wharton’s jelly ECM was implanted into mice along with green fluorescent protein-labeled osteocytes, and the osteocytes were observed to migrate into the matrix within 24 hours and were retained there for up to two weeks. These pre-clinical studies support the conclusion that decellularized Wharton’s jelly transforms an otherwise cellsparse tissue into a bioactive scaffold, providing MSCs with a niche that amplifies their survival, proliferation, and regenerative capacity.

Minimally manipulated Wharton’s jelly under the microscope: a quantitative assessment of cell content

Minimally manipulated Wharton’s jelly products are typically marketed as tissue-matrix allografts, however, the specific processing steps used to generate them are typically not described, and their final composition is likewise not clearly defined. These products are not expected to be fully decellularized since certain mechanical, chemical, or enzymatic methods would exceed the definition of minimal manipulation. However, processing methods such as rinsing, mechanical trimming, low-shear agitation, or filtration may be used to generate these preparations (Table 3).

Although direct analyses of cellular content in minimally manipulated Wharton’s jelly products may not be available, there is evidence indicating that some cryopreserved Wharton’s jelly preparations may be effectively acellular, even without the application of a formal decellularization process. This would likely reflect the absence of intentional methods to preserve MSCs during processing. In a published report, viable MSCs could not be isolated from cryopreserved Wharton’s jelly tissue fragments after thawing [47]. Since standard cryopreservation methods are generally insufficient to maintain MSC viability within intact tissues, specialized cryoprotectants and controlled-rate freezing protocols have been explored to identify optimized conditions for preserving MSC viability, supporting tissue banking strategies for MSC-based therapies [77].

We examined commercially available, cryogenically preserved human Wharton’s jelly specimens sourced from different vendors and marketed as minimally manipulated tissues. Six different specimens were thawed and analyzed to quantify the total cells and viable cells (Table 3). These studies were conducted in triplicate for each product and repeated in two independent experiments conducted in different laboratories. Examination of total cell counts by trypan blue exclusion showed that all six minimally manipulated Wharton’s jelly products

contained very low total cell numbers ranging from 3369 cells/cc to 111,170 cells/cc. In terms of the viable cell content, between 0 and 19% of the cells were viable, with the absolute numbers of viable cells ranging from no cells up to 18,348 cells/cc. These data demonstrate that commercial minimally manipulated Wharton’s jelly allografts are virtually devoid of viable cells. It is also worth noting that these viable cell numbers are orders of magnitude below a minimally effective therapeutic dose of MSCs, and the residual MSCs are insufficient to exert any meaningful biological or therapeutic activity.

Additionally, flow cytometry was used to assess the MSC content in the commercial Wharton’s jelly samples by assessing the typical MSC surface markers CD90, CD105, and CD73. Data for culture-expanded Wharton’s jelly-derived MSCs were also included as positive controls, which showed uniform staining for CD90, CD105, and CD73 (Fig. 1). Expectedly, negative control cells comprising peripheral blood mononuclear cells comprised virtually no MSCs. Analysis of three minimally manipulated Wharton’s jelly samples that contained cellular material revealed highly variable staining for the MSC surface markers. Based on the very low event counts and low forward scatter profiles of the cells, it is possible that the samples contained smaller, dying, or fragmented MSCs, which often lose surface marker expression.

In another experiment, the Wharton’s jelly samples were cultured for 24 hours and then visualized microscopically to evaluate the morphology of the biological material alongside in-house cultured Wharton’s jelly-derived MSCs (Fig. 2). As anticipated, the cultures of MSCs showed adherence of cells to the tissue culture vessel, displaying the expected fibroblast-like morphology. In contrast, the commercial matrix preparations comprised a gelatinous structure in which cells were not visible.

Taken together, these data clearly show that minimally manipulated Wharton’s jelly products contain only trace, largely non-viable MSCs, and as such, should be regarded as ECM-based therapies rather than cell-based interventions, with claims of MSC-mediated therapeutic effects considered unsupported.

Table 3 Total cells and viable cells in commercial Wharton’s jelly matrix preparations

Sample	Total Cells	Cells/cc	% Viable	Viable Cells/cc
1	9,375	4,261	7.5	492
2	62,500	28,409	19.05	4,329
3	261,083	111,170	15.77	18,348
4	7,749	3,369	0	0
5	45,500	81,185	1.5	596
6	16,999	14,897	8.63	956

Minimally manipulated Wharton’s jelly samples purchased from commercial vendors (6 different products) were thawed and analyzed for cell content. Total cells and viable cells were quantified by manual counting methods (trypan blue exclusion) in triplicate samples. The values shown represent the average total number of cells, number of cells/cc, and number of viable cells/cc from the two separate experiments conducted in different laboratories

Conclusions
Wharton’s jelly-derived products represent a promising frontier in regenerative medicine, offering accessible sources of biologically active materials for tissue repair and structural support. These products encompass two complementary components: the ECM, which provides a hydrated, growth factor-rich scaffold capable of supporting tissue regeneration, and MSCs, which contribute multipotent differentiation potential and a broad spectrum of trophic and immunomodulatory activities. While both components have demonstrated preclinical and, to

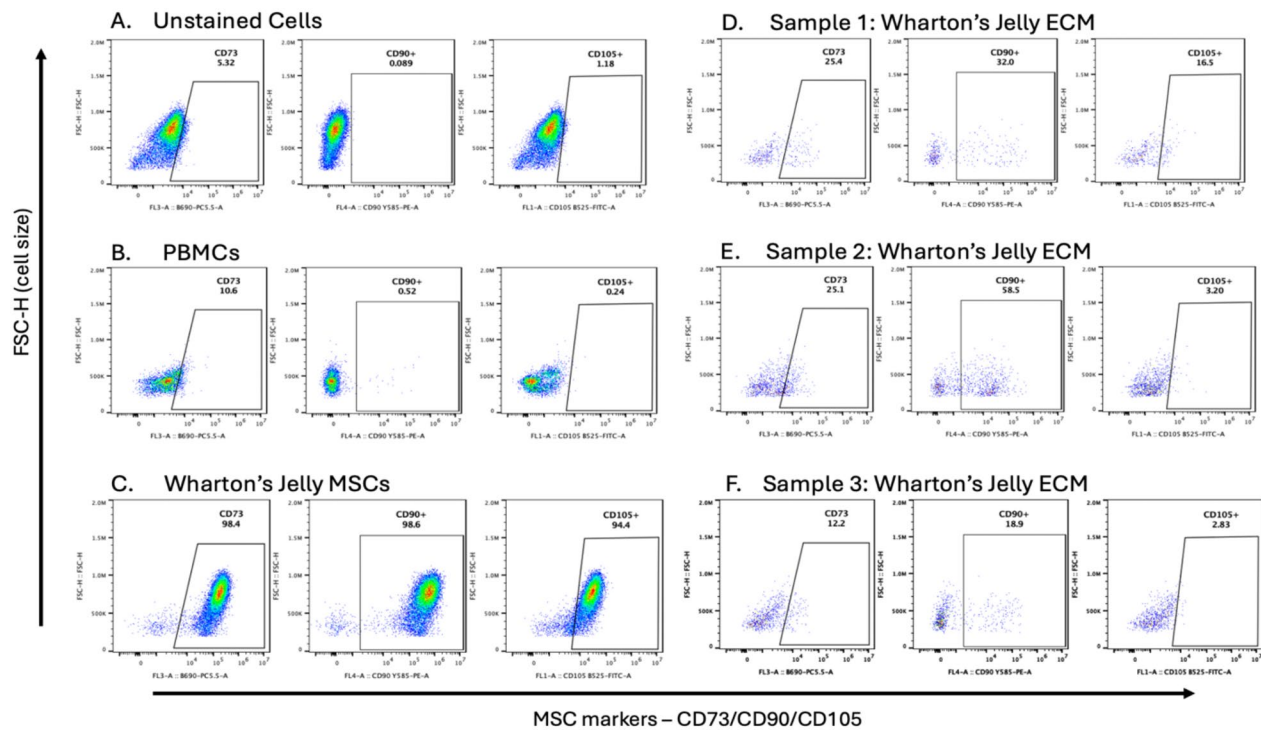


Fig. 1 Flow cytometric assessment of mesenchymal stem cell markers in Wharton's jelly-derived biologics. Commercially sourced Wharton's jelly matrix samples purchased from different vendors ($n=3$) were analyzed by flow cytometry for residual MSCs using the canonical MSC surface markers CD73, CD90, and CD105. An additional three commercial samples did not have sufficient cells to apply to this analysis. Events were gated on forward scatter versus fluorescence intensity for surface markers. MSCs are presented as the percentage of total counted events. Cultured Wharton's jelly-derived MSCs served as positive controls. Also shown are dot plots for unstained cells and peripheral blood mononuclear cells (PBMCs), which contain negligible MSCs, as negative controls

a more limited extent, clinical efficacy for degenerative, inflammatory, and traumatic conditions, they differ fundamentally in composition, mechanisms of action, and appropriate therapeutic application. This distinction underscores the necessity of a precise biological understanding of their compositions and functions to inform their development and use.

The expanding commercial availability of injectable Wharton's jelly products comprising minimally manipulated ECM has highlighted a critical need for clarity of product compositions. Despite misconceptions to the contrary, this study demonstrates that ECM-based Wharton's jelly products are largely devoid of viable MSCs. In fact, the MSC quantities in minimally manipulated Wharton's jelly are insufficient to have meaningful

biological activity, being present at levels that are orders of magnitude lower than a minimum effective dose for a true MSC-based therapy. Even with optimal isolation conditions for MSCs directly from fresh Wharton's jelly, achieving therapeutic cell doses from this tissue requires in vitro culture and expansion of isolated MSCs. The scientific evidence presented from the literature reinforces that it is essential to identify the compositions of ECM preparations to avoid mischaracterizing these products. With careful scientific scrutiny and judicious clinical deployment, Wharton's jelly products have the potential to meaningfully advance regenerative therapies while avoiding overextension beyond their biologically appropriate roles.

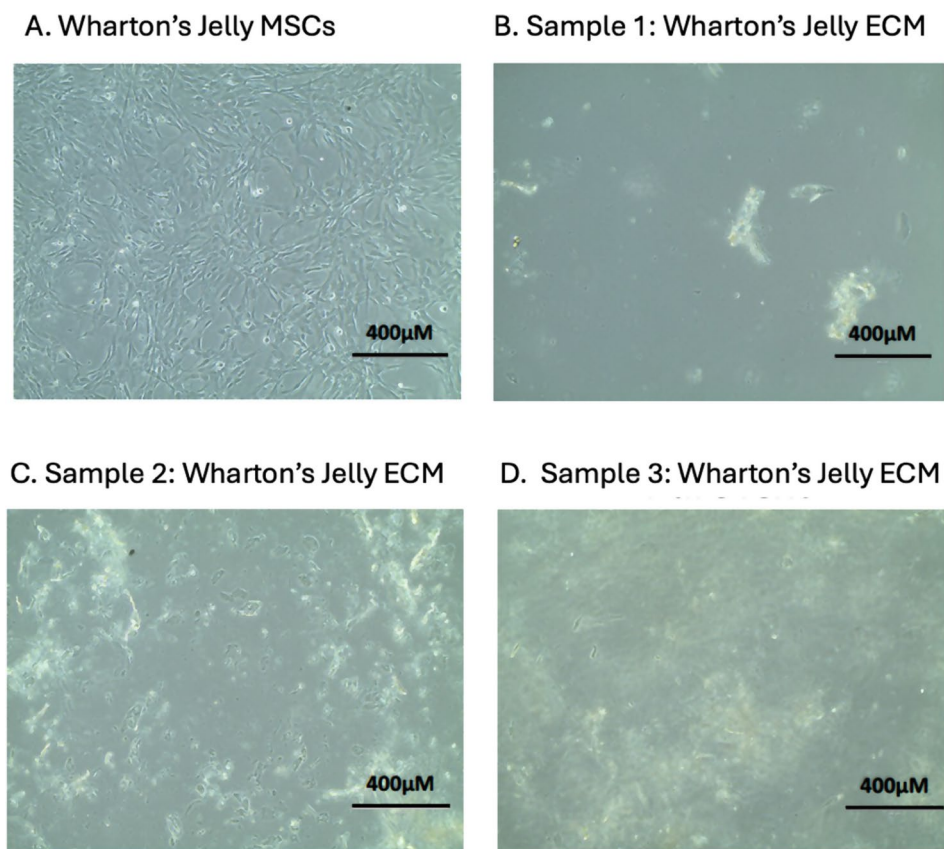


Fig. 2 Morphology of commercial Wharton's jelly extracellular matrix preparations compared to cultured MSCs. Commercially sourced Wharton's jelly matrix samples were thawed, plated, and cultured for 24 hours before microscopic evaluation. In parallel, in-house cultured Wharton's jelly-derived MSCs were included as positive controls. Representative images are shown for three independent commercial samples

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Authors contributions

AMM, JRP, PJ, and EC designed the experiments. JRP, PJ, PA, SM, and EOF conducted the experiments. AMM compiled data from source articles to create the tables and wrote the manuscript. JRP, PJ, FMM, RW, LH, DG, and EC critically revised the manuscript for content. EC conceptualized the manuscript. All authors read and approved the final manuscript.

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Data availability

All relevant data analyzed during this study are included in this published article. No proprietary materials were generated in the course of this work.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors consent to publication of this manuscript.

Competing interests

This review was supported by TAM Global and Cellular Performance Institute. All authors are employees or consultants of TAM Global and/or Cellular Performance Institute. The authors declare no other competing interests.

Author details

¹Immune Advisors, San Diego, CA 92122, USA

²Translational and Advanced Medical (TAM) Global, Nashville, TN 37011, USA

³Center for Scientific Research and Higher Education at Ensenada, Ensenada, Baja California 22860, Mexico

⁴Longevity LA, Los Angeles, CA 90025, USA

⁵Compass Human Performance, Nashville, TN 37205, USA

⁶Cellular Performance Institute, Tijuana, Baja California 22504, Mexico

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References

1. Davies JE, Walker JT, Keating A. Concise review: Wharton's jelly: the rich, but enigmatic, source of mesenchymal stromal cells. *Stem Cells Transl Med*. 2017;6(7):1620–30.
2. Ferguson VL, Dodson RB. Bioengineering aspects of the umbilical cord. *Eur J Obstet Gynecol Reprod Biol*. 2009;144 Suppl 1:S108–13.
3. Drobiova H, et al. Wharton's jelly mesenchymal stem cells: a concise review of their secretome and prospective clinical applications. *Front Cell Dev Biol*. 2023;11:1211217.
4. Gornicki T, et al. Wharton's jelly mesenchymal stem cells (WJ-MSCs), a "holy grail" in tissue bioengineering and reconstructive medicine. *Biomed Pharmacother*. 2025;192:118570.
5. Sobolewski K, et al. Collagen and glycosaminoglycans of Wharton's jelly. *Biol Neonate*. 1997;71(1):11–21.
6. Main BJ, et al. Umbilical Cord-Derived Wharton's jelly for regenerative medicine applications: a systematic review. *Pharmaceuticals (basel)*. 2021;14(11).

7. Gogiel T, Bankowski E, Jaworski S. Proteoglycans of Wharton's jelly. *Int J Biochem Cell Biol.* 2003;35(10):1461–69.
8. Ramos-Rodriguez DH, Leach JK. Decellularized cell-secreted extracellular matrices as biomaterials for tissue engineering. *Small Sci.* 2025;5(2):2400335.
9. Troyer DL, Weiss ML. Wharton's jelly-derived cells are a primitive stromal cell population. *Stem Cells.* 2008;26(3):591–99.
10. Donders R, et al. Human Wharton's jelly-derived stem cells display a distinct immunomodulatory and proregenerative transcriptional signature compared to bone marrow-derived stem cells. *Stem Cells Dev.* 2018;27(2):65–84.
11. La Rocca G, et al. Isolation and characterization of oct-4+/HLA-G+ mesenchymal stem cells from human umbilical cord matrix: differentiation potential and detection of new markers. *Histochem Cell Biol.* 2009;131(2):267–82.
12. Dominici M, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International society for cellular therapy position statement. *Cytotherapy.* 2006;8(4):315–17.
13. Kim DW, et al. Wharton's jelly-derived mesenchymal stem cells: phenotypic characterization and optimizing their therapeutic potential for clinical applications. *Int J Mol Sci.* 2013;14(6):11692–712.
14. Weiss ML, et al. Immune properties of human umbilical cord Wharton's jelly-derived cells. *Stem Cells.* 2008;26(11):2865–74.
15. Huang P, et al. Comparison of biological characteristics of human umbilical cord Wharton's jelly-derived mesenchymal stem cells from extremely pre-term and term infants. *Tissue Eng Regen Med.* 2023;20(5):725–37.
16. Prasanna SJ, et al. Pro-inflammatory cytokines, IFN γ and TNF α , influence immune properties of human bone marrow and Wharton jelly mesenchymal stem cells differentially. *PLoS One.* 2010;5(2):e9016.
17. Deuse T, et al. Immunogenicity and immunomodulatory properties of umbilical cord lining mesenchymal stem cells. *Cell Transpl.* 2011;20(5):655–67.
18. Park KS, et al. Enhancement of therapeutic potential of mesenchymal stem cell-derived extracellular vesicles. *Stem Cell Res Ther.* 2019;10(1):288.
19. Vizoso FJ, et al. Mesenchymal stem cell secretome: toward cell-free therapeutic strategies in regenerative medicine. *Int J Mol Sci.* 2017;18(9).
20. Trigo CM, et al. Mesenchymal stem cell secretome for regenerative medicine: where do we stand? *J Adv Res.* 2025;70:103–24.
21. Widowati W, et al. The potential of human Wharton's jelly mesenchymal stem cells secretome based topical gel for therapeutic application. *Avicenna J Med Biotechnol.* 2024;16(4):233–43.
22. Aw YB, et al. Development and functional testing of a novel in vitro delayed scratch closure assay. *Histochem Cell Biol.* 2024;162(3):245–55.
23. Chin JS, et al. Secretome from prolonged high-density human Wharton's jelly stem cell culture accelerates wound healing in both in vitro and in vivo models. *Int Wound J.* 2025;22(5):e70033.
24. Kwieciën E, et al. Umbilical cord matrix (Wharton jelly) mesenchymal stem cells in Next-generation myocardial repair and regeneration: mechanisms and pre-clinical evidence. *Curr Cardiol Rev.* 2025;21(5):76–103.
25. Ghamrawi A, et al. Wharton's jelly mesenchymal stem cells: shaping the future of osteoarthritis therapy with advancements in chitosan-hyaluronic acid scaffolds. *Stem Cells Dev.* 2025;34(1–2):1–16.
26. Aratikatla A, et al. Wharton's jelly and osteoarthritis of the knee. *Br Med Bull.* 2024;149(1):13–31.
27. Kannan S, et al. Characteristics of pooled Wharton's jelly mesenchymal stromal cells (WJ-MSCs) and their potential role in rheumatoid arthritis treatment. *Stem Cell Rev Rep.* 2022;18(5):1851–64.
28. Pochon C, et al. Wharton's jelly-derived stromal cells and their cell therapy applications in allogeneic haematopoietic stem cell transplantation. *J Cell Mol Med.* 2022;26(5):1339–50.
29. McGuirk JP, et al. Wharton's jelly-derived mesenchymal stromal cells as a promising cellular therapeutic strategy for the management of graft-versus-host disease. *Pharmaceuticals (basel).* 2015;8(2):196–220.
30. Al Madhoun A, et al. Clinical application of umbilical cord mesenchymal stem cells preserves beta-cells in type 1 diabetes. *Stem Cells Transl Med.* 2024;13(2):101–06.
31. Mrahleh MA, et al. Human Wharton's jelly-derived mesenchymal stromal cells primed by tumor necrosis factor- α and interferon- γ modulate the innate and adaptive immune cells of type 1 diabetic patients. *Front Immunol.* 2021;12:732549.
32. Perussolo MC, et al. Cellular therapy in experimental autoimmune encephalomyelitis as an adjuvant treatment to translate for multiple sclerosis. *Int J Mol Sci.* 2024;25(13).
33. Donders R, et al. Human Wharton's jelly-derived stem cells display immunomodulatory properties and transiently improve rat experimental autoimmune encephalomyelitis. *Cell Transpl.* 2015;24(10):2077–98.
34. Nilforoushzadeh MA, et al. Promotion of cutaneous diabetic wound healing by subcutaneous administration of Wharton's jelly mesenchymal stem cells derived from umbilical cord. *Arch Dermatol Res.* 2023;315(2):147–59.
35. Nilforoushzadeh MA, et al. Topical spray of Wharton's jelly mesenchymal stem cells derived from umbilical cord accelerates diabetic wound healing. *J Cosmet Dermatol.* 2022;21(10):5156–67.
36. Moreira A, et al. Intranasal delivery of human umbilical cord Wharton's jelly mesenchymal stromal cells restores lung alveolarization and vascularization in experimental bronchopulmonary dysplasia. *Stem Cells Transl Med.* 2020;9(2):221–34.
37. O'Reilly M, et al. Late rescue therapy with cord-derived mesenchymal stromal cells for established lung injury in experimental bronchopulmonary dysplasia. *Stem Cells Dev.* 2020;29(6):364–71.
38. Hu J, et al. Long term effect and safety of Wharton's jelly-derived mesenchymal stem cells on type 2 diabetes. *Exp Ther Med.* 2016;12(3):1857–66.
39. Shim J, et al. Safety and efficacy of Wharton's jelly-derived mesenchymal stem cells with teriparatide for osteoporotic vertebral fractures: a phase I/IIa study. *Stem Cells Transl Med.* 2021;10(4):554–67.
40. Ashoobi MT, et al. Wharton's jelly mesenchymal stem cells transplantation for critical limb ischemia in patients with type 2 diabetes mellitus: a preliminary report of phase I clinical trial. *Cell Tissue Res.* 2024;395(2):211–20.
41. Pochon C, et al. Efficacy of Wharton jelly mesenchymal stromal cells infusions in moderate to severe SARS-Cov-2 related acute respiratory distress syndrome: a phase 2a double-blind randomized controlled trial. *Front Med (Lausanne).* 2023;10:1224865.
42. Malicev E, Jazbec K. An overview of mesenchymal stem cell heterogeneity and concentration. *Pharmaceuticals (basel).* 2024;17(3).
43. Varaa N, et al. Wharton's jelly mesenchymal stem cell: various protocols for isolation and differentiation of hepatocyte-like cells. *Narrative Rev. Iran J Med Sci.* 2019;44(6):437–48.
44. Chu W, et al. A GMP-compliant manufacturing method for Wharton's jelly-derived mesenchymal stromal cells. *Stem Cell Res Ther.* 2024;15(1):131.
45. Vangsness CT, Sternberg H, Harris L. Umbilical cord tissue offers the greatest number of harvestable mesenchymal stem cells for research and clinical application: a literature review of different harvest sites. *Arthroscopy.* 2015;31(9):1836–43.
46. Tsagias N, et al. Isolation of mesenchymal stem cells using the total length of umbilical cord for transplantation purposes. *Transfus Med.* 2011;21(4):253–61.
47. Chatzistamatiou TK, et al. Optimizing isolation culture and freezing methods to preserve Wharton's jelly's mesenchymal stem cell (MSC) properties: an MSC banking protocol validation for the Hellenic cord blood Bank. *Transfusion.* 2014;54(12):3108–20.
48. Karahuseyinoglu S, et al. Biology of stem cells in human umbilical cord stroma: in situ and in vitro surveys. *Stem Cells.* 2007;25(2):319–31.
49. Fu YS, et al. Transformation of human umbilical mesenchymal cells into neurons in vitro. *J Biomed Sci.* 2004;11(5):652–60.
50. Fong CY, et al. Derivation efficiency, cell proliferation, freeze-thaw survival, stem-cell properties and differentiation of human Wharton's jelly stem cells. *Reprod Biomed Online.* 2010;21(3):391–401.
51. Kabat M, et al. Trends in mesenchymal stem cell clinical trials 2004–2018: is efficacy optimal in a narrow dose range? *STEM Cells Transl Med.* 2020;9(1):17–27.
52. Muthu S, et al. What is the clinically significant ideal mesenchymal stromal cell count in the management of osteoarthritis of the knee? - meta-analysis of randomized controlled trials. *J Clin Orthop Trauma.* 2022;25:101744.
53. Noriega DC, et al. Intervertebral disc repair by allogeneic mesenchymal bone marrow cells: a randomized controlled trial. *Transplantation.* 2017;101(8):1945–51.
54. Bates D, et al. Low-dose mesenchymal stem cell therapy for discogenic pain: safety and efficacy results from a 1-year feasibility study. *Future Sci OA.* 2022;8(5):FSO794.
55. Mushahary D, et al. Isolation, cultivation, and characterization of human mesenchymal stem cells. *Cytometry A.* 2018;93(1):19–31.
56. Buyl K, et al. Evaluation of a new standardized enzymatic isolation protocol for human umbilical cord-derived stem cells. *Toxicol In Vitro.* 2015;29(6):1254–62.
57. Han YF, et al. Optimization of human umbilical cord mesenchymal stem cell isolation and culture methods. *Cytotechnology.* 2013;65(5):819–27.
58. Skiles ML, et al. Comparison of umbilical cord tissue-derived mesenchymal stromal cells isolated from cryopreserved material and extracted by explantation and digestion methods utilizing a split manufacturing model. *Cytotherapy.* 2020;22(10):581–91.

59. Yoon JH, et al. Comparison of explant-derived and enzymatic digestion-derived MSCs and the growth factors from Wharton's jelly. *Biomed Res Int*. 2013;2013:428726.
60. Zheng S, et al. A robust and highly efficient approach for isolation of mesenchymal stem cells from Wharton's jelly for tissue repair. *Cell Transpl*. 2022;31:9636897221084354.
61. Sobolewski K, et al. Wharton's jelly as a reservoir of peptide growth factors. *Placenta*. 2005;26(10):747–52.
62. Kochetova ES, et al. Selection of optimal protocol for decellularization of extracellular matrix of mesenchymal stromal cells of human umbilical cord tissue. *Bull Exp Biol Med*. 2025;178(4):535–40.
63. Dubus M, et al. Decellularization of Wharton's jelly increases its bioactivity and antibacterial properties. *Front Bioeng Biotechnol*. 2022;10:828424.
64. Jadalannagari S, et al. Decellularized Wharton's jelly from human umbilical cord as a novel 3D scaffolding material for tissue engineering applications. *PLoS One*. 2017;12(2):e0172098.
65. Beiki B, Zeynali B, Seyedjafari E. Fabrication of a three dimensional spongy scaffold using human Wharton's jelly derived extra cellular matrix for wound healing. *Mater Sci Eng C Mater Biol Appl*. 2017;78:627–38.
66. Ramzan F, et al. Decellularized human umbilical tissue-derived hydrogels promote proliferation and chondrogenic differentiation of mesenchymal stem cells. *Bioeng (Basel)*. 2022;9(6).
67. Penolazzi L, et al. Wharton's jelly-derived multifunctional hydrogels: new tools to promote intervertebral disc regeneration in vitro and ex vivo. *J Biomed Mater Res A*. 2024;112(7):973–87.
68. Wei C, et al. Enhancing the maturity of in vitro engineered cartilage from Wharton's jelly-derived photo-crosslinked hydrogel using dynamic bioreactors and its in vivo outcomes in animal models. *Regen Biomater*. 2025;12:rbaf037.
69. Lavrand A, et al. Hydrogels from Wharton's jelly as alternative to conventional extracellular matrix-based constructs. *Int J Biol Macromol*. 2025;328(Pt 1):147552.
70. Tajbakhsh F, et al. Wharton's Jelly Hydrogel: an innovative artificial ovary for xenotransplantation of isolated human ovarian follicles. *Biol (Basel)*. 2025;14(10).
71. Najafi R, et al. Fabrication and optimization of multilayered composite scaffold made of sulfated alginate-based nanofiber/decellularized Wharton's jelly ECM for tympanic membrane tissue engineering. *Int J Biol Macromol*. 2023;253(Pt 6):127128.
72. Kang S, et al. Injectable decellularized Wharton's jelly hydrogel containing CD56(+) umbilical cord mesenchymal stem cell-derived exosomes for meniscus tear healing and cartilage protection. *Mater Today Bio*. 2024;29:101258.
73. Converse GL, et al. Wharton's jelly matrix decellularization for tissue engineering applications. *Methods Mol Biol*. 2018;1577:25–33.
74. Wang Y, et al. Extracellular matrix deposited by Wharton's jelly mesenchymal stem cells enhances cell expansion and tissue specific lineage potential. *Am J Transl Res*. 2018;10(11):3465–80.
75. Penolazzi L, et al. Extracellular matrix from Decellularized Wharton's jelly improves the behavior of cells from degenerated intervertebral disc. *Front Bioeng Biotechnol*. 2020;8:262.
76. Tavajjohi Z, et al. Therapeutic Performance of hydrogel-derived extracellular Wharton's jelly matrix and Wharton's jelly mesenchymal stem cells in repairing infarcted myocardium of ischemic rats: a preclinical study. *Macromol Biosci*. 2025;25(9):e70007.
77. Shivakumar SB, et al. DMSO- and serum-free cryopreservation of Wharton's jelly tissue isolated from human umbilical cord. *J Cell Biochem*. 2016;117(10):2397–412.

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