Biologic Scaffolds for Regenerative Medicine 2025 Abstract

Title: A novel chemotactic factor derived from the extracellular matrix protein decorin recruits mesenchymal stromal cells in vitro and in vivo

Authors: Sandi G. Dempsey, Christopher H. Miller, Julia Schueler, Robert W. F. Veale, Darren J. Day, Barnaby C. H. May

This study explores the regenerative potential of ovine forestomach matrix (OFM), a decellularized extracellular matrix derived from sheep rumen, which has been clinically utilized in wound healing and abdominal wall repair. OFM contains extracellular matrix proteins, cytokines, and growth factors that promote tissue repair and regeneration. The research identifies a chemotactic fragment derived from decorin, named "MayDay," which is liberated through macrophage interactions with OFM. This fragment effectively recruits mesenchymal stromal cells (MSCs), both in vitro and in vivo, highlighting its role in tissue remodeling and repair. The findings suggest that the decorin-derived MayDay fragment supports the regenerative capacity of ECM biomaterials like OFM and introduces a new paradigm in macrophage-ECM-mediated tissue repair.

The study employed macrophage cultures on OFM to isolate the chemotactic factor, followed by mass spectrometry for protein identification. A recombinant version of the MayDay fragment was expressed and tested for its ability to recruit progenitor cells. In vitro assays demonstrated significant MSC migration in response to MayDay, while in vivo experiments confirmed its effectiveness in recruiting MSCs to damaged tissue sites. The proposed mechanism involves macrophage-mediated cleavage of decorin by MMP12, releasing the MayDay fragment, which then facilitates progenitor cell recruitment. These findings underscore the potential of MayDay as a standalone mediator of tissue repair and regeneration, paving the way for its application in clinical settings.

Enhanced Regenerative Therapies Using Crosslinked Porcine Small Intestine Submucosa Scaffolds with SP Peptide for Full-Thickness Wound Healing

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Porcine small intestine submucosa (SIS), primarily composed of collagen, is widely utilized in tissue engineering and regenerative medicine due to its non-toxic nature and intrinsic cytokines. To expand its biomedical applications, this study enhanced the physical properties of SIS through crosslinking with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and N-hydroxysuccinimide (NHS), forming amide bonds between carboxyl and amine groups. The crosslinked SIS (Cx-SIS) scaffold exhibited optimized porosity and structural integrity, maintaining functionality, in contrast to non-crosslinked SIS, which quickly degraded.

Incorporation of the chemoattractant Substance P (SP), further enhanced the scaffold's regenerative potential. SP+Cx-SIS scaffolds demonstrated controlled burst release of SP, significantly promoting the migration of human mesenchymal stem cells (hMSCs) in vitro. When applied to a full-thickness wound model, SP+Cx-SIS scaffolds accelerated tissue regeneration, reduced scar formation, and enhanced collagen deposition compared to control groups. Histological analysis confirmed improved stem cell migration and angiogenesis facilitated by SP. In vitro and in vivo experiments revealed the efficacy of Cx-SIS and SP+Cx-SIS scaffolds in promoting cellular interactions and tissue recovery. The study highlights the dual benefits of structural optimization and SP incorporation in achieving superior healing outcomes. These findings suggest that SP+Cx-SIS scaffolds hold significant potential for clinical applications, providing a promising approach for advanced wound care and regenerative therapies targeting complex tissue injuries.

Biologic Scaffolds for Regenerative Medicine 2025 Abstract

Title: A Large, Real-World, Prospective, Single-Arm Study Evaluating Outcomes Following Complex Lower Extremity Reconstruction with Ovine Forestomach Matrix Graft

Authors: John C. Lawlor, DPM, PA; Patrick Martyka, DPM, DABPM; Brandon Bosque, DPM, CWSP; Chris Frampton, PhD; D. Adam Young, PhD

Background: Complex and chronic lower extremity wounds have numerous etiologies and can progress to require eventual amputation. In addition to morbidity and mortality, chronic lower extremity soft tissue defects have a significant impact on patient quality-of-life and represent a significant cost burden to the healthcare system. Ovine forestomach matrix (OFM) graft was employed as a surgical limb salvage technique to achieve healing in chronic lower extremity soft tissue defects at high risk of major amputation. The purpose of this study was to assess prospective data to evaluate safety, cost-effectiveness, and clinical outcomes in complex surgical limb salvage using OFM.

Method: Prospective data was collected on 120 in-patients (totaling n=130 defects) reflecting a real-world cohort at high-risk of major lower extremity amputation from a single site as part of the "Myriad™ Augmented Soft Tissue Reconstruction Registry" (NTC05243966). All participants received OFM (graft^ and/or morselized*) for surgical reconstruction as a means of lower limb salvage. Progress of the soft tissue defect was monitored for time (days) to 75-100% granulation tissue formation and time (days) to complete defect closure.

Results: Participant demographics and defect characteristics were reflective of a real-world inpatient population with highly complex soft tissue defects. 95.8% of the cohort had one or more predictors of major lower extremity amputation. Median defect area was 7.5 cm^2 (IQR: 3.9, 14.9) (mean, 11.3±13.5). The median time to 75-100% granulation tissue formation was 30 (IQR: 20, 46.5) (mean, 36.1±26.2) days and the median time to complete defect closure was 127 (IQR:110.5, 143.5) (mean, 133.5±109.3) days. There was an 89.2% incidence of complete healing at 90 days. The median cost per episode was USD$253.90 (IQR: $253.90, $1,238.00) (mean, $954.60±$1,191.00) with a median of 1.0 (IQR: 1.0, 1.0) (mean, 1.4±0.89) application.

Conclusion: OFM was found to be a safe and effective limb salvage treatment for complex and chronic lower extremity defects requiring surgical intervention while controlling cost per-episode and per-defect exemplified by median of one application to achieve 100% depth fill and granulation. The real-world inclusion/exclusion criteria of these prospective data reflect those who are most vulnerable to life-altering limb loss and are frequently excluded from randomized controlled trials.

^Myriad Matrix®, Aroa Biosurgery Limited (Auckland, New Zealand)

*Myriad Morcells®, Aroa Biosurgery Limited (Auckland, New Zealand)

Title: Bioprinting of Bioactive Electroactive Constructs for Treating Skeletal Muscle Injuries

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Keywords: Electroactive, extrusion-based 3D bioprinting, musculoskeletal injuries, skeletal muscle tissue engineering.

1. Introduction:

Musculoskeletal injuries, especially volumetric muscle loss (VML), pose significant challenges for tissue regeneration due to the limited effectiveness of current treatment approaches. Although tissue-engineered constructs offer promise, they often lack sufficient cues to promote functional muscle regeneration and lack of re-innervation, leading to poor functional recovery. Bioelectrical signals, crucial for tissue regeneration, can be helpful to solve this vital limitation in skeletal muscle tissue engineering.

2. Objective:

This study aims to create electroactive constructs that could deliver bioelectrical cues to potentially treat injuries to soft tissues such as skeletal muscles and promote active regeneration.

3. Materials and Methods:

We developed piezoelectric bioink based on natural bioactive materials such as sodium alginate, gelatin, and chitosan. The composite bioink had suitable rheological properties. Next, we used extrusion-based 3D bioprinting to develop design-specific constructs that mimic muscle stiffness and generate electrical stimulation (E-stim) when subjected to forces. We tested the construct's mechanical properties and characterized their electrical properties by applying controlled force and frequency to generate electrical fields and impulses. The biocompatibility of these scaffolds was tested with the C2C12 muscle cell line. We have also characterized the differentiation of the cells on these scaffolds using MHC, MyoD, and Desmin markers and the morphology of the cells with the F-actin filament staining.

4. Result and Discussion:

The bioink demonstrated suitable rheological properties for 3D bioprinting, resulting in high-resolution composite sodium alginate–gelatin–chitosan scaffolds with good structural fidelity. The scaffolds exhibited a 42–60 kPa stiffness, similar to muscle. When a controlled force of 5N was applied to the scaffolds at a constant frequency of 4 Hz, they generated electrical fields and impulses (charge), indicating their suitability as a stand-alone scaffold to generate E-stim and instill bioelectrical cues in the wound region. The cell viability and proliferation test results confirm the scaffold's biocompatibility with C2C12s and the benefit of piezoelectricity in promoting muscle cell growth kinetics. Our study indicates that our piezoelectric bioink and scaffolds offer promise as autonomous E-stim-generating regenerative therapy for SMTE.

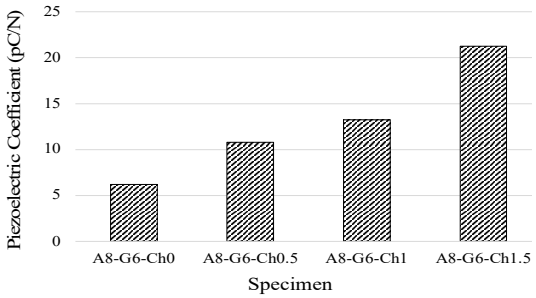

Fig 1: Piezoelectric Coefficient (d33) of the Various Constructs

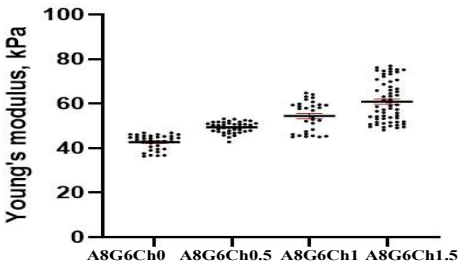

Fig 2: Young's Modulus of the Constructs

5. Conclusions:

This study presents the development of unique bioactive electroactive constructs capable of autonomously generating electrical stimulation to facilitate skeletal muscle tissue regeneration. By reintroducing bioelectrical cues, this construct offers a promising approach for enhancing the effectiveness of tissue regeneration strategies in treating musculoskeletal injuries, particularly VML.

6. References:

[1] S. Y. Sonaye et al., "Extrusion-Based 3D Bioprinting of Bioactive and Piezoelectric Scaffolds as Potential Therapy for Treating Critical Soft Tissue Wounds," Advances in Wound Care, vol. 0, no. 0, p. null, doi: 10.1089/wound.2024.0073.

7. Acknowledgment:

We acknowledge **Dr. Sikder's Startup grant** (STARTUP06) at Cleveland State University for this work.

Decellularized Placental Biomaterials for Management and Protection of Tendon Injuries

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STATEMENT OF PURPOSE:

Tendon injuries present significant clinical challenges, often leading to prolonged rehabilitation and compromised functional outcomes. Despite advancements in surgical techniques and rehabilitation protocols, managing tendon injuries remains a formidable task for clinicians. Current treatment modalities frequently fall short of fully restoring tendon function, underscoring the urgent need for innovative approaches in tendon repair. Decellularized placental biomaterials have emerged as a novel therapeutic option for tissue repair and regeneration, harnessing the regenerative potential of placental tissues while mitigating immunogenicity and promoting tissue integration. The decellularized placental tissue matrix can be derived from the entire placental connective tissue or specific tissues, such as umbilical cord tissue. The resulting matrix can take various formats (e.g., particulate, flowable) for diverse application purposes. The impact of these differences on the interaction between the tissue matrix and cells remains unknown. This work explores the application of various decellularized placental biomaterials, including connective tissue matrix (CTM) and umbilical cord matrix (UCM), in tendon management both in vitro and in vivo. The focus is on assessing their biomechanical properties, immunomodulatory effects, and preclinical outcomes to advance our understanding of their potential in tendon repair. We hypothesize that decellularized placental biomaterials, CTM and UCM, provide a suitable matrix for tendon management and healing.

METHODS:

Three human placental biomaterials were selected for comparison: (1) a minimally manipulated non-viable cellular particulate (MM-CTM); (2) a liquid matrix (L-CTM); and (3) a decellularized flowable CTM (DF-CTM). Outcome variables included tenocyte adhesion, proliferation, migration, phenotype maintenance, and inflammatory response. Adhesion and proliferation were evaluated using cell viability assays and tenocyte migration using a transwell migration assay. Gene expression of tenocyte markers and pro-inflammatory markers were assessed using quantitative polymerase chain reaction. Phenotypic markers included scleraxis (SCX), tenascin-C (TNC), type I collagen (COL1A1), type III collagen (COL3A1), and decorin (DCN). Inflammatory markers included interleukin 8 (CXCL8), tumor necrosis factor α (TNF- α), transforming growth factor beta 1 (TGFβ1) and beta 3 (TGFβ3), and matrix metallopeptidase 1 (MMP1). Additionally, a decellularized, umbilical cord derived matrix (UCM) was evaluated in vitro for tenocyte proliferation and phenotype maintenance. The sheet format of UCM and its barrier properties compared to CTM flowable, made it an ideal choice for testing in vivo. Using a rabbit Achilles partial tenotomy model for tendon healing UCM was compared to a predicate at both 4 and 10 weeks. The UCM was also evaluated in an infraspinatus and patellar stab wound insult model in purpose-bred research beagles 3 months post application.

SUMMARY OF RESULTS:

Although MM-CTM supported significantly more tenocyte adhesion than DF-CTM ($p = 0.004$), tenocyte proliferation was significantly higher on DF-CTM than MM-CTM and L-CTM ($p < 0.001$). Unlike MM-CTM, tenocyte migration was higher for DF-CTM than the control ($p = 0.005$). In tenocytes cultured on DF-CTM, gene expressions (SCX, TNC, COL1A1, and COL3A1) significantly increased over time ($p < 0.001$). Conversely, in tenocytes cultured on MM-CTM, gene expressions remained unchanged (SCX and TNC, $p \geq 0.102$) or significantly decreased over time (COL1A1 and COL3A1, $p \leq 0.018$). DCN expression increased over time for both CTMs ($p < 0.001$). Compared with MM-CTM, DF-CTM diminished the effects of TNF-α, significantly reducing the expression of CXCL8 ($p = 0.024$) and MMP1 ($p < 0.001$). Over time, tenocytes cultured on MM-CTM promoted the expression of CXCL8 and MMP1, while DF-CTM promoted the expression of antifibrotic growth factor TGFβ3. Therefore, of the three forms of CTMs, DF-CTM appeared to best support the functionalities of tenocytes. In the rabbit Achilles model, the findings revealed substantial equivalence between the decellularized UCM and the reference bovine collagen matrix. This was evident in terms of immature and mature tendon fibers at both the 4- and 10-week timepoints, indicating an active and healthy repair process. Furthermore, histological analysis demonstrated substantial equivalence in the extent of tissue attachments between the decellularized UCM and the reference. The observed more advanced degradation and reduced macroscopic tissue attachments in the decellularized UCM treated group suggest a trend towards more advanced healing in animals receiving this treatment. The study in the infraspinatus and patellar stab models showed complete incorporation of the UCM three months post-implantation (Figure 1). Additionally, histological examination showed a mostly absent or mild/moderate inflammatory response (Figure 2), foreign body reaction, and tissue attachment.

During the in vitro evaluation of decellularized placental biomaterials, CTM interacted more favorably with human tenocytes as evidenced by significantly higher tenocyte proliferation, significantly better maintenance of tenocyte phenotype, and a significantly attenuated inflammatory response. Furthermore, in vitro evaluation of UCM showed enhanced tenocyte attachment, growth, and phenotype maintenance. In vivo evaluation in two clinically relevant models demonstrated more advanced healing in the UCM treated group, and complete incorporation of UCM into the tendon, within 3 months post implantation. This data indicates that human placental decellularized biomaterials represent an emerging promising matrix suitable for tendon management and healing.

CONCLUSION:

The favorable interaction observed between cells and decellularized placental tissue matrix (CTM and UCM), both in vitro and in vivo, highlights the promising potential of advanced placental biomaterials in tendon repair. A thorough evaluation of the current state of tendon repair and the drawback of existing methods emphasizes the critical requirement for clinical studies of innovative interventions to enhance clinical outcomes and patient satisfaction.

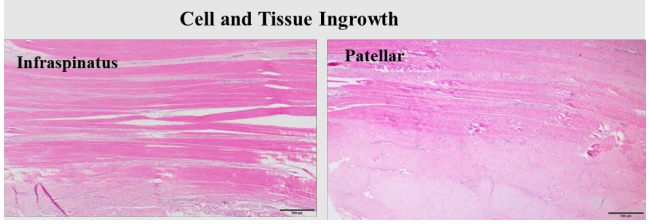

Figure 1. Complete incorporation of UCM observed in 18 of 18 tendon defects in an infraspinatus and patellar stab wound insult model

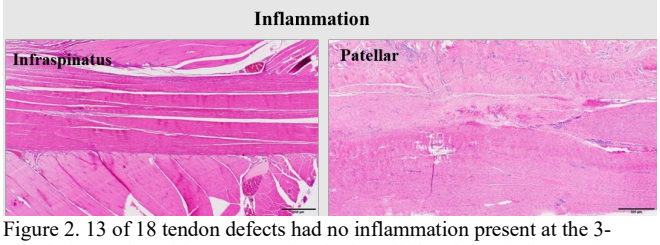

Figure 2. 13 of 18 tendon defects had no inflammation present at the 3-month time point with UCM; 5 of 18 had a mild/moderate inflammation score. Average score: 0.39 (1=Mild inflammation score)

ACKNOWLEDGEMENTS: Dr. James Cook, University of Missouri, Department of Orthopedic Surgery, Nicole M. Protzman, Healthcare Analytics LLC. Celularity Degenerative Disease R&D Team.

ECM Degradation Products Influence Esophageal Adenocarcinoma (EAC) Phenotype via PI3K-Akt and BMP4 Pathways

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Biologic materials composed of extracellular matrix (ECM) or its components have been successfully used for tissue repair and reconstruction. Preclinical studies, and a cohort study following stage T1A esophageal adenocarcinoma (EAC) resection have demonstrated that ECM biomaterials can restore esophageal mucosa and submucosa without cancer recurrence. Previous *in vitro* studies showed that ECM degradation products from nonmalignant esophageal (eECM) and urinary bladder (ubECM) tissues downregulate neoplastic cell phenotype through distinct, tissue-specific mechanisms. While ubECM decreased metabolism, eECM downregulated PI3K-Akt-mTOR signaling in cancer esophageal cells. This study further investigates the *in vitro* effects of eECM and ubECM degradation products on EAC cell behavior and associated signaling pathways. Both ECM sources significantly reduced OE33 cell proliferation, with eECM producing a more potent response—decreasing proliferation to 25% at 24 hours and 7% at 72 hours compared to pepsin control. Both ECM types downregulated the surface markers CD164 and CXCR4 (~50% reduction in CXCR4 protein), but only eECM markedly suppressed cell migration and reduced BMP4 expression and its downstream EMT mediators (pSMAD1/5/8, ID2, and SNAI2). These findings support the concept that nonmalignant ECM-derived cues can modulate neoplastic cell behavior. Given the roles of PI3K-Akt and BMP4 signaling in EAC progression, ECM-based strategies may warrant further investigation as potential therapeutic approaches following esophageal cancer resection.

Defining the Role of Matrix-Bound Nanovesicles in Modulating Epithelial and Mesenchymal Cells in the Tumor Microenvironment (TME) Remodeling

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Recent research has highlighted Matrix Bound Nanovesicles (MBV), a specialized subset of extracellular vesicles (EV), as pivotal regulators of tissue homeostasis within the extracellular matrix (ECM). Unlike exosomes, which are secreted into body fluids and readily available for cell-cell communication, MBV are associated with collagen fibers of the ECM and are believed to become accessible during matrix remodeling, a dynamic process that is particularly active in wound healing, inflammation, and metastasis. Recent advances in vesicle isolation techniques have enabled the distinction between liquid-phase and solid-phase EV populations, revealing MBV as a functionally and molecularly distinct class enriched in protein and microRNA cargo with immunomodulatory potential. While MBV have been shown to influence macrophage phenotype, their role in regulating epithelial and mesenchymal cell behavior—particularly in the context of cancer progression—remains incompletely understood. Here, we demonstrate that MBV isolated from porcine urinary bladder matrix (ubMBV) are internalized by epithelial cells and modulate their migratory phenotype, in part through the downregulation of the TGF-β signaling pathways. TGF-β is a key molecule in promoting tumor progression in the TME. This study represents a comprehensive analysis of MBV-mediated cellular responses across epithelial and mesenchymal populations and provides new mechanistic insights into how ECM-associated vesicles contribute to tissue remodeling and potentially influence neoplastic progression.

Characterization of the ECM-Based Multi-Tissue Platform Technology

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[1]FetTech, Ft. Lauderdale, FL

The Multi-Tissue Platform (MTP) technology is unique among ECM-based medical products in that it is made from multiple tissue sources. FDA-cleared in two forms – MTP Powder (XCelliStem Wound Powder) and MTP Gel (ReyaGel) – it has been used in hospitals for the management of a wide range of wound types since 2018. More recently, the material has been found to display antiviral activity against enveloped viruses. Here we present an in-depth characterization of this unique ECM-based technology including structural component & growth factor characterization, proteomics & exosome analysis, antiviral activity, and clinical performance.

Whereas most ECM-based medical products are 90% or more collagen, MTP comprises 44% collagen (including types, I, III, IV, XII, and others) by total dry weight, with higher percentages of elastin (25%), laminin (6%), fibronectin (18%), and other biomolecules. VEGF-A, FGF-2, and EGF were consistently identified by ELISA in all MTP samples tested.

Proteomic analysis detected 687 unique protein features in MTP, with 98.3% of total protein abundance shared between MTP Powder and MTP Gel. A swine wound healing model validated the equivalence of the powder and gel formulations, showing equivalent healing times and tissue quality. Extracellular vesicles isolated from MTP (quantified in MTP Gel at $\geq$56 billion/mL) contain peptides involved in erbB2 signaling, regulation of inflammation, keratinization & cornification, and structural molecular activity including cytoskeletal and actin binding.

MTP has also been found to have broad-spectrum antiviral activity against enveloped viruses within one minute of exposure *in vitro,* in a dose-dependent manner. Further testing against herpesvirus in *ex vivo* skin and animal models showed that MTP prevents Varicella Zoster (chickenpox/shingles) attachment, entry, and spread for up to 24h and is effective when treatment is initiated even 5 days post-infection.

Clinically, MTP Powder and MTP Gel have been used in a variety of wound healing procedures including post-laser surgery, surgical wounds, donor sites/grafts, partial and full-thickness chronic vascular and diabetic wounds, second degree burns, and tunneled/undermined wounds.

Taken together, these data and the excellent clinical results achieved thus far in wound care point to MTP as a unique technology with a wide range of potential future applications in regenerative medicine. The development of a high-performing, FDA-cleared liquid form opens MTP to applications not previously feasible for sheet and powder ECMs. Professional collaborations are needed to fully explore MTP in new clinical settings and fields of investigational research.

Biologics Scaffolds for Regenerative Medicine

13th Symposium, Napa, California, May 2025

Abstract for poster presentation

Title: Porcine cartilage as inflammation modulator in a monoiodoacetate-induced arthritis model

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Affiliations:

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Abstract

Joint arthritis is a chronic inflammatory condition that affects millions of patients worldwide with an approximate incidence of 13%, depending on the age group [1]. Swelling, pain and stiffness are the main symptoms that affect the patient's quality of life. Current treatments are ineffective at preventing these symptoms and/or involve undesirable secondary effects such as compromise of the immune system. Alternatively, supplements that improve or substitute current treatments are being investigated. Collagen type II has been proposed as a supplementation to ameliorate joint arthritis, which could regulate inflammation through an immune oral tolerance mechanisms [2]. In this pilot study, we investigated the potential of porcine cartilage as a source of collagen type II and as an oral supplement in a monoiodoacetate (MIA)-induced arthritis model in rats (N=5). The study involved a daily oral supplementation of a 3 mg/kg dose of porcine cartilage after arthritis induction by MIA injection in rat knees. After 2 weeks, rats were euthanized, blood was collected for cytokine analysis by ELISA and knees were harvested for histopathological analysis. MIA injection effectively triggered sustained chronic inflammation and swelling for the 2 weeks of the study. The group that included porcine cartilage oral supplementation revealed a regulation of relevant inflammatory cytokines such as IL-12p70, IL-17A, Eotaxin and RANTES at systemic level. Histological analysis of safranin-O stained sections also showed a trend in cartilage quality improvement assessed by OARSI score. In addition, porcine cartilage group rats did not show weight loss related to pain and stress, contrary to MIA group without supplementation, while showing trends of improvements in functional movement analysis. Overall, these results show a tendency of inflammation and pain amelioration in rats with MIA-induced arthritis after porcine cartilage oral supplementation. Future studies will be aimed at investigating the oral tolerance mechanisms behind these anti-inflammatory effects. Additional preclinical studies that include a larger sample size and clinical trials will confirm these findings.

References

1) IJMS. 24,7 6405. (2023)
2) Nov Tech Arthritis Bone Res 3(4) (2019)

Acknowledgements

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Characterization and Bioactivity of Human Joint Tissue-derived Matrix Bound Nanovesicles: Identification of Potential Biomarkers for Osteoarthritis

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Chronic degenerative joint diseases such as rheumatoid arthritis (RA), osteoarthritis (OA), and post-traumatic osteoarthritis (PTOA) represent a significant burden to the population, affecting over 500 million people worldwide, and ranking among the leading causes of permanent disability. The progression of these diseases is driven by multiple factors such as obesity, aging, and genetic predisposition, complicating efforts to fully elucidate their underlying mechanisms. Pathological changes commonly observed include articular cartilage destruction, subchondral bone thickening, osteophyte formation, synovitis, degeneration of ligament and menisci, and joint capsule hypertrophy. Current treatments remain primarily palliative, aimed at reducing morbidity without addressing the biological processes leading to joint degeneration.

Recently, a novel subset of extracellular nanovesicles (EV), named Matrix-Bound Nanovesicles (MBV), have been identified as repositories of proteins and miRNA within the extracellular matrix (ECM). MBV, which are tightly bound to collagen fibers, are known to have a key role in maintaining tissue homeostasis. When released from the ECM, MBV exhibit potent immunomodulatory effects. For example, MBV isolated from porcine urinary bladder matrix (UBM) have been shown to mitigate synovial inflammation and bone damage in a pristane-induced rat model of RA. However, the specific roles of MBV in disease progression and tissue remodeling remain largely unexplored.

The objective of the present study is to isolate and characterize MBV from human joint tissues—including cartilage, bone, synovial fluid, fad pad—and to identify changes in their protein, lipid, and miRNA composition associated with age, sex, and disease progression. This work aims to uncover novel biomarkers for understanding chronic joint disease progression and to identify new targets for MBV-based immunomodulatory treatments.

Preliminary findings are presented, detailing the successful isolation and characterization of MBV from human joint tissues. MBV from donors of varying ages are analyzed for molecular and biochemical differences. In addition, their biological activity—specifically effects on cell viability,

metabolic activity, immunomodulation—is assessed in human adult primary chondrocytes and murine bone marrow-derived macrophages.

The successful identification of MBV derived from human joint tissues represents a key advancement in understanding joint disease pathology. By elucidating how MBV contribute to degenerative processes, this study establishes the groundwork for developing targeted therapeutic interventions tailored to the needs of individuals affected by chronic joint diseases.

Matrix Bound Nanovesicle-Induced Mitigation of Periprosthetic Osteolysis: Novel Mechanisms of Action

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Total joint arthroplasty (TJA) is a widely used intervention for end-stage arthritic or traumatic joint conditions. Despite advancements in implant materials, prolonged and repetitive mechanical loading can lead to the release of metallic and ultra-high molecular weight polyethylene (UHMWPE) wear debris. This debris can trigger aseptic loosening of orthopedic implants, ultimately resulting in prosthetic failure. At the cellular level, phagocytosis of these indigestible nano- and microscale particles induces a chronic inflammatory response characterized by immune cell activation. This sustained immune activation promotes osteoclastogenesis via the receptor activator of nuclear factor kappa-B ligand (RANKL)/RANK axis signaling, leading to periprosthetic bone destruction.

Extracellular matrix (ECM)-based biomaterials offer a biocompatible scaffold for tissue repair and regeneration and have shown promise in multiple medical applications due to their immunomodulatory properties—largely mediated through the modulation of macrophage phenotypes. Recent studies have identified matrix-bound nanovesicles (MBV), a unique class of extracellular vesicles (EV) integrally associated with ECM, as key effectors of these immunomodulatory effects. MBV have distinct composition, cargo, and function compared to other extracellular vesicle types. They have been shown to attenuate inflammation in several preclinical models, including influenza-induced cytokine storms and pristine-induced rheumatoid arthritis (RA), and to prevent adverse bone remodeling in RA.

However, the role of MBV on osteoclast differentiation and function remains unexplored. In the present study, we investigated the effects of MBV using RANKL-treated RAW264.7 monocyte/macrophages as an *in vitro* model of osteoclastogenesis and a UHMWPE particulate-induced calvarial osteolysis murine model for the *in vivo* analysis.

Results demonstrate that MBV significantly attenuate osteoclast differentiation and activity by suppressing the NF-κB signaling pathway and downstream targets, including NFATc1, DC-STAMP, c-Src, and Cathepsin K. *In vivo*, local administration of MBV reduced UHMWPE-induced osteolysis, bone resorption, and periosteal inflammation. These results suggest that MBV may serve as a promising therapeutic strategy to prevent periprosthetic loosening and associated bone loss.

Title: Intraluminal Extracellular Matrix Therapy for Anastomotic Leak: A Novel Solution to a Persistent Challenge

Authors: Vincent P Anto[1,2], Charles J Patterson[2], Catalina Pineda Molina[2], David S Medich[1], George S Hussey[2,3,4], Stephen F Badylak[1,2]

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Introduction:

Anastomotic leaks are a significant complication of rectal resection, often necessitating temporary diverting stomas, which carry their own risks. Reducing the incidence of anastomotic leaks could eliminate the need for diversion and its associated complications. Our work explores the intraluminal application of extracellular matrix (ECM) products as a novel therapeutic approach to enhance anastomotic healing and reduce leak rates in a rodent model.

Methods:

Rats underwent standardized distal colonic resections and anastomoses and were randomized into four groups: control, biologically inert hydrogel, urinary bladder matrix hydrogel, or colloidal dermal hydrogel. Outcomes were assessed at acute and chronic time points through clinical evaluation for anastomotic leaks, comprehensive histological analysis of healing quality, and biomolecular assessment of inflammatory markers at the anastomotic site.

Results:

Anastomotic leaks occurred in nearly 50% of the control and inert hydrogel groups. In contrast, ECM-treated groups demonstrated a significant reduction in leak rates. Histological analysis revealed enhanced healing and restoration of normal colonic architecture in ECM-treated anastomoses. Biomolecular analysis showed a marked reduction in inflammatory responses associated with ECM application.

Conclusion:

ECM products have a well-established role in promoting tissue healing and structural restoration but have been underexplored in colorectal surgery. This study demonstrates that intraluminal ECM application significantly improves anastomotic healing and reduces a detrimental inflammatory response, offering a promising strategy to prevent or treat anastomotic leaks. Future work will pursue translating these findings into human clinical practice.