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# Augmentation of a Rotator Cuff Suture Repair Using rhPDGF-BB and a Type I Bovine Collagen Matrix in an Ovine Model

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*Investigation performed at Colorado State University, Fort Collins, Colorado*

**Background:** Rotator cuff tears are a common source of shoulder pain. High rates (20%-94%) of structural failure of the repair have been attributed to multiple factors, including poor repair tissue quality and tendon-to-bone integration. Biologic augmentation using growth factors has potential to promote tendon-to-bone integration, improving the function and long-term success of the repair. One such growth factor is platelet-derived growth factor–BB (PDGF-BB), which has been shown to improve healing in tendon and bone repair models.

**Hypothesis:** Recombinant human PDGF-BB (rhPDGF-BB) combined with a highly porous type I bovine collagen matrix will improve the biomechanical function and morphologic appearance of the repair in a dose-dependent manner, relative to a suture-only control, after 12 weeks in an acute ovine model of rotator cuff repair.

**Study Design:** Controlled laboratory study.

**Methods:** An interpositional graft consisting of rhPDGF-BB and a type I collagen matrix was implanted in an ovine model of rotator cuff repair. Biomechanical and histologic analyses were performed to determine the functional and anatomic characteristics of the repair after 12 weeks.

**Results:** A significant increase in the ultimate load to failure was observed in repairs treated with 75  $\mu\text{g}$  ( $1490.5 \pm 224.5$  N,  $P = .029$ ) or 150  $\mu\text{g}$  ( $1486.6 \pm 229.0$  N,  $P = .029$ ) of rhPDGF-BB, relative to suture-only controls ( $910.4 \pm 156.1$  N) and the 500- $\mu\text{g}$  rhPDGF-BB group ( $677.8 \pm 105.9$  N). The 75- $\mu\text{g}$  and 150- $\mu\text{g}$  rhPDGF-BB groups also exhibited increased tendon-to-bone interdigitation histologically. No differences in inflammation or cellularity were observed among treatments.

**Conclusion:** This study demonstrated that an interpositional graft consisting of rhPDGF-BB (75 or 150  $\mu\text{g}$ ) and a type I collagen matrix was able to improve the biomechanical strength and anatomic appearance in an ovine model of rotator cuff repair compared to a suture-only control and the 500- $\mu\text{g}$  rhPDGF-BB group.

**Clinical Relevance:** Recombinant human PDGF-BB combined with a type I collagen matrix has potential to be used to augment surgical repair of rotator cuff tears, thereby improving clinical success.

**Keywords:** rotator cuff repair; platelet-derived growth factor–BB; biomechanics; histology

Rotator cuff tears are a common source of shoulder pain that often require surgery to adequately restore strength and function, with as many as 150 000 procedures performed in the United States in 2004.<sup>37,45</sup> Although surgery is often able to improve clinical assessments of shoulder function, high rates of postoperative structural failures have been reported. A large range of retear rates (20%-94%) have been reported, with outcomes dependent on multiple factors, including the size of the tear, age of the patient, and degree of activity.<sup>5,19,21,23,26,38,60</sup> The highest rates (46%-94%) of structural failures in rotator cuff

repairs occur in large to massive tears.<sup>19,38,48,60</sup> Overcoming the propensity for repeat failure and effectively repairing rotator cuff tears requires minimizing gap formation between the tendon and bone through good suture technique and improving tendon-to-bone healing. Much emphasis has been placed on the suture method for minimizing the gap between the tendon and bone.<sup>8,14,18</sup> Additionally, augmentation of the repair environment to improve the mechanical integrity<sup>#</sup> or biologic activity<sup>\*\*</sup> is being investigated as a means for promoting successful reintegration of the tendon to the bone, thereby improving the long-term success of the repair.

Many scaffold-based and biologic approaches have been investigated in the effort to improve healing in rotator cuff repairs. Natural<sup>1,9,13,41,46</sup> and synthetic<sup>36,45</sup> matrices have been used to provide immediate mechanical integrity and/or a scaffold for cell and tissue ingrowth. While clinical studies have been conducted to evaluate the efficacy of a variety of matrices, definitive conclusions regarding their benefit for augmenting rotator cuff repair have not been reached and further investigations are necessary to support their use in the clinic.<sup>35</sup> Growth factors have also been investigated as a method to optimize the tendon-to-bone healing in rotator cuff repair.<sup>††</sup> One such growth factor is platelet-derived growth factor–BB (PDGF-BB),<sup>57,58</sup> which is released by platelets early in the wound-healing cascade and acts as a chemotactic and mitogenic factor on tenocytes, osteoblasts, and mesenchymal stem cells,<sup>6,10,29,44,52,53</sup> stimulating bone and tendon tissue repair. Platelet-derived growth factor–BB is a homodimer of B-chains of PDGF, which is able to bind both the  $\alpha$  and  $\beta$  PDGF receptors with high affinity, making it the universal PDGF isoform.<sup>28</sup> The contributions of PDGF-BB to soft and hard tissue wound healing have made it a promising therapeutic for orthopaedic applications. While recombinant human PDGF-BB (rhPDGF-BB) has been used clinically to repair periodontal hard and soft tissue defects and to augment hindfoot and ankle fusion,<sup>12,28,40</sup> it is still in the preclinical development stage for sports medicine applications. Platelet-derived growth factor–BB is endogenously expressed in tendon in response to injury,<sup>17,31,55,59</sup> an indication of its involvement in the repair process. Exogenous addition of rhPDGF-BB to animal models of bone<sup>2,28,29</sup> and tendon<sup>7,22,50,53,57,58</sup> injury has shown beneficial effects on tissue repair *in vivo*. This suggests that augmentation of rotator cuff repair with rhPDGF-BB may lead to improved tendon repair and tendon-to-bone integration.

Previous studies have specifically investigated the potential role of PDGF-BB with regard to enhancing rotator cuff tendon healing. In a rat model of chronic rotator cuff repair, tendon fibroblasts transduced to express PDGF-BB and seeded on a polyglycolic acid scaffold showed improved histologic outcomes when applied at the tendon transection site.<sup>15,58</sup> Similar histologic findings were observed in an ovine model of rotator cuff repair in which sutures coated with rhPDGF-BB were used. In

that study, the tendons repaired with rhPDGF-BB-coated sutures exhibited more organized gap tissue, with extensive cartilage formation at the tendon-bone interface and more highly organized collagen fibers, compared with the noncoated suture repairs.<sup>57</sup> Additionally, this study exhibited a significantly increased stiffness for the repairs utilizing rhPDGF-BB-coated suture. While both of these studies suggest that rhPDGF-BB could play a beneficial role in improving rotator cuff healing, they also highlight an issue associated with the use of growth factors: the application of the appropriate dose to achieve the desired biomechanical and morphologic properties. Although benefits were observed histologically, neither study showed significant improvements in the biomechanical strength of the repaired tendons, possibly due to the low doses of rhPDGF-BB used (rat model: not determined; ovine model: approximately 12  $\mu$ g). Nevertheless, the improved morphologic healing demonstrated by these studies provides an impetus for further investigation of rhPDGF-BB for rotator cuff repair. A study to understand the effect of increasing the delivered dose of rhPDGF-BB, using a tissue-specific matrix, is important to further elucidate the potential of rhPDGF-BB in improving rotator cuff healing after injury.

The objective of this study was to evaluate the dose-dependent ability of rhPDGF-BB to improve tendon-to-bone healing in an ovine rotator cuff repair model. We hypothesized that rhPDGF-BB combined with a highly porous type I bovine collagen matrix would improve the biomechanical function and morphologic appearance of the tendon-bone repair in a dose-dependent manner, relative to a suture-only control, after 12 weeks in an acute ovine model of rotator cuff repair.

## MATERIALS AND METHODS

### Power Analysis

This study was designed to detect a 50% difference in the ultimate force at failure between the rhPDGF-BB/collagen matrix-augmented repair and the collagen matrix-only control with a power of 0.9. The power analysis for this study, performed on preliminary data using a similar ovine infraspinatus tendon repair model, indicated that a minimum of 8 sheep was required for each experimental group. The histopathology was not powered for statistical significance.

††References 15, 16, 20, 30, 39, 42, 49, 57, 58.

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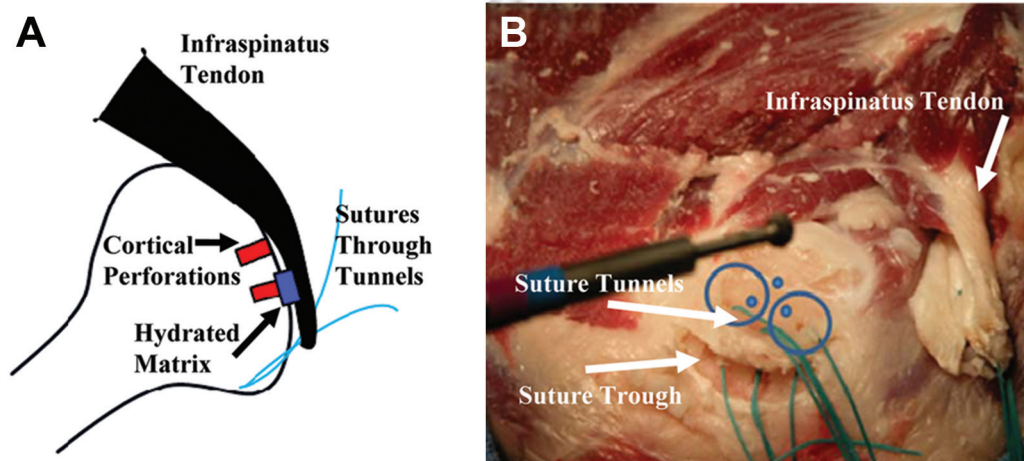
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**Figure 1.** A, schematic of a cross-section of the repair showing the hydrated matrix positioned over the cortical perforations between the infraspinatus tendon and the greater tuberosity. B, image of the prepared tendon footprint showing the detached infraspinatus tendon with sutures passed through the bone tunnels. The solid small circles indicate the location of the cortical perforations and the large open circles show the position of the hydrated collagen pads.

### Experimental Design

All animal procedures were performed at an accredited hospital for veterinary medicine under a protocol approved by the Institutional Animal Care and Use Committee. An ovine model of rotator cuff injury<sup>32,33,42,46,47,49</sup> was used for this study. A total of 60 skeletally mature Rambouillet-Columbia cross ewes (3.5+ years old, 65-105 kg) underwent an acute infraspinatus tendon detachment and repair. Five treatment groups (n = 12 per group) were used to assess the ability of rhPDGF-BB and a type I collagen matrix to augment rotator cuff healing: (1) suture only, (2) suture + collagen matrix + 20 mM sodium acetate buffer (0  $\mu$ g rhPDGF-BB), (3) suture + collagen + 75  $\mu$ g rhPDGF-BB, (4) suture + collagen + 150  $\mu$ g rhPDGF-BB, and (5) suture + collagen + 500  $\mu$ g rhPDGF-BB.

### Test Article Formulation

The matrix used in this study was a highly porous (>90%), type I collagen matrix (Integra LifeSciences Corporation, Plainsboro, New Jersey). For each animal, 2 disks (8-mm diameter) were each hydrated with 50  $\mu$ L of buffer (20 mM sodium acetate) or rhPDGF-BB (BioMimetic Therapeutics, Franklin, Tennessee) (0.15, 0.3, or 1.0 mg/mL in buffer). After placement of the hydrated collagen matrix, the remaining 0.4 mL of buffer or rhPDGF-BB was carefully dispensed over the decorticated footprint to achieve the final dose.

### Surgical Procedure

After successful administration of anesthesia, the right shoulder of the sheep was prepared and sterilely draped. A 6-cm curved incision was made over the posterolateral aspect of the shoulder joint. The acromial head of the deltoid muscle was split along the tendinous division between its acromial and scapular heads. The superficial head and

insertion of the infraspinatus tendon was isolated and sharply detached from its insertion on the proximal greater tuberosity. The footprint of the tendon, approximately 20 mm  $\times$  20 mm, was decorticated to provide a bleeding bone surface followed by preparation of 3 transosseous tunnels through which sutures were passed during the repair. In addition to surface decortication, 3 small cortical perforations (1 mm in diameter) were placed within the tendon footprint in a standardized manner, centered between suture tunnels, 2 mm posterior to the line connecting the suture tunnels, with the third hole located 2 mm posterior and centered between the 2 front perforations. The tendon was repaired with 2 sutures using a modified Mason-Allen suture configuration. For animals randomized to receive the collagen matrix  $\pm$  rhPDGF-BB, the matrix was hydrated as described in the Test Article Formulation section above. The hydrated collagen matrices were placed on the surface of the decorticated bone after completion of the initial suture placement and before final tightening of the sutures, placing each disc at the anterior corners of the prepared tendon footprint. A schematic of the tendon footprint, cortical perforation locations, suture tunnel location, and placement of the collagen matrix can be seen in Figure 1. The remaining 0.4 mL of buffer or rhPDGF-BB was carefully dispensed over the collagen pads and decorticated bone surface. The sutures were then tightened through the suture tunnels and tied in the suture trough in order to secure the tendon to the bone surface. The end result was an interpositional graft with the hydrated collagen matrix located between the tendon and bone.

### Postoperative Care

Upon recovery from anesthesia, all animals were allowed to ambulate normally. Analgesia, consisting of percutaneous fentanyl and oral phenylbutazone, commenced 24 hours before surgery and continued for 72 hours after surgery.

Assessment of pain was recorded daily on a scale from 0 to 4 in each of 5 categories in all sheep using an Institutional Animal Care and Use Committee–approved scoring system based on animal alertness, movement, flock behavior, feeding behavior, and respiratory rate. The animals were placed in a small pen for the first 6 weeks to limit activity. After 6 weeks, the sheep were moved to a larger pen for the remainder of their convalescence and were allowed unrestricted activity. The sheep were humanely euthanized 12 weeks after surgery. A 12-week time point is a common end point for assessing early healing in the reparative cascade for the ovine model and has previously been shown by others<sup>32,33,42,45,46</sup> to result in inferior mechanical strength in suture-only repairs relative to intact control tendons. This study utilized the time scale investigated by these authors to evaluate the ability of this novel augmentation strategy to improve healing during the early rehabilitation period, when the repair is most susceptible to mechanical failure.

### Biomechanical Analysis

Specimens composed of the bone-tendon-muscle complex ( $n = 9$  per group) were cleaned of muscle tissue and the humerus was potted in 2-cm-diameter polyvinylchloride pipe using high-strength polymethylmethacrylate. Additionally, a total of 6 contralateral limbs were collected and tested to determine the properties of intact infraspinatus tendons. After polymerization, the potted specimens were wrapped in saline-soaked gauze sponges and frozen at  $-20^{\circ}\text{C}$  until the time of testing. On the day of testing, specimens were thawed and rehydrated in saline. The potted humerus was attached to a custom-designed testing fixture rigidly coupled to a Mini Bionix II servohydraulic testing system (MTS, Eden Prairie, Minnesota) and 5-kN load cell. A custom-designed brass cryoclamp, implemented to preserve the natural cross-section of the infraspinatus tendon and minimize soft tissue slippage, was used to apply a uniaxial traction force to the construct at an angle of approximately  $135^{\circ}$  to the potted humerus. This traction angle was chosen to mimic the physiologic force vector of the tendon. Testing commenced when a thermocouple attached to the cryoclamp was below  $-22^{\circ}\text{C}$ , a critical temperature that has been previously reported to be sufficient to ensure secure coupling between the tendon and clamp.<sup>45</sup> Specimens were kept moist during the entire preparation and mechanical testing procedure with a saline spray. The biomechanical testing regimen consisted of an initial preconditioning cycle followed by a quasistatic load-to-failure ramp.<sup>45</sup> All tendons were preconditioned to normalize viscoelastic effects and testing variability through application of a static, force-controlled 10-N preload for 2 minutes followed by cyclic loading (in load control) from 10 to 50 N at 0.25 Hz for 60 cycles. Preconditioning was followed by a quasistatic load-to-failure ramp at 1 mm/s. Biomechanical parameters of interest included the ultimate load-to-failure, quasistatic stiffness, elongation, and failure location. Failure was characterized as the first significant decrease in the monotonically increasing load-displacement profile. Stiffness was defined as the linear portion of the force-displacement curve.

TABLE 1  
Summary of Histologic Scoring Scale

Characteristic	Grading	Score
Vascularity	None	0
	Some	1
	Abundant	2
Inflammatory cells	None	0
	Some	1
	Many	2
Collagen fiber orientation	None	0
	Some	1
	Mostly	2
	Completely	3
Collagen fiber density	Low	1
	Medium	2
	High	3
Bone-tendon interface (interdigitation/Sharpey fibers)	0% tendon-bone attachment area integrated	0
	25%	1
	50%	2
	75%	3

### Histology

Histologic specimens ( $n = 3$  per group) were fixed, decalcified, processed, and embedded using standard paraffin histology techniques and equipment (Sakura Tissue TEK V.I.P. Processor, Sakura Finetek USA, Torrance, California and Shandon Histocentre 2, ThermoShandon, Pittsburgh, Pennsylvania). Five histologic sections were taken at a thickness of  $8\ \mu\text{m}$  from the central region of the infraspinatus-humerus repair site at increments of  $250\ \mu\text{m}$ . Sections were stained with hematoxylin and eosin and graded according to a semiquantitative grading scale (Table 1) to assess the degree of tendon retraction and evaluate the reparative/healing tissue and the tendon-bone interface, including vascularization, inflammation, collagen fiber orientation/alignment, and presence of Sharpey fibers (interdigitation) at the insertion site. Hematoxylin and eosin was chosen for ease of use and ability to discern and qualitatively evaluate the morphologic features of interest to this particular research. The semiquantitative scoring system was developed to make relative comparisons among groups. Bright-field (vascularization and inflammation) and polarized-light (collagen alignment and interdigitation) microscopy were used for evaluation. Sections were assessed blinded to treatment and evaluated for overall healing compared to one another and given a healing score. High-resolution digital images were acquired using an Image Pro imaging system (Media Cybernetics, Silver Spring, Maryland) and a Nikon E800 microscope with polarized light capabilities (AG Heinze, Lake Forest, California), SPOT digital camera (Diagnostic Instruments, Sterling, Heights, Michigan), and a Pentium IBM-based computer with expanded memory capabilities (Dell Computer Corp, Round Rock, Texas). The degree of tendon retraction was measured via calibrated gross digital images using Image Pro Plus imaging system (Media Cybernetics).

TABLE 2  
Summary of Biomechanical Data<sup>a</sup>

Treatment	Load at Failure, N	Stiffness, N/mm	Elongation, mm	Failure Location, no.	
				Repair Tissue	Avulsion
Suture only	910.4 ± 156.1	131.4 ± 14.2	9.0 ± 0.6	9	0
Collagen + 0 µg rhPDGF-BB	1120.4 ± 157.4	157.3 ± 19.0	10.2 ± 1.0	9	0
Collagen + 75 µg rhPDGF-BB	1490.5 ± 224.5 <sup>b</sup>	134.4 ± 15.5	15.2 ± 1.0 <sup>c</sup>	3	6
Collagen + 150 µg rhPDGF-BB	1486.6 ± 229.0 <sup>b</sup>	147.5 ± 13.7	15.4 ± 2.4 <sup>c</sup>	4	5
Collagen + 500 µg rhPDGF-BB	677.8 ± 105.9	104.3 ± 21.4	11.5 ± 1.3	9	0
Intact tendon	4211.6 ± 229.6	300.3 ± 17.7	16.8 ± 1.3	0	6

<sup>a</sup>Treatment group: n = 9; intact control: n = 6. rhPDGF-BB, recombinant human platelet-derived growth factor–BB.

<sup>b</sup>Indicates significant difference compared to suture only and collagen + 500 µg rhPDGF-BB.

<sup>c</sup>Indicates significant difference compared to suture only and collagen + 0 µg rhPDGF-BB.

TABLE 3  
Histologic Score Raw Data (n = 3)<sup>a</sup>

Treatment Group	Gap Length, mm	Vascularity	Inflammatory Cells	Collagen Fibers		Sharpey Fibers
				Orientation	Density	
Suture only	29.6	2	1	1	1	0.2
Suture only	24.7	2	1	1.4	2	0.5
Suture only	29.8	2	1	1.2	2.2	0.5
Collagen + 0 µg rhPDGF-BB	43.1	2	1	1.9	2.3	0.3
Collagen + 0 µg rhPDGF-BB	40.4	2	1	1	1.6	0.5
Collagen + 0 µg rhPDGF-BB	33.7	2	1.5	1.3	1.5	0
Collagen + 75 µg rhPDGF-BB	38.1	2	1	1.3	2	1
Collagen + 75 µg rhPDGF-BB	42.3	2	0.9	2.4	2.5	2
Collagen + 75 µg rhPDGF-BB	45.0	2	0.6	1.5	2.5	1.9
Collagen + 150 µg rhPDGF-BB	44	2	0.8	1.7	2	1
Collagen + 150 µg rhPDGF-BB	55.5	2	1.2	1.7	1.9	0.1
Collagen + 150 µg rhPDGF-BB	36.3	2	0.7	2	2.5	3
Collagen + 500 µg rhPDGF-BB	31.4	2	1	1	1.4	0.1
Collagen + 500 µg rhPDGF-BB	42.7	2	1	1.1	1.2	0.3
Collagen + 500 µg rhPDGF-BB	48.7	2	1	1	0	0.1

<sup>a</sup>Individual scores are shown as the average score of 5 graded sections. rhPDGF-BB, recombinant human platelet-derived growth factor–BB.

## Statistical Analysis

Statistical differences in the biomechanical response (stiffness, ultimate load, elongation) between experimental groups were determined using a 1-way analysis of variance and post hoc Fisher least significant difference at a significance level of 5% (SigmaStat, Systat Software Inc, Richmond, California). Statistics were not performed on the histopathology scores because of the low sample numbers. Biomechanics data are presented as the mean ± standard error of the mean and histopathologic scores are presented as the median with range.

## RESULTS

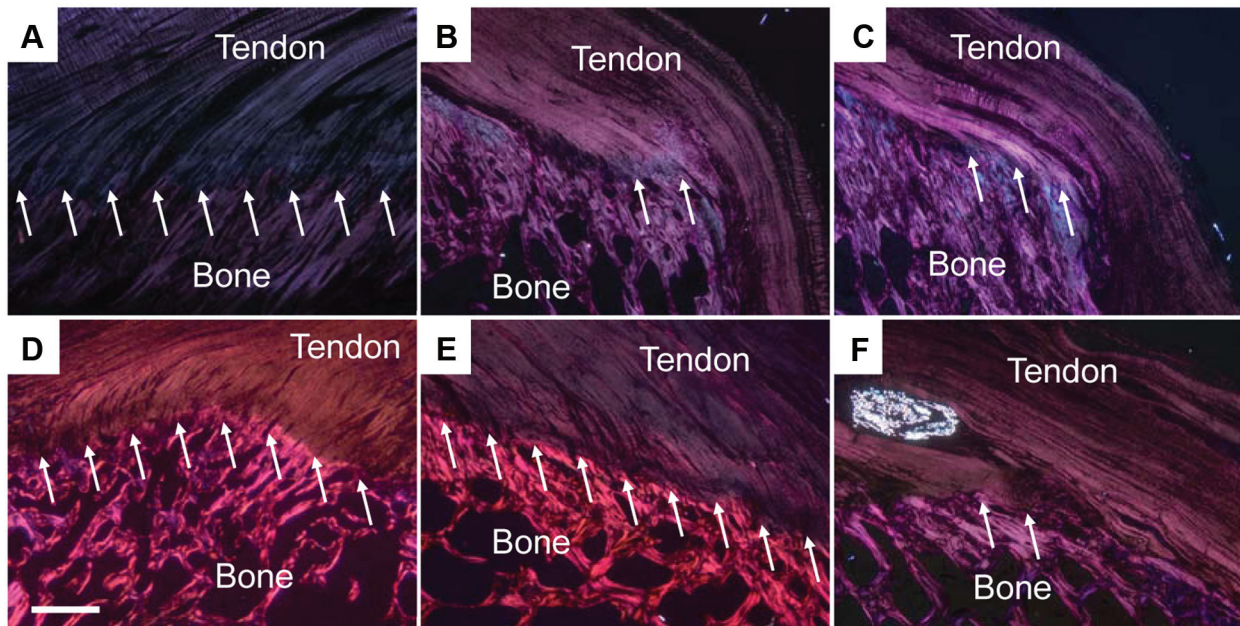
### Gross Observations

There were no intraoperative complications and all animals were load-bearing within 60 minutes of surgery. By

postoperative day 2, the pain scores were 0 to 1, and by postoperative day 3, the scores were 0 in all animals. After day 3, provision of analgesics was discontinued. During convalescence, there were no complications resulting from the surgical rotator cuff repair, no evidence of postoperative infection or drainage from the skin incisions, and no mortality in the 12-week survival period. Upon inspection at necropsy, all specimens felt robust upon palpation and no gross failures of the repair were noted. All specimens had a fibrous repair tissue evident between the tendon end and bony insertion.

### Biomechanical Analysis

Biomechanical results are presented in Table 2. After the 12-week recovery period, repairs augmented with 75-µg and 150-µg rhPDGF-BB resulted in a significant 63.7% ( $P = .029$ ) and 63.3% ( $P = .029$ ) increase in load to failure relative to the suture-only group and a significant 120%



**Figure 2.** Polarized light images of hematoxylin and eosin-stained sections show regions of interdigitation (arrows) of the repaired tendon with bone at the infraspinatus insertion site. Scale bar = 1 mm). A, native tendon; B, suture only; C, collagen + 0 µg rhPDGF-BB (recombinant human platelet-derived growth factor-BB); D, collagen + 75 µg rhPDGF-BB; E, collagen + 150 µg rhPDGF-BB; F, collagen + 500 µg rhPDGF-BB.

( $P = .003$ ) and 119.3% ( $P = .003$ ) increase relative to the 500-µg rhPDGF-BB dose. The 75-µg and 150-µg rhPDGF-BB doses were not significantly different relative to each other ( $P = .988$ ) or to the 0-µg matrix-only group ( $P = .155$  and  $P = .160$ , respectively). There were no significant differences observed in the load to failure among the suture-only control, 0-µg, and 500-µg rhPDGF-BB groups ( $P > .05$ ). No significant differences in construct stiffness were identified among groups ( $P = .254$ ). The 75-µg and 150-µg rhPDGF-BB groups exhibited significantly greater elongation at failure relative to the suture-only group ( $P = .018$  and  $P = .024$ , respectively) and 0-µg rhPDGF-BB group ( $P = .015$  and  $P = .024$ , respectively). No significant differences in elongation at failure were identified between the 75-µg, 150-µg, and 500-µg rhPDGF-BB groups ( $P > .05$ ).

The construct failure location (Table 2) in the suture-only, 0-µg, and 500-µg rhPDGF-BB treatment groups was manifested as midsubstance tissue failure in the tendon repair tissue. No humeral avulsion failures were noted in any ( $n = 27$ ) of the tendons in these 3 groups. In contrast, the failure locations in the 75-µg and 150-µg rhPDGF-BB groups were mixed, manifesting as either midsubstance tissue failure in the tendon repair tissue or as midsubstance tissue failure combined with some bony avulsion. Specifically, 6 of 9 (66.7%) of the shoulders in the 75-µg rhPDGF-BB group and 5 of 9 (55.6%) of the shoulders in the 150-µg rhPDGF-BB group exhibited some degree of failure within the bone leading to avulsion of the bone surface rather than intrasubstance tissue failure in the tendon repair tissue.

## Histology

Tendon gap lengths and semiquantitative histologic scores are shown in Table 3. All specimens exhibited retraction of the tendon, with the area between the native tendon end and the humeral insertion filled with reparative tissue consisting of a fibrovascular tissue (highly vascularized fibrous tissue) with active fibroplasia and polarizable collagen fibers present. The average gap length was lowest in the suture-only group ( $28.0 \pm 2.9$  mm), with the gap lengths similar among the 0-µg ( $39.1 \pm 4.8$  mm), 75-µg ( $41.8 \pm 3.5$  mm), 150-µg ( $45.3 \pm 9.7$  mm), and 500-µg ( $40.9 \pm 8.8$  mm) rhPDGF-BB groups. All treatment groups received similar scores for vascularization and presence of inflammatory cells. The median collagen fiber orientation and collagen fiber density were increased in the 75-µg (1.5 [range, 1.3-2.4] and 2.5 [range, 2.0-2.5], respectively) and 150-µg (1.7 [range, 1.7-2.0] and 2.0 [range, 1.9-2.5], respectively) rhPDGF-BB groups relative to the suture-only (1.2 [range, 1.0-1.4] and 2.0 [range, 1.0-2.2], respectively), 0-µg (1.3 [range, 1.0-1.9] and 1.6 [range, 1.5-2.3], respectively), and 500-µg (1.0 [range, 1.0-1.1] and 1.2 [range, 0.1-1.4], respectively) rhPDGF-BB groups. The median score for the bone-tendon interface (tendon interdigitation/Sharpey fibers) was increased in the 75-µg (1.9 [range, 1.0-2.0]) and 150-µg rhPDGF-BB groups (1.0 [range, 0.1-3.0] relative to the suture-only (0.5 [range, 0.2-0.5]), 0-µg (0.3 [range, 0.0-0.5]), and 500-µg (0.1 [range, 0.1-0.3]) rhPDGF-BB groups. The bone-tendon interface score corresponded to a qualitatively observed

interdigitation over approximately 30% to 40% of the total bone surface in the 75- $\mu$ g and 150- $\mu$ g rhPDGF-BB groups, compared with approximately 5% to 10% in the other 3 treatment groups (Figure 2).

## DISCUSSION

Biologic augmentation of suture repairs of the rotator cuff may have the potential to improve the integrity of the repair, thereby improving the long-term outcomes for clinical patients. In this study, an ovine infraspinatus detachment model of a large and challenging rotator cuff tear was used. Application of 75  $\mu$ g and 150  $\mu$ g of rhPDGF-BB with a type I collagen matrix resulted in significant increases in the ultimate load to failure relative to the standard of care (suture only) and the high-dose rhPDGF-BB groups (500  $\mu$ g) in this model. The average load to failure was decreased in the 500- $\mu$ g rhPDGF-BB group compared with the suture-only control ( $P = .368$ ) and increased in the 75- $\mu$ g and 150- $\mu$ g groups compared with the matrix-only group ( $P = .155$  and  $P = .160$ , respectively). Neither of these results was significant, potentially as a result of the sample size used in this study. Additionally, the morphologic appearance, including the integration of the tendon with the bone, was improved in the 75- $\mu$ g and 150- $\mu$ g rhPDGF-BB groups. These results are consistent with the efficacious effect of rhPDGF-BB in tendon repair observed in previous studies.<sup>7,22,50,53,57,58</sup>

There are some limitations to the ovine model of rotator cuff repair that must be considered when extrapolating the results to the human condition. One such limitation is that the anatomy of the sheep shoulder differs from that in the human. Sheep lack an acromial arch, which has been implicated in rotator cuff degeneration in humans.<sup>4,54</sup> Additionally, while most tears in the human rotator cuff occur in the supraspinatus tendon, the infraspinatus tendon is used in the ovine model because its size and function are similar to the human supraspinatus tendon.<sup>††</sup> Further, the ovine infraspinatus tendon is extra-articular and has no contact with synovial fluid, as opposed to the human rotator cuff, which contacts synovial fluid. In addition to the anatomic differences, gap formation is commonly observed in the ovine model of rotator cuff repair,<sup>32,33,42,46,47,49,56</sup> as the sheep are load-bearing immediately postoperatively and the load is borne solely by the suture repair, whereas the minimization of gap formation is crucial in the human clinical situation.<sup>8,14,18</sup> Immobilization has been investigated in the ovine model as a means of reducing gap formation<sup>25,33,42</sup>; however, the long-term biomechanical properties of immobilized repairs were not significantly different from nonimmobilized repairs.<sup>33</sup> Based on this finding and our Institutional Animal Care and Use Committee's unwillingness to approve immobilization protocols using the ovine model of rotator cuff repair, immobilization was not used in this study. Tendon retraction was observed in all specimens in this study, with the gap between the tendon end and the humeral insertion

filled with a fibrous repair tissue. However, formation of a fibrous repair tissue in the gap indicates that the tear may be able to heal without repair. In an ovine chronic model of rotator cuff repair, Gerber et al<sup>25</sup> demonstrated that this fibrous repair tissue was evident without suture repair, although the repair tissue was intrinsically and mechanically weak. Therefore, the study design included only treatment groups that more closely follow clinical treatments rather than a nonrepaired group. The increased strength of the repair tissue with 75- $\mu$ g and 150- $\mu$ g doses of rhPDGF-BB, relative to the suture-only control and 500- $\mu$ g rhPDGF-BB groups, suggests that rhPDGF-BB is able to improve the quality of the healing between the tendon and bone in a dose-dependent manner. While it is important to be cognizant of the limitations of the ovine model, valuable information, such as the ability of rhPDGF-BB and a collagen matrix to improve the quality of the tendon repair, tendon-to-bone integration, and biomechanical function, can still be inferred from the results of this study.

A major hurdle for the clinical use of exogenous growth factors is the ability to determine the safest and most efficacious dose. In a previous study using rhPDGF-BB-coated sutures for rotator cuff repair,<sup>57</sup> histologic analysis showed improved results in the rhPDGF-BB groups with no differences observed in the biomechanical properties, possibly because of the dose of rhPDGF-BB applied (approximately 12  $\mu$ g). A dose-dependent effect on biomechanical properties has been observed in studies in which rhPDGF-BB was applied to tendon and ligament repair models, with increasing doses resulting in improved properties.<sup>3,7,27</sup> Therefore, this study used a collagen matrix with higher doses of rhPDGF-BB to determine if increasing the dose of rhPDGF-BB could improve on the results found by Uggen et al.<sup>57</sup> The interpositionally applied saturated matrix was intended to confine the matrix to the repair site, promoting localized delivery of rhPDGF-BB, and to allow for tissue ingrowth of the bone and tendon. The matrix was not rigidly fixed in place; however, no observations were noted on gross examination at necropsy or histologically to suggest that any migration of the matrix attributable to lack of fixation had any negative effect on the repair. Although local delivery of rhPDGF-BB occurs quickly (>92% released at 24 hours) based on the *in vitro* release profile,<sup>34</sup> the effect of rhPDGF-BB on cells (proliferation and cell density) and extracellular matrix composition (collagen cross-linking) have been shown to be affected for up to 7 to 42 days after application, either as a free rhPDGF-BB injection or in a fibrin delivery matrix.<sup>7,27,50,53</sup>

The primary function of a tendon is to transfer the mechanical load from muscle to bone. A decreased ability of the repaired tendon to support a load can lead to functional deficits and, ultimately, failure of the clinical repair.<sup>51</sup> A dose-dependent increase in the mechanical properties was observed in the current study, with the 75- $\mu$ g and 150- $\mu$ g rhPDGF-BB doses resulting in a significantly higher load to failure and elongation at failure relative to the suture-only control and the 500- $\mu$ g rhPDGF-BB dose groups after 12 weeks of healing. This suggests

††References 11, 32, 33, 42, 43, 46, 47, 49, 56.



a therapeutic range that is able to promote significantly increased biomechanical integrity in the acute period and may decrease the potential for premature failure of the repair. However, it should be noted that the failure loads reported for the 75- $\mu$ g and 150- $\mu$ g rhPDGF-BB doses were approximately 35% of the values seen in native, intact tendons ( $4211.6 \pm 229.6$  N), an expected result after only 12 weeks of healing. Nevertheless, the early increase in mechanical properties is important as it may allow for earlier implementation of a rehabilitation program. Additional monitoring of the biomechanical properties of the repair over longer durations, along with the application of a proper rehabilitation program, would likely allow for continued maturation of the bone-tendon interface and further improvement of the mechanical properties of the repaired rotator cuff.

Interestingly, we noted an apparent 26% decrease in load to failure and a 21% decrease in the stiffness in the 500- $\mu$ g rhPDGF-BB-augmented group relative to the suture-only controls. While this finding was not significant ( $P = .368$  and  $.266$ , respectively), future studies with higher sample size and power may be warranted to more precisely determine the effects of such a high dose of the therapeutic protein on rotator cuff repair in the ovine model. It is important to note that although the high dose was no better than the suture-only controls, there were no gross failures noted at necropsy, indicating that all of the repairs were above the biomechanical failure threshold in this ovine model. This high-dose phenomenon was not reported for orthopaedic ligament and tendon repair,<sup>3,7,27</sup> but it has been demonstrated in human periodontal bone and ligament repair.<sup>40</sup> The doses used in this study (75, 150, and 500  $\mu$ g) were all higher than the maximum doses used in those previous studies, which investigated the effect of rhPDGF-BB in rat patellar tendon repair (1  $\mu$ g),<sup>7</sup> rat medial collateral ligament repair (5  $\mu$ g),<sup>3</sup> and rabbit medial collateral ligament repair (20  $\mu$ g).<sup>27</sup> While the overall doses are similar when adjusted for the size of the animal, it is possible that the previous studies have not reached a high enough dose level to observe similar effects. Additionally, the current study involved tendon-to-bone healing, rather than tendon-to-tendon, where the integration of the tendon and bone contributes to the overall strength of the repair and may require a different dose for proper repair. The dose-dependent effect of rhPDGF-BB observed in this study is consistent with a previous 180-patient multicenter, randomized controlled human clinical trial using rhPDGF-BB for periodontal bone and ligament repair in which 150  $\mu$ g rhPDGF-BB resulted in greater (although not statistically significant) bone and periodontal ligament regeneration than did 500  $\mu$ g.<sup>40</sup> Collectively, the data from the current study, as well as from a previous large randomized controlled human clinical trial, suggest that there is a dose-dependent range for the efficacy of rhPDGF-BB, after which no further beneficial effect may be expected and inhibition of healing may even occur. These dose-dependent findings will be important as future clinical trials are designed to determine the safety and effectiveness of rhPDGF-BB for improving the function of repaired rotator cuff tendons.

Histologically, the vascularity and inflammatory response to injury and treatment were similar among groups, indicating that the rhPDGF-BB and collagen matrix were well tolerated. Gaps filled with repair tissue between the native tendon and the humerus were observed in all groups. While the average gap length was smaller in the suture-only group, there was not a corresponding increase in strength of the repaired tendon-bone specimen in this group. The median collagen fiber alignment, median collagen fiber density, and median tendon-to-bone interdigitation scores were higher in the 75- $\mu$ g and 150- $\mu$ g groups, relative to the other groups. Interdigitation of the tendon collagen fibers into the bone provides a mechanical anchor for the tendon and serves to transfer stress from tendon to bone, giving rise to the mechanical properties.<sup>51</sup> The improved interdigitation scores were consistent with the failure location observed in biomechanical testing, where only the intact controls (6 of 6), 75- $\mu$ g (6 of 9) and 150- $\mu$ g (5 of 9) rhPDGF-BB-treated tendons failed with some degree of bony avulsion. This is beneficial to the long-term outcome of rotator cuff repair, as the lack of integration has been suggested as a reason for repeated tearing of the rotator cuff.<sup>24,46,49</sup> Although the histopathology scores were not analyzed statistically because of the low sample number for each group, the results suggest an improved repair in these groups, which is consistent with improved biomechanical properties and illustrates the potential of the combination of rhPDGF-BB and a collagen matrix for rotator cuff repair.

Taken together, the results of this study suggest that rhPDGF-BB, in combination with a type I collagen matrix, has promise as a therapeutic treatment for improving the healing of rotator cuff tears. Clinical trials appear warranted to determine the safety and effectiveness of this therapeutic modality to improve healing of rotator cuff tears in humans.

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