



## Mechanical restoration and failure analyses of a hydrogel and scaffold composite strategy for annulus fibrosus repair



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### ABSTRACT

Unrepaired defects in the annulus fibrosus of intervertebral disks are associated with degeneration and persistent back pain. A clinical need exists for a disk repair strategy that can seal annular defects, be easily delivered during surgical procedures, and restore biomechanics with low risk of herniation. Multiple annulus repair strategies were developed using poly(trimethylene carbonate) scaffolds optimized for cell delivery, polyurethane membranes designed to prevent herniation, and fibrin-genipin adhesive tuned to annulus fibrosus shear properties. This three-part study evaluated repair strategies for biomechanical restoration, herniation risk and failure mode in torsion, bending and compression at physiological and hyper-physiological loads using a bovine injury model. Fibrin-genipin hydrogel restored some torsional stiffness, bending ROM and disk height loss, with negligible herniation risk and failure was observed histologically at the fibrin-genipin mid-substance following rigorous loading. Scaffold-based repairs partially restored biomechanics, but had high herniation risk even when stabilized with sutured membranes and failure was observed histologically at the interface between scaffold and fibrin-genipin adhesive. Fibrin-genipin was the simplest annulus fibrosus repair solution evaluated that involved an easily deliverable adhesive that filled irregularly-shaped annular defects and partially restored disk biomechanics with low herniation risk, suggesting further evaluation for disk repair may be warranted.

#### Statement of significance

Lower back pain is the leading cause of global disability and commonly caused by defects and failure of intervertebral disk tissues resulting in herniation and compression of adjacent nerves. Annulus fibrosus repair materials and techniques have not been successful due to the challenging mechanical and chemical microenvironment and the needs to restore biomechanical behaviors and promote healing with negligible herniation risk while being delivered during surgical procedures. This work addressed this challenging biomaterial and clinical problem using novel materials including an adhesive hydrogel, a scaffold capable of cell delivery, and a membrane to prevent herniation. Composite repair strategies were evaluated and optimized in quantitative three-part study that rigorously evaluated disk repair and provided a framework for evaluating alternate repair techniques.

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**Abbreviations:** AF, annulus fibrosus; IVD, intervertebral disk; NP, nucleus pulposus; FibGen, genipin-crosslinked fibrin gel; PTMC, poly(trimethylene carbonate); PMMA, polymethylmethacrylate; PBS, phosphate buffered saline; DMSO, dimethyl sulfoxide; ROM, range of motion.

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### 1. Introduction

Lower back pain affects up to 70% of people in their lifetimes [1] and is the leading cause of global disability [2,3]. Defects of the annulus fibrosus (AF) can result in herniation of intervertebral disk (IVD) material and compression of the nerve root, inducing back or leg pain. Discectomy is the most common and effective surgical

procedure at reducing leg pain related to IVD herniation [4–6]. It consists of removing extruded and loose nucleus pulposus (NP) tissue through an incision in the AF. However, both small and large defects in the AF can lead to altered biomechanics and increased degeneration risk [7–10]. A systematic review of the discectomy literature indicated that discectomy procedures have up to 27% risk of re-herniation requiring further surgery, and the prevalence depends on the size of the annular defect and the amount of material removed [11,12]. There also remains a relatively high risk of degeneration and persistent low back pain in longer-term follow-up, particularly if excess IVD material was removed to lower the reherniation risk. While discectomy procedures are very effective at reducing leg pain, there are opportunities to improve this procedure with AF repair techniques that reduce the rate of reherniation, improve biomechanics and can potentially be part of a disk regeneration strategy.

Annular defects result in loss of NP pressurization and AF integrity. A functional AF repair strategy must restore IVD height, neutral zone characteristics, and torsional biomechanics to the healthy condition without risk of herniation under the high physiological loads occurring in the spine [8]. Current AF repair strategies include sutures, plugs, adhesives and hydrogels [13]. Suturing the IVD during a discectomy procedure adds substantial complications to the procedures and extends the operation time. Suturing did not restore the intradiscal pressure of IVDs with different annular defects in sheep [14], suggesting suturing alone provided inadequate biomechanical repair. An alternative to manual sutures was a commercially available suture delivery system, the Xclose Tissue Repair System (Anulex Technologies, Minnetonka, MN). The Xclose device was designed to strengthen the suturing procedure and simplify the suturing process via an elongated suture delivery system allowing arthroscopic access. In a two year prospective, randomized control trial there was no difference in functional or disability outcomes between microdiscectomy performed with and without XClose sutures, although there was a significant reduction in re-herniation surgery observed in a subset cohort with predominant leg pain at 3 and 6 months [15]. The reduction in re-herniation rates was promising for a sutured AF repair, but no data was reported on disk height, biomechanical restoration of the motion segment, or MRI signal intensity providing no evidence that this technique would successfully prevent accelerated degeneration following discectomy procedures. An annulus closure plug had favorable biomechanical results *in vitro* but showed deformation and herniation after 6 weeks in an *in vivo* goat model [16]. Alternately, Barricaid is a device resembling a shield that is secured with an anchor into the adjacent inferior vertebral body to reduce the risk of tissue expulsion following a discectomy procedure (Intrinsic Therapeutics, Inc., Woburn, MA). In an *in vitro* test of 6 IVDs, no herniation was seen after more than 100,000 cycles of dynamic bending, indicating a low risk of herniation, however, the IVD height loss due to loading was not decreased [17] indicating limited biomechanical restoration. Barricaid demonstrated a reduced risk of facet degeneration [18], suggesting AF repair strategies capable of retaining NP pressurization following discectomy are likely to have improved outcomes. While several mechanical annular repair strategies exist, they all complicate discectomy procedures, several have risk of herniation, and none completely restore IVD biomechanics.

The broad aim of this study was to evaluate the repair of large AF defects using a composite repair strategy involving fibrinogenipin (FibGen) hydrogel adhesive to seal the AF defect, a poly(trimethylene carbonate) (PTMC) space-filling scaffold capable of cell delivery, and a polyurethane membrane to prevent herniation. Design criteria we considered necessary for an effective AF repair strategy included low risk of herniation, restoration of IVD biomechanics to the healthy (intact) condition, ease of delivery, and the

potential to be functionalized to deliver cells or drugs in order to promote long-term healing or regeneration. This three part biomechanical study assessed the performance of multiple composite repair strategies using these components evaluated under multiple degree of freedom biomechanical testing using bovine caudal IVD injury models. Part 1 applied a torsional stiffness test to evaluate whether the repair restored AF integrity since mechanical integrity of annulus fibrosus integrity is most sensitive to torsion [9,19]. Part 1 tested the hypothesis that the composite repair strategy with scaffolds would best restore biomechanics to intact levels but the adhesive alone would have the lowest herniation risk. Part 2 selected the most promising repairs from Part 1 and after procedure refinement, evaluated them for herniation risk and biomechanical restoration in axial compression and two bending degrees of freedom. Bending was evaluated since it can rigorously test for herniation risk. Part 2 tested the hypothesis that the FibGen adhesive alone and the composite repair with suturing augmentation could restore biomechanics and disk height loss without risk of herniation. Part 3 used the most successful repair strategies from Parts 1 & 2 and evaluated mechanical restoration using a cruciate-style defect to be more representative of the variety of defects found clinically following herniation and discectomy procedures [12] (rather than biopsy defects) and to evaluate if FibGen could adhere to irregularly-shaped defects. Part 3 used an angle control with moment limits test in 3 rotational degrees of freedom (i.e., torsion, flexion–extension & lateral bending). Part 3 was performed at the University of Bern (rather than Mount Sinai). Part 3 tested the hypothesis that the FibGen can seal a cruciate-style defect and restore the biomechanical behaviors to intact levels in bending, flexion–extension, and axial rotation.

## 2. Materials and methods

### 2.1. Material selection

FibGen involved a genipin-crosslinked fibrin gel with a formulation previously tuned to match the shear properties of the native AF tissue [20]. The space filling PTMC scaffolds consisted of 5000 g/mol oligomers crosslinked with stereolithography to ensure a precise structure that mimicked the complex architecture of the AF collagen bundles which are oriented in an angle-ply fashion that evolve from  $\pm 30^\circ$  in the inner AF to  $\pm 45^\circ$  in the outer AF [21]. Two scaffold geometries were evaluated: a truncated cone shape and a cylindrical shape. A polyurethane membrane was designed to prevent extrusion of IVD tissue and provide a barrier between the IVD and the adjacent sensitive nerve. The polyurethane membrane was adhered to the native AF tissue using FibGen adhesive as well as suturing.

### 2.2. Animal model, dissection and storage

Bovine coccygeal IVDs are large and comparable to human lumbar IVD [22,23], easily available and well-studied. Motion segments (bone–IVD–bone) were harvested from skeletally mature bovine tails obtained from a local abattoir (Green Village Packing, Green Village, NJ). Following dissection, IVDs were wrapped in saline soaked tissue and frozen at  $-20^\circ\text{C}$  until testing. On the day of testing, all specimens were thawed for 3 h in 1 L PBS at  $37^\circ\text{C}$  and warm to touch, then potted in polymethylmethacrylate (PMMA). No disks underwent additional freeze–thaw cycles in order to decrease the change in biomechanics due to freeze–thaw cycles [24]. To minimize variability in injury and repair procedures, a single biomedical engineer performed injury and repair procedures for each Part (as described in Sections 2.3–2.5) following training by a spine surgeons and extensive practice on all techniques.

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