SPECIFIC AIMS: GROUP 3

A certain cartilage type, labral cartilage, is particularly prone to tearing; labral tears have been observed in 93% of cadavers. The labrum acts as a seal to secure the hip socket and to distribute weight on the hip joint. Labral tears have been identified as a precursor to osteoarthritis, a degenerative cartilage disease affecting 49.7% of the U.S. population age 65 and up. While implantable cartilage treatments such as Carticel © for cartilage repair exist, they are specifically designed for patients with substantial cartilage loss, not for cartilage tears. Furthermore, many are not approved for use in the hip. Currently, labral tears are treated either by debridement (trimming the torn edges) or via suturing with standard surgical sutures. Cell therapies such as cell injection and cell-seeded sutures are currently being used to treat other tissues. However, oftentimes, these methods do not allow for high cell delivery efficiency and retention. Cell-embedded sutures made using chondrocytes derived from mesenchymal stem cells (MSCs) could be used to repair torn cartilage, eliminating the scar tissue formation found with standard surgical sutures by inducing growth in the cartilage itself, which would maintain the function of labral cartilage and reduce the patient's risk of developing osteoarthritis.

Aim 1: **Create braided graphene oxide/ultra-high molecular weight polyethylene composite (GO/UHMWPE) sutures and addition of an outer layer made of chitosan embedded with chondrocytes.**

Hypothesis: We will achieve high cell viability, greater than 90%, in the outer layer of our suture.

Method: Single graphene oxide/ultra-high molecular weight polyethylene strands will be made using a spinneret. The fiber strands will be collected on a spindle and braided using a micro-braiding technique described in an article written by Kobayashi et al. An outer layer, consisting of chondrocytes encapsulated in chitosan, will be added to the braided GO/UHMWPE composite using a cylindrical mold.

Aim 2: **Measure physical properties of the fabricated sutures compared to commonly used suture material for labral tears, and assess chondrocyte viability in the outer layer.**

Hypothesis: The efficiency of the cell-embedded suture is dependent on the density and strength of the stitching.

Method: After fabrication, the sutures will be evaluated in-vitro. Because it is desirable to have a suture material which can withstand force without breakage, the tensile strength and durability must be assessed, and will be analyzed with an Instron. Knot type and slippage will also be evaluated, including single-pass, simple stitch, and vertical mattress techniques. Suture degradation and viability of embedded cells will also be evaluated over the course of 28 days. The results will be compared to literature and strength of sutures used in medical practice.

Aim 3: **Compare post-surgery healing effects of cell-embedded sutures in an animal model vs post-surgery healing effects of typical sutures.**

Hypothesis: The cell-embedded sutures will improve healing rate in labral cartilage repair when compared to standard sutures.

Method: Labral capsulotomies and then repairs will be performed on 36 New Zealand rabbits in the anterior quadrant of the hip joint using either placebo injections, MSC injections, cell-embedded sutures, or regular surgical sutures. All rabbits will be given MRIs at 6, 12, and 18 weeks to check for developed cartilaginous abnormalities and healing progress. Additionally, 4 rabbits from each treatment group will be sacrificed at these time points, and the hip joint will be dissected, revealing the labral cartilage. Hematoxylin-eosin stain will be applied to prepared biopsy slices of the repaired area, and comparative healing status will be assessed visually.

No attempts to create cell-embedded sutures have been made prior to this study; this is a novel biomaterial with numerous and varied future applications. Cell-embedded sutures made of chondrocytes would be the first treatment for the regrowth of torn cartilage, which can occur in any joint of the body. If successful, these sutures would be the preferred labral cartilage repair method and would likely lead to a dramatic decrease in the prevalence of osteoarthritis in the population. Additionally, cell-embedded sutures could be used to repair muscles, cartilage, and organs, while causing minimal scarring.

SIGNIFICANCE

The labrum, also known as the cotyloid ligament, is a fibrocartilaginous rim that attaches to the circumference of the acetabulum, or cotyloid fossa, deepening the socket for the femoral head to sit in. (Figure 1). The labrum consists of an inner, articular-sided layer of fibrocartilage and an outer, capsular layer of dense connective tissue oriented in circular collagen type I fibrils [1]. This circular orientation and the transverse acetabular ligament form a continuous, usually triangular, structure surrounding the acetabulum, resulting in hip stability. The labrum acts as a sensitive shock absorber, joint lubricator, pressure distributor, and aids in stability [2]. According to available studies, the labrum has been shown to deepen the acetabulum by 21% and increases the surface of the acetabulum by 28%, which helps distribute weight and decrease stress on the articular cartilage [2]. The labrum also acts as a seal to maintain the synovial fluid and fluid pressure between the femoral head and the labrum, resulting in lower stresses and strains across the hip joint and prevention of cartilage deterioration [1]. Without the labrum, the stress on the hip joint increases by as much as 92% [2].

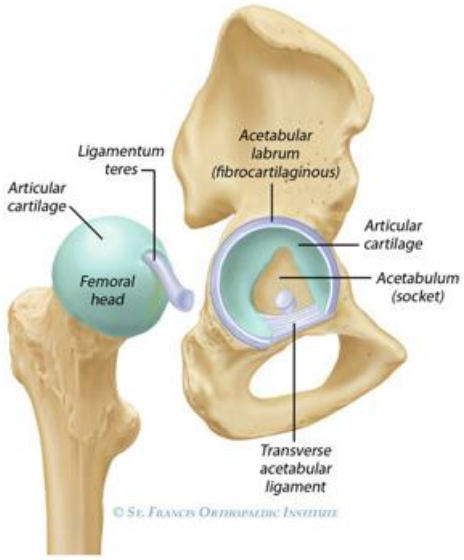

Figure 1: Acetabular Labral Anatomy [3]

Acetabular labral tears can cause pain and stiffness in the hip joint. The tear usually occurs when the labrum is torn, frayed, or damaged. Repetitive trauma to the hip joint, hip dysplasia, or excessive external rotation of the joints are common causes of labral tear. However, 75% of cases of labral tears have an unknown direct cause [2]. Labral tears have been observed to be the precursors to osteoarthritis, which affects 49.7% of U.S. population of adults age 65 years or older [4]. 73% of patients with labral tears were observed to have developed cartilage degradation, the beginning stages of osteoarthritis [5]. According to McCarthy et al, 93% of cadavers (average age = 78 years, range = 48 - 102 years) have at least one labral tear [6].

Currently, labral tears are treated with physical therapy or arthroscopic surgery, depending on the severity of the tear and the pain. Arthroscopic surgery is a procedure in which an arthroscope and surgical tools are inserted via small incisions in the skin. Depending on the severity of the tear, labral tears are treated either by debriding, or trimming, the torn edges, or via suturing with standard surgical sutures [2]. However, debridement reduces the ability to of the labrum to seal synovial fluid into the joint, resulting in future hip degeneration. In an attempt to avoid this functional loss, surgeons sometimes turn to suturing the labrum with standard surgical sutures, which cause a thin layer of scar tissue to form in the healed labral. This is problematic because the smoothness and flexibility of cartilage is integral to the proper pain-free functioning of the joint. Additionally, patients with suture-repaired labral cartilage were found to have the slowest recovery time, and the cartilage re-tore in 17% of patients, requiring a second procedure [5].

If cell-embedded sutures were made using chondrocytes, these sutures could be used to repair labral tear. The cell-embedded sutures would regenerate the damaged labrum by inducing growth, eliminate scar tissue while maintaining the function of the labrum and reducing the risk of developing osteoarthritis in patients.

INNOVATION

1. Innovative sutures will be the first attempt to treat torn cartilage with chondrocytes.

Prior to this innovation, standard surgical sutures used in arthroscopic hip surgery were the only method of treatment for labral tears. The standard surgical sutures often cause a thin layer of scar tissue to form over the spot, impairing the smoothness and flexibility needed in the cartilage. Patients with suture-repaired labral cartilage were found to have the slowest recovery time, and the cartilage re-tore in 17% of patients, requiring a second procedure [9]. So far,

the only other chondrocyte treatment methods, such as Carticel ©, are specifically for patients with much more severe and complete cartilage damage [10]. Cartilage tears such as labral tears are measured in the millimeters and so don't require large-scale intervention. Additionally, treatments such as Carticel © have slower healing rates than standard treatments, though they do provide better long-term healing.

Currently, many physicians do not suggest surgery for patients with asymptomatic or slightly symptomatic labral tears, presumably as the scar tissue resulting from surgery could actually lead to an increase in pain [11]. However, as 73% of patients with labral tears develop more serious cartilage degradation as a result of losing the sealing ability of the labrum, inaction on labral tears likely contributes to the high U.S. rates of cartilage degradation and osteoarthritis [2]. If a treatment method existed that would not cause scar tissue formation in the cartilage, the main barrier to prescribing surgery for slightly symptomatic labral tears would be removed, leading to a decrease in the number of patients who then go on to develop osteoarthritis.

2. Innovative sutures will be the first attempt at creating and using a cell-embedded suture.
Cell-embedded sutures have never been created before. We hypothesize that by creating a suture consisting of an inner non-absorbable layer made of braided graphene oxide/ultra-high molecular weight polyethylene strands and an outer absorbable layer made of chondrocyte embedded chitosan, we will be able to control the release of chondrocytes into the cartilage defect. This new suture will allow for the implementation of the first-ever chondrocyte treatment for cartilage tears.

APPROACH
We seek to develop a new and innovative suture for the repair of torn cartilage, particularly labral cartilage, in order to drastically improve surgical outcomes for labral repair and to decrease the percentage of people that go on to develop osteoarthritis, a prevalent and costly condition. Ultra-high molecular weight polyethylene (UHMWPE) has been found to have low surface hardness and poor wear, which can lead to osteolysis [12]. Chen et al. have reported that the incorporation of graphene oxide in UHMWPE matrices enhanced surface hardness and improved tensile strength as compared to pure UHMWPE [12]. Our sutures will consist of an inner non-absorbable layer made of braided graphene oxide/ultra-high molecular weight polyethylene strands and an outer absorbable layer made of chondrocyte embedded chitosan.

Aim 1: **Create braided graphene oxide/ultra-high molecular weight polyethylene composite (GO/UHMWPE) sutures and addition of an outer layer made of chitosan embedded with mesenchymal stem cell (MSC) derived chondrocytes.**
Hypothesis: We will achieve high cell viability, greater than 90%, in the outer layer of our suture.

1. Extrusion and collection of single GO/UHMWPE strands
A solution of 0.5% graphene oxide (w/v) in alcohol will be sonicated for 30 minutes. One percent ultra-high molecular weight polyethylene (w/v) will be stirred into the GO solution and sonicated again for one hour [12]. The GO/ UHMWPE solution will be extruded in a 60 °C oil bath using a spinneret (see Figure 2). The fibers will then be placed in a wash bath and collected on a spindle. After this, the spindles will be placed in an oven at 60 °C to dry. Samples of the strands will be taken and imaged using a scanning electron microscope (SEM). The single strands should have a smooth surface as well as a uniformed diameter throughout the whole length of the fiber (see Figure 3A). Braided GO/UHMWPE composite sutures will be fabricated using a micro-braiding technique discussed in an article by Kobayashi et al. The final structure of the braided suture will have a diameter of 500 μm and should look like the braided fiber shown in Figure 3B.

2. MSC derived chondrocytes

Mesenchymal stem cells from bone marrow will be differentiated into chondrocytes by culturing isolated MSCs pellets in serum-free complete chondrogenic medium (CCM) with transforming growth factor (TGF)- β3 [13]. The cells will be cultured for 24 days and chondrogenesis will be confirmed by staining with Alcian Blue and performing reverse-transcription polymerase chain reaction (RT-PCR) analysis on five chondrogenic markers: collagen II and X, aggrecan, COMP, and Sox9 [14, 15].

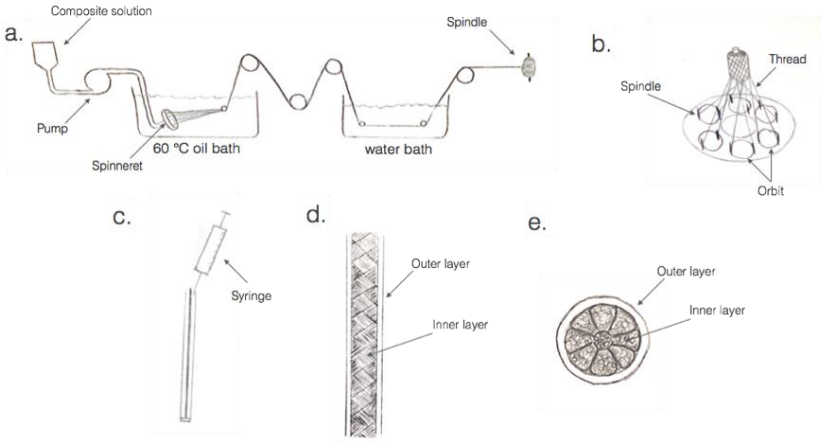

Figure 2: Schematic of suture fabrication. (a) Extrusion of GO/UHMWPE composite a into 60 °C oil bath, using a spinneret, and collection of strands on a spindle. (b) Braiding of composite strands. (c) Addition of outer layer by injecting chondrocyte encapsulated chitosan into a cylindrical mold. (d) Close up of final suture construct. Inner layer made of braided GO/UHMWPE composite. Outer layer made of chondrocyte encapsulated chitosan. (e) Cross-section of suture.

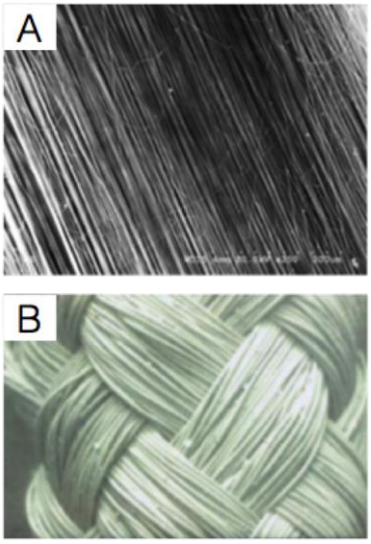

Figure 3: SEM image of (A) monofilament fiber, and (B) braided fiber [17].

3. Addition of an outer layer

Braided GO/UHMWPE composite sutures will be sterilized by immersing the sutures in povidone iodine 10% solution for 10 minutes and rinsed with deionized water [16]. The braided sutures will then placed in a 600 μm capillary tube, as shown in Fig. 2. A solution of crosslinkable and water-soluble chitosan derivative (CML) and chondrocytes will then be inserted into the space around the suture and incubated at 37 °C for 8 minutes. The resulting suture construct would then be removed from the capillary tube and stored in media.

Potential Problems:

Needle gauge size as well as ejections flow rates can influence cell viability in chitosan. Using a 34G needle would be the best**,** but studies have shown that injecting cells with a 30G needle at a flow rate of 150 μL/min leads to 99.9% cell viability, while a 34G needle—at the same flow rate—results in only 70% cell viability [18]. Although the 30G needle would be the best choice, the size of the needle could be too large for our purpose.

Aim 2: **Measure physical properties of the fabricated sutures compared to commonly used suture material for labral tears, and assess chondrocyte viability in the outer layer.**

<u>Hypothesis:</u> The efficiency of the cell-embedded suture is dependent on the density and strength of the stitching.

1. In-vitro evaluation of tensile strength in knots used to repair torn cartilage.

The strength that sutures must withstand changes with the thickness of the cartilage being repaired, and different methods of knotting are used in conjunction with suture anchors or screws in close proximity to the injury (approximately 2 mm). Three common knot techniques used in practice with their corresponding thickness can be seen in Table 1.

Fabricated sutures will be examined by replicating knot types in-vitro. First, sutures will be removed from the saline solution from which they were stored, and allowed to air dry on absorbent paper. The sutures will then be moistened with an application of a saline drip, and 50 mm of suture material will be placed on an S-shaped hook, connected to the loading clamp of an Instron tensiometer. Tensile force will be applied to each type of knot in both the created

material as well as #2 FiberWire at 20mm/min [19]. Ultimate tensile strength will be calculated from the maximum load, where the suture either slips or undergoes clinical failure, whereby knot length increases by 3 mm [20]. Testing will be replicated on standard #2 FiberWire sutures, a common material selected for labral repair.

Thickness of Labrum	Preferred Refixation Technique
> 5 mm	LBR with vertical mattress
3-5 mm	LBR with single-pass technique
< 3 mm	Looped simple stitch technique

Table 1: Three types of knots used in practice for differing cartilage thickness surrounding injured area [21].

2. Analysis of suture strength degradation and chondrocyte viability.
An aspect important to investigate is the degradation of sutures over time after implementation. To assess this parameter, sutures will be stored in medium with composition of dimethyl sulfoxide, fetal bovine serum, and Dulbecco Modified Eagle Medium in a ratio of 1:2:7 (v/v) [22], which simulates the avascular nature of cartilage while allowing chondrocytes to be exposed to nutrients to sustain them. Sutures will be stored in the medium, and samples will be taken for Instron testing on days 1, 7, 14, and 28, and tensile testing will be performed to clinical failure or slippage. Medium will be replaced on each sampling day. The sutures will again be compared to #2 FiberWire to determine whether or not the fabricated sutures are significantly stronger or weaker than currently used materials. On each of these sampling days, a live/dead assay will be done on final suture constructs using Calcein AM and ethidium homodimer-1 to test the viability of the cells at each time point to assess the presence of living chondrocytes.

Potential Problems:
The strength of fabricated sutures could be significantly stronger or weaker than what is used currently, and in this case, the composition of graphene oxide may need to be adjusted. The addition of the outer layer to sutures may change the tendency of suture knots to affix to a surface and may hinder Instron testing. The viability of chondrocytes may depend on the medium in which sutures are stored and may not reflect in-vivo implementation.

Aim 3: **Compare post-surgery healing effects of cell-embedded sutures in an animal model vs post-surgery healing effects of typical sutures.**
Hypothesis: The cell-embedded sutures will improve healing rate in labral cartilage repair when compared to standard sutures.

1. Creation of animal model of labral cartilage tear physiology 36 New Zealand rabbits over 3 kg will be anesthetized with 55 mg/kg of ketamine intravenously, and isoflurane will be administered through a breathing tube to maintain relaxation [23]. The New Zealand breed is common to use as a rabbit model as the breed is known for its docility and general lack of health problems [24]. Additionally, rabbits over 3 kg are known to have a better ability to handle surgical trauma [24]. Standard labral capsulotomies will be performed in the anterior quadrant of the left hip joint of each rabbit, leaving the right hip joint as a control [25]. The capsulotomy will be performed arthroscopically, with a 5 mm scalpel being used to create a capsule labral lesion, as seen in Figure 4. Repairs will then be performed on 24 of the rabbits, using cell-embedded sutures in 12 of the rabbits and regular surgical sutures in 12 of the rabbits. This suturing will be done in a manner resembling the suturing in Figure 5. The remaining 12 rabbits will have no repairs performed. Pulse oximeters will be utilized to monitor the oxygen saturation of the rabbits during surgery to ensure full anesthetic effectiveness. If the rabbits show signs of waking, the dosage of ketamine will be increased to 60 mg/kg. An IV tube will be placed to allow for fluids to be delivered to the rabbits, as they are prone to dehydration [24]. Additionally, a heating pad will be placed underneath the rabbits to combat their susceptibility to hypothermia [24].

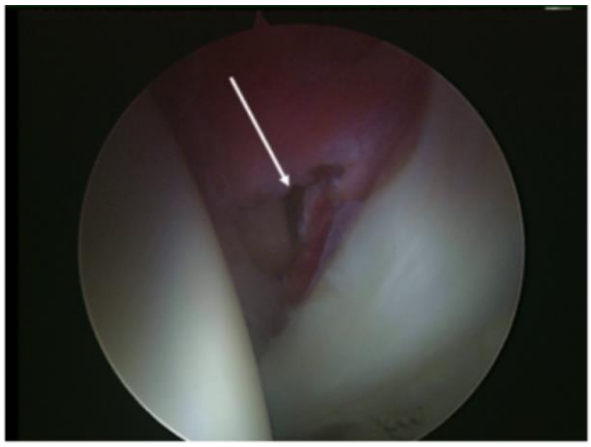

Figure 4: Induced labral capsulotomy injury [25].

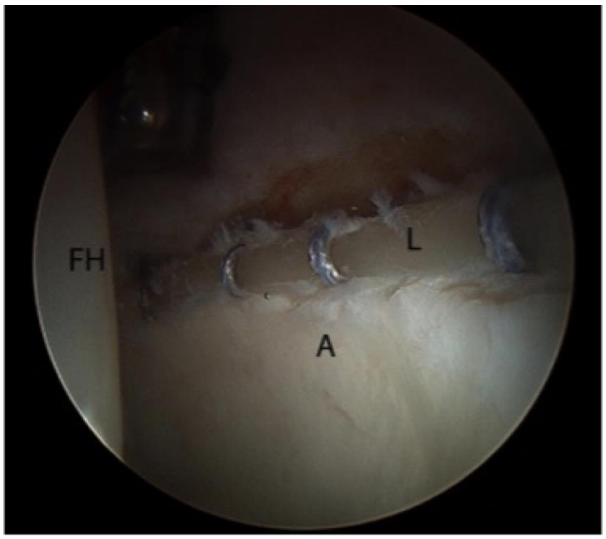

Figure 5: Labral repair with sutures [26].

After surgery, 0.3 mg/kg butorphanol will be administered via subcutaneous injection in the hip to the rabbits every 3 hours for 4 days to combat the pain [27]. Rabbits will be monitored for signs of distress, including extreme lethargy, whimpering, inability to move, or rejection of food more than 24 hours post-surgery. If these signs are observed and do not improve with medication, the rabbit will be euthanized with a barbiturate overdose of 0.22 mL/kg Euthasol® [27]. The rabbits will likely be lethargic and slow-moving for the first week post surgery but will be monitored during the second week and placed on a rear-suspension sling if needed to avoid excess weight being placed on the hip. After the second week, the hip will be classified as having reached full weight-bearing status. As humans typically need 4 weeks on crutches after labral repair surgery, and rabbits have twice the number of weight-bearing limbs and a fraction of the body weight, the recovery time of rabbits to full weight-bearing status is presumed to be less than for humans [23].

2. Evaluation of labral healing in animal model and comparison of cell-embedded suture effectiveness to standard suture effectiveness

All rabbits will be given MRIs at 6, 12, and 18 weeks to check for developed cartilaginous abnormalities and healing progress. The rabbits will be sedated with isoflurane administered through a breathing tube for the process. The MRI images taken will be from both of the anterior and posterior quadrants for a total of 4 MRI images per rabbit showing all sides of the hip. Additionally, 4 rabbits from each treatment group (no suturing, cell-embedded sutures, and standard surgical sutures) will be sacrificed at each of these time points, and the hip joint will be dissected, exposing the labral cartilage. Samples of cartilage from each hip of each rabbit will be excised and stained with hematoxylin-eosin stain to visually assess comparative cartilage healing [23]. The injured hip will be compared against the healthy control hip for each rabbit to determine a rough recovery level. Additionally, the injured hip from all rabbits will be compared against both the injured hips from their cohort and the injured hips from all of the sacrificed rabbits to determine which treatment method is most effective in healing the labral cartilage. This entire process is laid out in Figure 6. It is expected that the cell-embedded sutures will contribute to the most effective and quickest healing, as the release of chondrocytes in the wound area is predicted to allow for better wound healing.

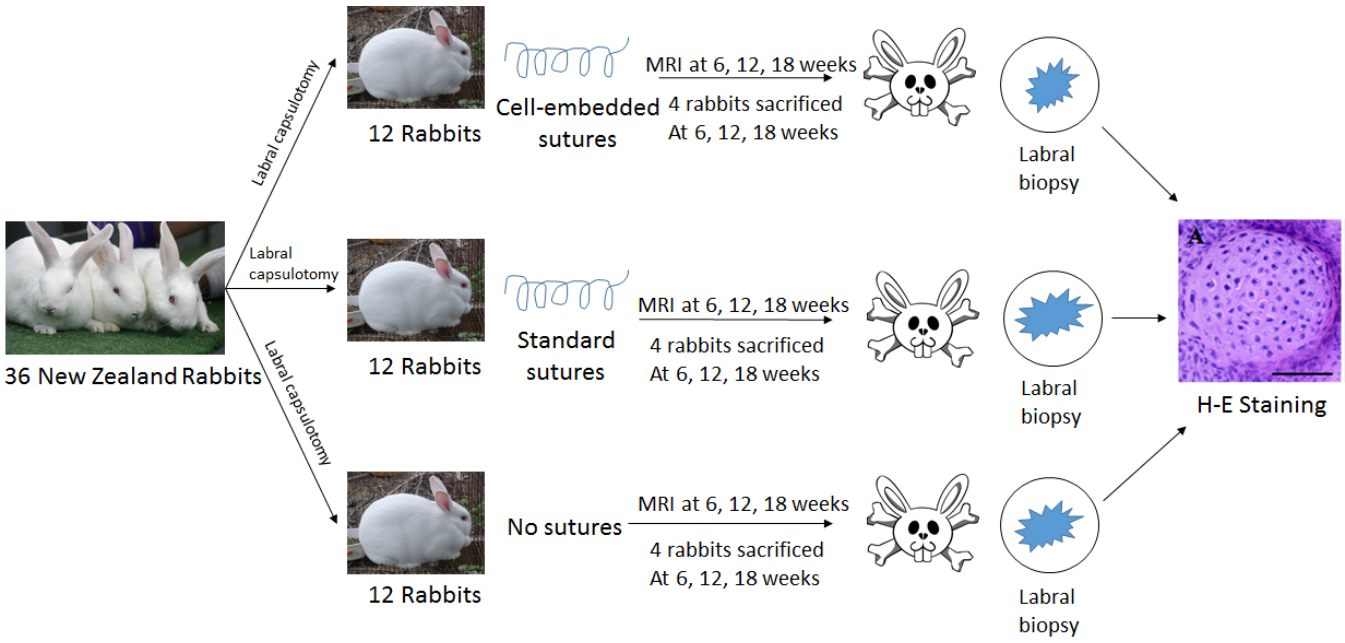

Figure 6: Aim 3 experiment diagram. Rabbits will be separated into 3 cohorts, which will each have a different repair done to an induced labral injury. MRIs will occur at 6, 12, 18 weeks, and rabbits will be sacrificed from each group at those time points. Labral biopsies will be taken and analyzed with hematoxylin-eosin staining.

Potential Problems:

As this procedure has been successfully completed before in a study of osteoarthritis at Universidad de León in Spain, there are not expected to be any complications with the procedure itself [23]. The sedation and health of the rabbits will be carefully monitored during the entire experiment, and care will be taken to modify the sedation process along the way if the rabbits require more anesthetic.

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