Design of an Implantable Ulnar Collateral Ligament Repair System

GXP- 2001

A Major Qualifying Project Report Submitted to the Faculty of

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In partial fulfillment of the requirements for the Degree of Bachelor of Science by

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Abstract

There is a need for a device that aids in restoring function to partial tears of the ulnar collateral ligament (UCL) in overhead throwing athletes. This project's goal is to design an implantable device to aid in the repair of damaged tissue and restore valgus stability. It will provide an additional therapeutic option that better matches the extent of their UCL injury. The scaffolds developed in this project may allow for return to pre-injury performance without complete surgical reconstruction.

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Abbreviations

ACL: Anterior Cruciate Ligament

dPBS: Dulbecco's phosphate-buffered saline

FGF-2: Fibroblast Growth Factor 2

hBMSC: Human bone marrow stem cells

MLB: Major League Baseball

PCC: Pairwise Comparison Chart

PRP: Platelet Rich Plasma

RTP: Return to Play

RTT: Return to Throw

TGF-β: Transforming Growth Factor β

UCL: Ulnar Collateral Ligament (of the elbow)

UNX: Uncrosslinked

XL: Crosslinked

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1. Introduction

According to a 2013 study produced by Bleacher Report, nearly one third (34 %) of all active Major League Baseball (MLB) players have undergone Ulnar Collateral Ligament (UCL) reconstructive surgery (Carroll, 2013). This translates to 124 out of a possible 360 players who fit the study's criteria (Carroll, 2013). Between the years 1991-2016, there were 292 major league baseball players that underwent total UCL reconstruction (Zaremski, 2017). While autografting techniques have demonstrated considerable success, there remain limitations associated with tissue availability, surgical integration and the rate of functional tissue regeneration. Additionally, the cost of UCL reconstruction can be between $10,000-$26,000, which will severely limit the access of treatment (MedRepublic, 2020). Patients with partial tears of their UCL currently must choose between physical therapy or surgical reconstruction. These methods were developed to address ligament stretching and complete tears, respectively. As such, there remains a significant need to develop an off-the-shelf, minimally invasive implantation system to facilitate UCL healing and tissue regeneration for partial tear injuries.

The UCL connects the humerus to the ulna. The ligament consists of three functional divisions: the anterior, posterior, and intermediate bundles. These divisions work in tandem to stabilize the arm when performing overhead motions. There is a plethora of actions that cause injury to the UCL; however, most cases tend to be collegiate or professional pitchers. Injuries of the UCL can be sorted into three categories or grades. Grade I consist of mild structural injury, such as sprains or stretches in the ligament. Grade II consists of partial tears, which is when there is structural damage without complete compromise of the ligament. Grade III consists of complete ruptures and compromise of ligament structure. Both Grade I and II injuries can be mild enough for a patient to continue their normal routines without major invasive treatment. However, they can also be painful and destabilizing enough to prevent normal function, leading to more invasive treatments. These extremes can vary from patient to patient. Grade III injuries

require full surgical reconstruction for patients to return to normal function. This report focuses on the Grade II injuries.

For Grade I & III injuries, there is precedent and accepted procedure when addressing UCL therapies. It is generally recommended that for Grade I injuries the patient regularly utilizes physical therapy to promote proper healing (Zaremski, 2017). This form of injury does not require a major operation to heal. Grade III injuries are complete tears, and therefore require reconstruction. This can be achieved using the widely accepted Jobe Technique, or a variation of it (Armstrong et al., 2005). Grade II injuries do not have a universal treatment approach. Current treatment for athletes with a partial tear begins with an often-underwhelming course of physical therapy, as 58% of players never return to the previous level of competition (Rettig, 2001). Subsequently, a player can opt for an aggressive ligament reconstruction, such as Tommy John Surgery. This is done if physical therapy alone was deemed insufficient. The currently available surgical options are intended for complete tears, a more severe injury than the athlete has. Therefore, an athlete must choose between continuing to play with an injured ligament (which causes pain, instability, and can easily progress to a more serious full rupture), or to receive a surgery that comes with a yearlong recovery and other potential complications (Clark, 2018).

Playing with sustained Grade II injuries can present a nagging problem for over-head throwing athletes who are accustomed to a certain level of performance. The decrease in strength and stability at the elbow caused by the partial tear, along with pain and other nerve related symptoms can seriously hinder an athlete's ability. To achieve relief and eventually return to a high level of play, many athletes opt for complete reconstruction when it is ultimately not completely necessary (Vance, 2019). Though this allows the patients to return to play, they must go through the lengthy rehabilitation processes related to complete reconstructions. This approach does not attempt to regenerate the native ligament at all. It treats the injury by

bypassing the injured ligament altogether and replacing it with a graft, relying on the structural integrity of the graft and the graft anchoring system.

The goal of this project is to design and develop an approach to partial UCL repair that allows patients to return to their pre-injury conditions without undergoing complete reconstruction. To fulfill this goal, a scaffold with structural and mechanical cues to promote endogenous wound healing was created. We anticipate that this design will promote healing of the injured ligament and allow it to function analogously to the native tissue after a shorter rehabilitation period. The design will be evaluated through appropriate benchtop tests for degradation, drug elution, and mechanical characterization to ensure the design meets the intended objectives.

2. Literature Review

To develop a better understanding of the current climate surrounding UCL repair and reconstruction, the design team conducted an in-depth literature review. The following sections contain a compilation of that research.

2.1. Clinical Need

Over the past 15 years, UCL reconstruction has become a common procedure among both adolescent and elite-level athletes (Erickson, 2015). While autografting techniques have demonstrated considerable success, there remain limitations associated with tissue availability, surgical integration and the rate of functional tissue regeneration. As such, there remains a significant need to develop an off-the-shelf, minimally invasive implantation system to facilitate UCL healing and tissue regeneration. Patients with partial tears of their UCL currently must choose between often insufficient physical therapy or a drastic full, surgical reconstruction.

2.2. An Overview of Collagen and Ligaments

Collagen is used in many biomedical applications due to its biological and mechanical properties. Collagen molecules have a tightly packed triple helix structure that provides it with strong lateral properties (Shoulders & Raines, 2009). Ligament and tendon tissue are comprised of high concentrations of this protein.

Ligaments follow a hierarchical structure as seen in figure 1 below.

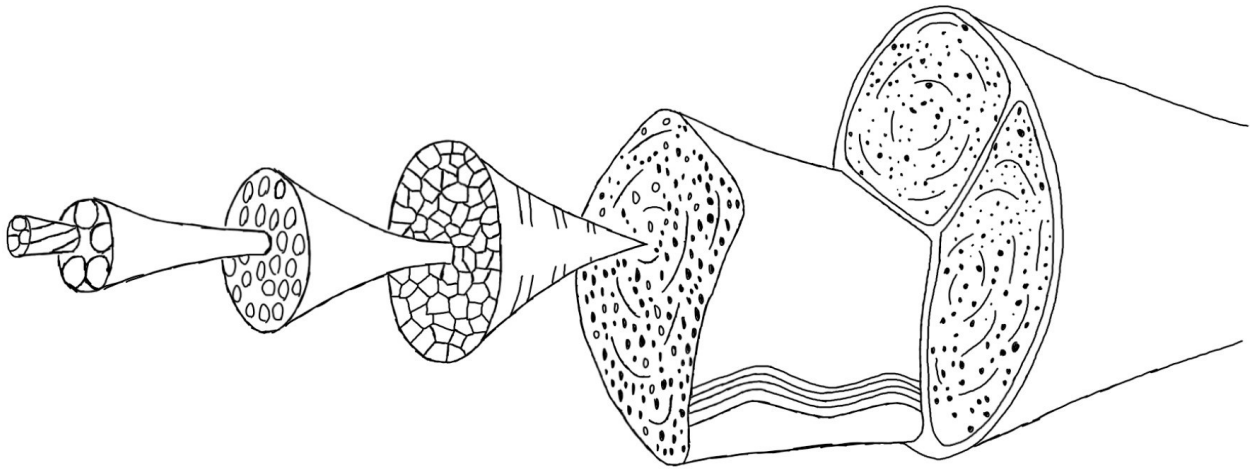

Figure 1. Schematic of ligament hierarchical structure, adapted from Weiss and Gardiner, 2001

It begins with a collagenous fibril unit (1.5 nm in diameter) that aligns itself to build a bundle called a microfibril (3.5 nm in diameter). Similarly, microfibrils bundle to create a subfibral unit (10-20 nm in diameter). This same pattern builds the fibril (50-500 nm in diameter), then fascicle (50-300 μm in diameter), and finally the ligament (Kastelic et al., 1978). These units are arranged in parallel and follow a crimped pattern along their longitudinal axis. A visual representation can be seen in Figure 1 above.

This arrangement allows for ligaments to be stretched a certain amount due to loading without compromising its structural integrity or the rigidity of the collagen. As these fibrils become uncrimped, the entire collagen backbone is being stretched; simply, the greater the load applied to the ligament, the stiffer it becomes. As individual fibrils within the ligament are damaged, stiffness is reduced, and the ligament begins to fail. Thus, a key concept is that the overall behavior of ligaments and tendons depends on the individual crimp structure and failure of the collagen fibrils within the bundles.

2.3. An Overview of the UCL

The UCL is a complex structure consisting of three bundles: anterior, posterior, and intermediate. The function of the UCL is to support and stabilize the elbow during motion, specifically over-head throwing motions (Fuss, 1991). The ligament has its origin at the surface of the medial epicondyle of the humerus, and its insertion points on the sublime tubercle of the ulna (Labott, Aibinder, Dines, & Camp, 2018). The posterior bundle is responsible for constraining flexion, while the anterior bundle is responsible for extension constraints (Fuss, 1991). The intermediate bundle seems to serve little to no function regarding the elbow joint (Morrey & An, 1985). It is the balance between the anterior and posterior bundles that allows proper control and stability of the rotation of the elbow joint. This can be seen in figure 2 below.

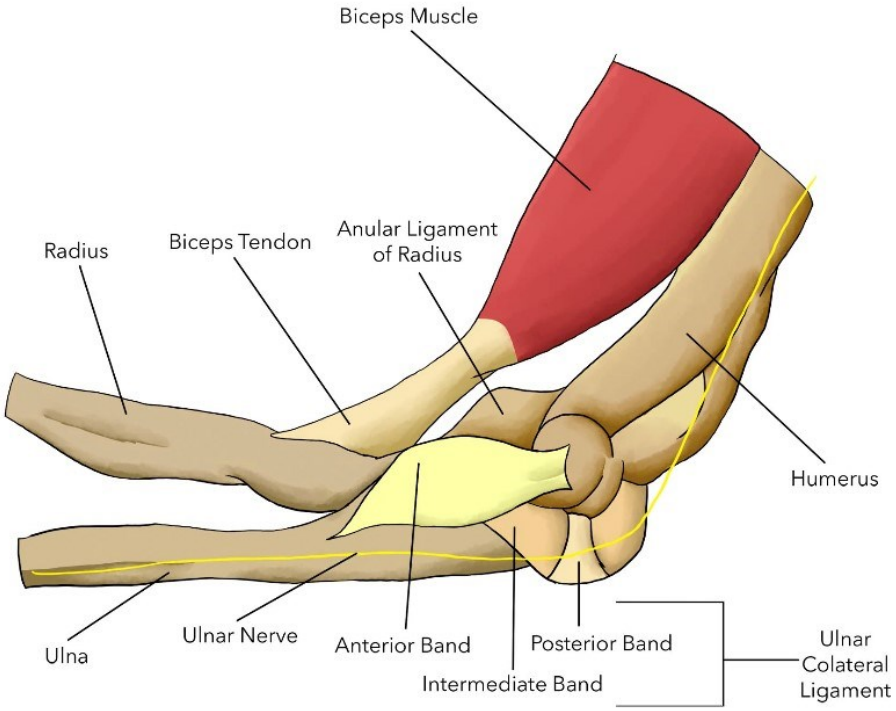

Figure 2. Anatomy of the Elbow (Adapted from Eygendaal & Safran, 2006)

2.4. UCL Injury

UCL injuries generally present in a very small patient population. From 2000-2016 there were only 136 amateur (non-professional) athletes from ages 11-22 with sports related UCL injuries (Zaremski, 2017). In the past years the rate of surgeries performed on adolescents, 15-19 years old, has been steadily increasing by approximately 9% per year (Erickson et al., 2015). The circumstances surrounding injuries are often specific to baseball players and other athletes where a major component of their sport is an overhead throwing motion. Injuries may be scarce, but they are still well characterized by orthopedic specialists. These injuries are diagnosed by MRI, as well as physical exams and patient history (Chauhan et al., 2019).

2.4.1. How Injuries Occur

Many studies regarding UCL injuries primarily follow baseball players performing at high levels, from high school to professional play. Baseball players, specifically pitchers, are especially susceptible to UCL injuries when compared with any other demographic. The biomechanics of throwing a baseball put the elbow under a unique stress, reproduced by very little other than other overhead throwing motions. Throwing a baseball, or in fewer cases a javelin or a football, can introduce a valgus stress to the elbow, the magnitude of which the anterior bundle of the UCL was not developed to withstand over time (Smith, 2019). Valgus stress refers to the stress placed on a joint and connective tissue therein when the distal limb is forced away from the midline of the proximal limb (Karbach & Elfar, 2017). For example, a pitcher throwing a baseball at a high velocity will experience a high valgus stress on the ligaments in the elbow at the top of the throwing arc, as demonstrated in figure 3 below.

Figure 3. Pitcher demonstrating valgus stress at the elbow, near the top of his pitching arc.

Ligament injuries to the UCL are often acute-on-chronic; patients will often have symptoms of damage to the ligament and continue to use it over time until a more severe injury occurs. The repeated exposure to valgus stress is a common pathway to UCL injury (Magit, 2019).

2.4.2. Where Injuries Occur

UCL injuries often occur at the anterior bundle of the ligament complex. This site is exposed to the greatest effects of valgus stress. However, injury sites can occur throughout the

length of the bundle. Tears can occur proximally at the origin on the humerus, distally at the insertion to the ulna, or somewhere in the middle of the ligament referred to as midsubstance. The location of the injury on the ligament may play a key role in the outcomes of patients (Ramkumar et al., 2018). One small-scale study describes distal tears as "[failing] nonoperative management" at a rate near 80% in the case of partial tears (Frangiamore et al., 2017). Comparatively, the same study determined proximal injuries do *not* fail non-surgical treatment paths at roughly the same rate (Frangiamore et al., 2017). Though the literature regarding the importance of injury location is scarce, it is an important consideration.

2.4.3. Gradation

Classifications of injuries are vital to communicating detailed diagnoses. Physicians use these when determining treatment pathways. An important step in diagnosing a UCL injury is gradation. A common grading system for UCL injuries classifies the severity of the injury by ascending numbers. In this system, Grade I refer to a milder sprain or stretch of the ligament, Grade II refers to a partial tear, and Grade III refers to a full thickness rupture ("UCL Injuries of the Elbow," 2017). In the realm of UCL injuries, different gradations of the same injury are treated very differently. Where a Grade I sprain may be treated with a standard course of physical therapy, a Grade III full tear will likely be addressed with a surgical reconstruction (Magit, 2019). This grading system can be seen in figure 4 below.

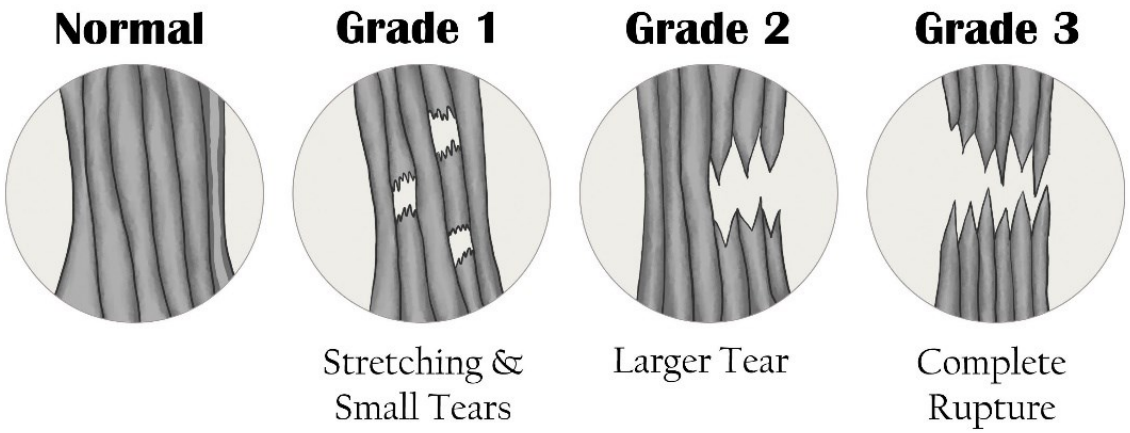

Figure 4. Illustration of Ligament Injury Gradation (Adapted from "Sprained Ankle - Treatment, Rehabilitation & Exercises," 2019).

However, not all grading schemes are the same. Ramkumar et al uses a grading system that details not only the severity, but the location of the injury as well (Ramkumar et al., 2018). In this system, grades are still distributed on a 1-3 scale, where 1 is a proximal injury, 2 is midsubstance, and 3 is distal (Ramkumar et al., 2018). The gradation is also attributed either an A or a B following the number to denote a partial tear or a full rupture respectively (Ramkumar et al., 2018). The former grading system has been adopted by the design team and is referred to repeatedly in this report.

2.5. Existing Solutions

Before a problem is solved existing solutions must first be considered. A close analysis of them will show where they succeed, but more importantly address where they fail. This section will give an overview of different options. Section 2.6 will go into more detail regarding the shortcomings of the current solutions, which will guide the entire design process.

2.5.1. Nonoperative Therapies

Nonoperative therapies are common in treating UCL injury and are often the first step before surgery is considered (Savoie, Trenhaile, Field, & Ramsey, 2008). Nonoperative treatment consists of resting, bracing, the use of anti-inflammatory drugs, and physical therapy (Chauhan et al., 2019). The literature had a dearth of information about the efficacy of nonoperative treatment. In fact, an article published October 2019 wrote that, "To date, no comparative studies have been performed on professional baseball players who have undergone nonoperative treatment…for UCL injuries" (Chauhan et al., 2019). That study went on to explain that the rates of return to play are 54%, and this is lower than athletes receiving operative treatment. The average time until return to play is longer for nonoperative athletes (Chauhan et al., 2019).

2.5.2. Modified Jobe Technique

Also known as Tommy John Surgery, the Jobe technique is widely held as the gold standard in treating UCL injuries. First performed in 1974, the Jobe technique changed the way both the medical community and sports enthusiasts viewed severe UCL injuries (Kaplan et al., 2016). What was once a career ending injury in baseball pitchers could now be treated much more effectively (Kaplan et al, 2016). The Jobe technique became a means for elite level athletes to return to the field at the highest level of play. The original technique has since been refined with more modern surgical practices, but the basic concepts remain the same.

This procedure utilizes either a cadaveric allograft, or an autograft from the patient's palmaris longus of the forearm. Sometimes other tissue, such as hamstring tendon, may be harvested instead if the patient's palmaris longus is not sufficient in length. The palmaris longus is not even present in roughly 14% of people (Thompson, Mockford, & Cran, 2001). The method for graft attachment involves multiple bone tunnels bored into both the distal epicondyle of the humerus and the proximal epicondyle of the ulna. The graft is then passed

through these bone tunnels in a figure 8 pattern, as seen in Figure 5 below (Langer, Fadale, & Hulstyn, 2006). The resulting connection is able to be pulled taught by the surgeon to a desired tension, creating a strong, stable joint.

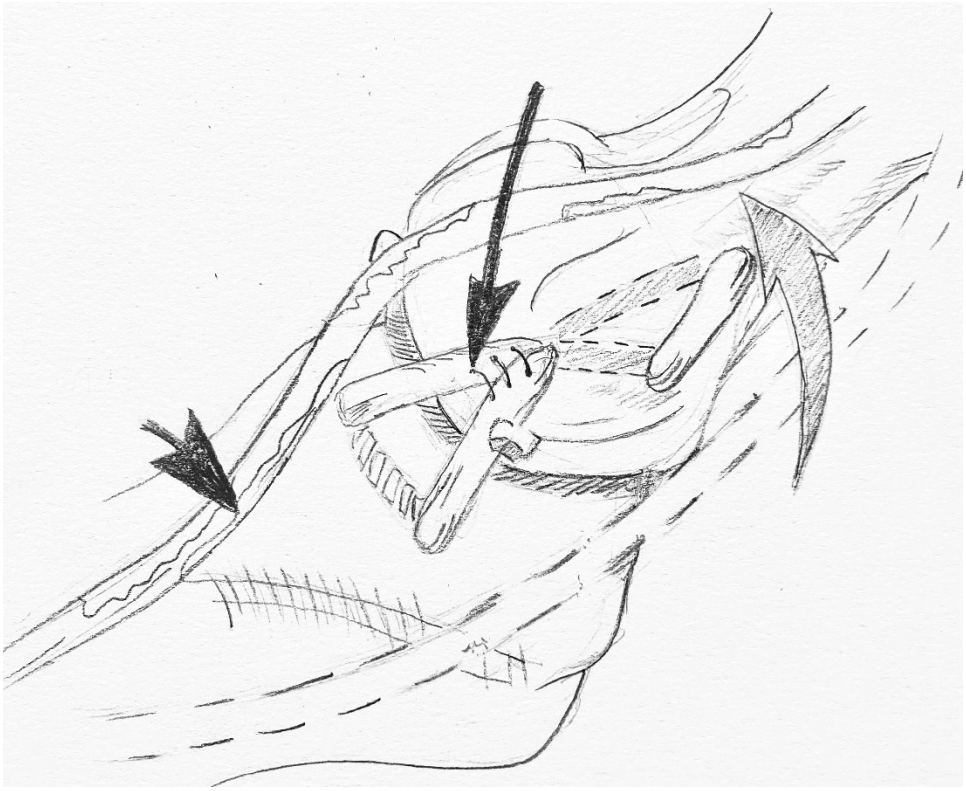

Figure 5. Graft configuration of Figure 8 pattern along with the required bone tunnel tracts in both the proximal ulna and distal humerus (Adapted from Langer, Fadale, & Hulstyn, 2006).

Recently, modified Jobe techniques have had positive outcomes. Though the surgery is intricate and a bit drastic in some circumstances such as Grade I or Grade II injuries, many athletes experience postoperative return to play rates of up to 77% (Watson, McQueen, & Hutchinson, 2014). Historically, the original Jobe technique has recorded players returning to the field at a rate of about 67% as reported by Dr. Frank Jobe himself (Watson, McQueen, & Hutchinson, 2014).

2.5.3. Docking Technique

The Jobe technique was able to develop the initial model for UCL reconstruction, this allowed for different approaches to evolve from it. The docking technique follows a similar procedure to the Jobe technique; however, the anterior limb was passed into the humeral tunnel, and the sutures from both limbs were tied over the bone bridge to secure the graft (Kaplan et al., 2016). The result can be seen in Figure 6 below.

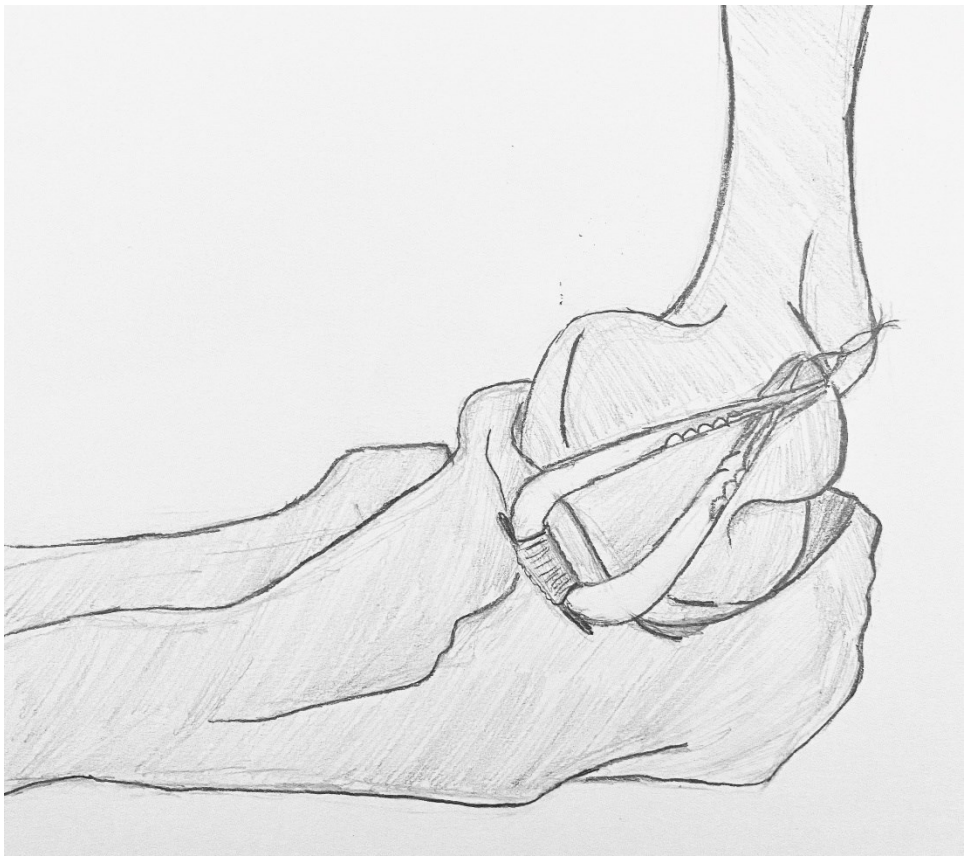

Figure 6. Graft configuration of docking technique (Adapted from Armstrong et al., 2005)

It allows for better control around the ulnar nerve and reduces the risk of complications by changing the approach when compared to the Jobe technique (Armstrong et al., 2005). Though it allows for easier control of the nerve, it does require an increased amount of

retraction and manipulation throughout the procedure. The surgical approach can be seen in figure 7 below.

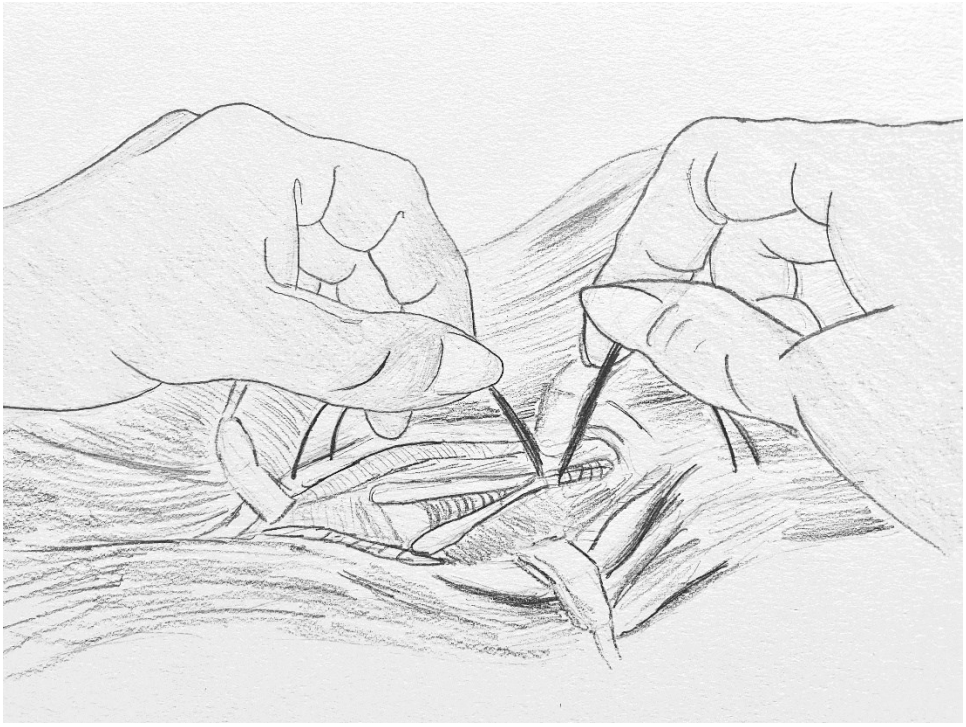

Figure 7. Illustration of the docking technique. Showing how the sutures from both limbs were tied over the bone bridge to secure the graft (Adapted from Rohrbough et al., 2002).

The docking approach decreases the number of tunnels drilled into the medial epicondyle of the humerus. This will help to lessen the risk of failure at the fixation point. The docking also acts as a reinforcement of the graft, causing higher load before failure compared to the Jobe technique. Unfortunately, to dock properly the graft must pass through those previously drilled tunnels, which can be difficult and if done improperly could compromise the structural integrity of the graft. There are tools used to smooth the tunnels and allow for less friction between graft and tunnel walls, even so care must be taken during fixation.

The docking technique has shown to be successful and boasts a return to play rate approaching 90% (Watson, McQueen, & Hutchinson, 2014). It presents a dependable and effective solution for the complete reconstruction of an injured UCL (Bowers et al., 2010; Arner et al., 2019).

2.5.4. Insertion Fixation

The Insertion Fixation technique attempts to simplify the graft-based reconstruction concept as seen in both the original and modified Jobe technique and the Docking technique. This technique utilizes only two bone tunnels, reducing the additional damage introduced to the bones in the other reconstruction methods. One tunnel is drilled on the distal medial epicondyle of the humerus and the other on the proximal epicondyle of the ulna (Ahmad, Lee, & ElAttrache, 2003). Similar to the other reconstructive techniques, a graft of the palmaris longus is generally used. The graft is screwed into place at the bone tunnel site at the humerus using an interference screw. To keep the graft taught while implanted in the elbow, the tunnel at the ulna is drilled all the way through the bone and a shuttling suture is passed through the tunnel and then through the skin (Ahmad, Lee, & ElAttrache, 2003). The shuttling suture is attached through the graft and is then able to be properly tensioned. A second interference screw is then installed to secure the tensioned graft to the ulna. The result can be seen in figure 8 below.

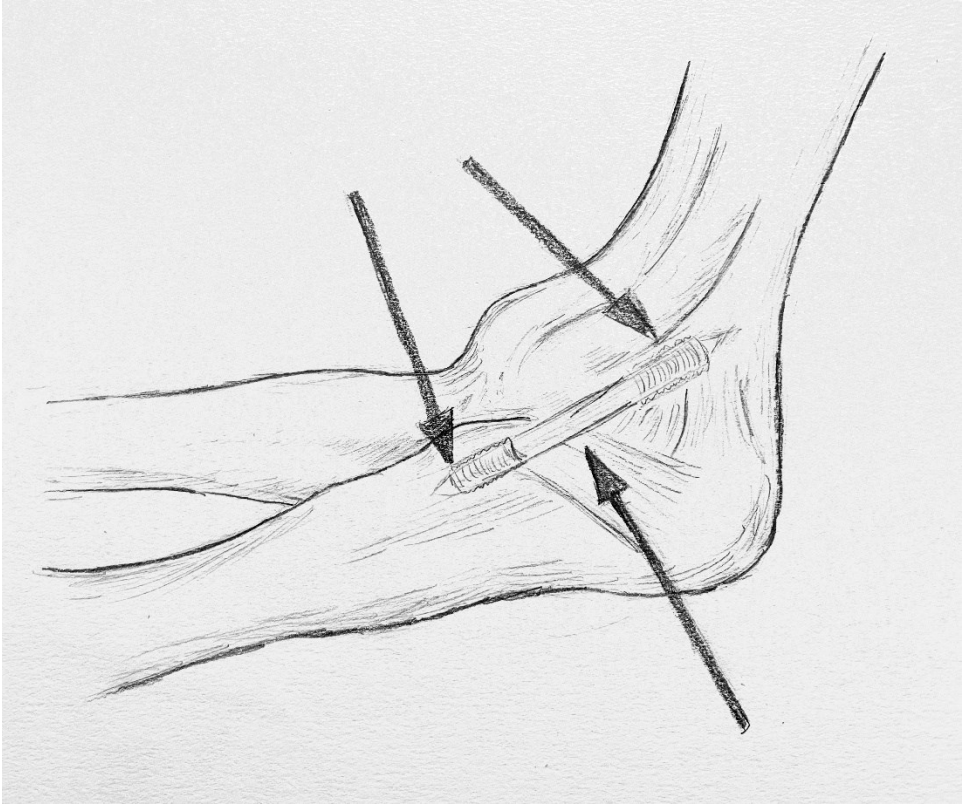

Figure 8. Illustration of graft configuration after insertion screw technique (Adapted from Watson, McQueen, & Hutchinson, 2014).

The Insertion Fixation technique is generally reserved for trauma cases (Magit, 2019). Even so, reports have stated that the reconstruction had a 90% rate of excellent results, however it comes with a few stipulations (Watson, McQueen, & Hutchinson, 2014). There was very little data on the return to play rate of the athletes that chose this reconstruction method. The study that had successful data had a patient population with 10% being baseball players, the rest were patients who are not consistent with the target demographic (Kodde, Rahusen, & Eygendaal, 2012). The technique is promising, but there is limited data on the results it has with professional baseball players.

2.5.5. Primary Repair Technique

Primary repair is not a method of reconstruction, instead it uses the native ligament and not a graft. Primary repair is generally used in proximal and distal injuries. It is a more popular

procedure in younger athletes. This is because the longer a player has been throwing the more worn down their entire ligament is. The young players, even with an injury, tend to have healthier ligaments overall (Savoie, Trenhaile, Field, & Ramsey, 2008).

Primary repair involves stretching the native ligament and attaching undamaged segments to the bone. This can be done through suturing or anchoring to bone. A 2008 article in the American Journal of Sports Medicine followed 60 young athletes who failed physical therapy and had a primary repair. Of these athletes, 93% had "good-to-excellent overall results," and 97% could play their sport "at the same or higher level as before the injury" just six months after their surgery (Savoie, Trenhaile, Field, & Ramsey, 2008).

2.5.6. Internal Brace

A similar variation of the primary repair technique is the internal brace. This product is new to the market and involves anchoring a large flat piece of suture tape proximally and distally to the ligament to provide mechanical support (Arthrex - UCL InternalBraceTM Ligament Augmentation Repair, n.d.). It involves no secondary surgical site for graft harvesting and claims comparatively faster healing rates than other operative interventions (Urch et al., 2018). It is a promising mechanical solution to UCL injury, but the large foreign body the brace adds to the body can irritate tissue without contributing biologically to the healing process (Jones et al., 2018; Magit, 2019).

2.6. Limitations of Existing Solutions

Of the three approaches to treatment, physical therapy, repair, and reconstructions, there is no perfect solution for patients with partially torn ligaments. Patients who do not have surgery only return to play half the time. Nonoperative treatment also takes time. If a patient spends three months doing physical therapy, but it fails that is three months that could have been spent recovering post surgically (Chauhan et al., 2019). When it comes to repairs, they

have their share of drawbacks. Some are only really useful in patients who have a young, minimally injured ligament (Savoie, Trenhaile, Field, & Ramsey, 2008), while others involve the insertion of a foreign body (*Arthrex - UCL InternalBrace™ Ligament Augmentation Repair*, n.d.), which can put a large foreign body burden on the patient (Magit, 2019). Reconstructions come with a host of risks and limitations. In fact, 1 in 25 patients who have a reconstruction experience a major complication, such as ulnar serve dysfunction (Cain et al., 2010). Reconstruction involves drilling many bone tunnels, each of which introduces a risk for fracture and can be difficult for the surgeon to make (Langer et al., 2006; Magit, 2019). There is also a yearlong recovery period, which is a long time in the career of a professional athlete (Langer, et al., 2006). Finally, reconstruction currently requires an autologous graft from a patients one native ligaments or tendons. Harvesting that requires a secondary surgical site, which can put a patient at risk of infection or other complications (Cain et al., 2010).

2.7. Biological Treatments in Orthopedic Applications

Many patients perceive orthopedics as a mechanical solution, fixing broken load bearing supports with screws and braces. While this is important, it is critical to remember the many biological factors affect orthopedic systems, especially when dealing with soft tissue orthopedics (Magit, 2019).

2.7.1. Collagen

Collagen is used in many biomedical applications due to its biological and mechanical properties. Collagen is a three-subunit protein consisting of three polypeptide chains twisted in a strong triple helix (Shoulders & Raines, 2009). Ligaments and tendons are primarily composed of collagen, specifically type I collagen (Liu et al., 1995). This type I collagen is in orderly fibrils, most of which are in the primary direction of loading of the ligament. These orderly fibrils contribute to the overall strength of the ligament (Liu et al., 1995).

Collagen has been studied extensively, and it has been in used in many clinical and laboratory applications (Cornwell, 2007). Collagen can be processed, through relatively simple laboratory procedures, into films, threads, and sponges (Cornwell, 2007). In fact, protocols for making collagen sponges and collagen films are noted in Appendix A and Appendix B, respectively.

One of the benefits of collagen is its crosslinkability. Crosslinking is a physical, chemical, or enzymatic process that builds covalent bonds between fibers in a material (Cornwell, 2007). Collagen crosslinking is not a practice that is only reserved for the lab bench. In fact, collagen is enzymatically crosslinked in the body normally (Cornwell, 2007). More information about the practice of crosslinking type I collagen is detailed in section 5.2.2 of this report. A simplified schematic of ultraviolet crosslinking is shown below in Figure 9

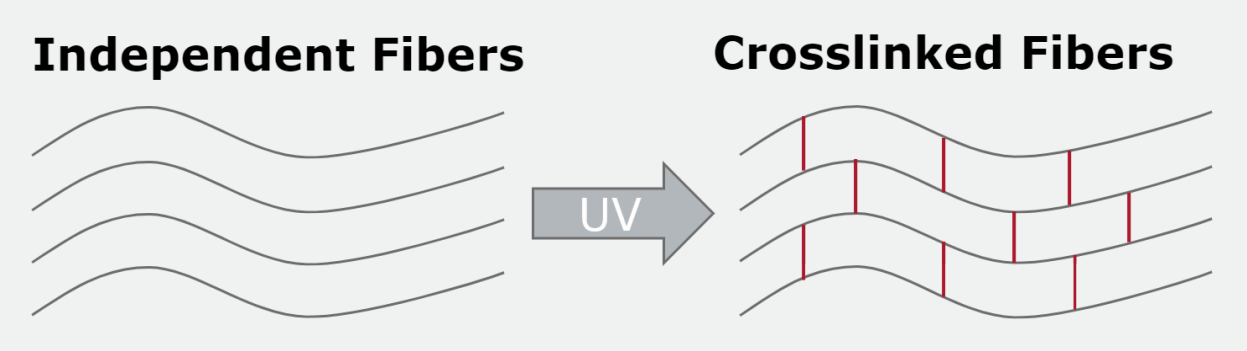

Figure 9. A simplified schematic that shows how crosslinking turns a collection of independent fibers into a web of connected fibers.

2.7.2. Growth Factors

Growth factors are signaling macromolecules that regulate the growth of tissue. They have been used as therapeutic agents for years (Wang, 2017). As they have been studied more, various methods have been designed to ensure efficient delivery of the growth factors without damaging the biofunctionality of the proteins (Wang, 2017).

Platelet rich plasma, as noted in section 2.7.3 is a solution that contains many growth factors. These include Fibroblast Growth Factor 2 (FGF-2), Transforming Growth Factor Beta

(TGF-β), Hepatocyte Growth Factor (HGF), and Platelet Derived Growth Factor (PDGF) (Krüger, 2013). It would be ideal to see one, some, or all these growth factors eluted at the location of a partial tear (Magit, 2019).

One growth factor of interest is FGF-2. This growth factor is present in high concentration in PRP (Krüger, 2013). On top of that, FGF-2 has shown benefits specifically in the healing of tendon and ligaments. In a study of anterior cruciate ligament (ACL) repair with FGF-2 shows that the ligament had an increased load to failure when the growth factor is included. (Kimura, 2008).

FGF-2 has demonstrated angiogenic properties (Cornwell, 2007) that are beneficial in the healing process. In addition to that, the addition of the growth factor has been shown to recruit human bone marrow stem cells (hBMSC) to the wound site, when used in tendons and ligaments (Yun et al., 2010). The literature shows that the concentration of FGF-2 can change how the hBMSCs behave (Yun et al., 2010), and thus if FGF-2 is used in a device, the dosage must be titrated to achieve proper effect.

One thing to note for FGF-2, and other fibroblast growth factors in general, is that when deployed in a solution they can diffuse away from the wound site and degrade enzymatically, and thus it is suggested that the growth factors be deployed in a controlled way directly to the wound site (Yun et al., 2010).

While many growth factors are possible to be added to an implantable device, FGF-2 was the most clinically relevant. Other teams can explore the use of other growth factors in the future.

2.7.3. Platelet Rich Plasma

Platelet rich plasma (PRP) is an injection of a concentrated solution of a patient's own platelets. It is used clinically to accelerate the healing of injuries in soft tissues (Alves and Grimalt, 2018). Platelets contain a cocktail of different growth factors that the body naturally sends to wound sites to heal and to clot such as FGF-2 and TGF-β (Oudelaar et al., 2003). PRP is

a method of filtering a patient's own blood to obtain a slurry that has a high concentration of platelets. This injection is obtained by taking a few tubes of blood and running it through a centrifuge with specific reagents. The resultant liquid can be delivered to a targeted site on the patient (Alves and Grimalt, 2018). It can be used in combination with or instead of purified growth factors. By introducing high concentrations of growth factors into the wound site the inflammatory response is greatly reduced (Alves and Grimalt, 2018). This will help promote the healing at the wound site and allow for a shorter recovery time.

2.8. Unmet Need

UCL reconstruction has become a common procedure among both adolescent and elite-level athletes. While autografting techniques have demonstrated considerable success, there are still limitations associated with tissue availability, surgical integration, and the rate of functional tissue regeneration (Magit, 2019). As such, there remains a significant need to develop an off-the-shelf, minimally invasive implantation system to facilitate UCL healing and tissue regeneration.

The current treatments available to patients include physical therapy, an internal bracing system, and full reconstructive surgery. These are generally dependent on the extent of their injury. The injuries can be categorized as a minor stretching injury of the ligament (grade I), a partial tear (grade II), or a complete rupture (grade III). Partial tears make up the majority of UCL injuries that receive surgical intervention (Magit, 2019). Physical therapy focuses on treating minor stretching injuries of ligaments but is often ineffective for treating partial or complete tears (Chauhan et al., 2019). Internal bracing systems are surgical procedures that utilize a strong, implantable, synthetic tape structure to provide augmented mechanical support in patients with partial ligament tears, but the bracing structure is a permanent implant and is not designed to facilitate the regeneration of native tissue. Ligament reconstructions are designed to treat complete ruptures of ligaments, but they are often deployed in partial tear injuries as well. A full reconstruction, however, may be too drastic of an approach for treating

partial tear injuries. Given the current state of treatment options available, there is a distinct lack of an approach that addresses partial ligament tears, with the goal of functional tissue regeneration and restoring the original anatomy.

Towards this goal, the team sought to design a device that can be implanted, promote healing, and integrate into the native tissue. This device needs to be a biological solution to heal damaged tissue and preserve the native anatomy, as opposed to simply addressing the mechanical needs of the injury. We anticipate that the major benefit of this device will be that patients with partial tears will no longer need to go through surgical reconstruction.

3. Project Strategy

The following chapter outlines the engineering design approach that the team utilized to address the project. It depicts the thought process surrounding the development of a solution and the intended approach the design team developed.

3.1. Initial Client Statement

Design, develop, and characterize an implantable collagen fiber-based treatment system to improve surgical outcomes for UCL repair procedures. Specifically, the goals of this project are: Develop reproducible collagen scaffolds (twisted or braided composite fiber bundles) with mechanical properties and degradation rates suitable to UCL repair. Develop a collagen scaffold / anchoring system that is suitable for bony implantation. Analyze scaffold/anchor system in an implant model of UCL repair. Evaluate feasibility of incorporating co-polymer or therapeutic molecules into the composite to enhance regeneration. Evaluate the feasibility of scaling up and commercializing the scaffold/anchor technology.

3.2. Stakeholders

In any engineering project there are many people who stand to gain (or lose) based on the implementation of whatever is designed. These people or organizations, known as stakeholders, must be considered in the design process. Every step along the process stakeholders are involved, from manufacturers to insurance companies. The three main stakeholders who will be considered the most in the design process were determined to be the surgeons, the designers, and the patients. The relationship between these parties is illustrated in Figure 10 and further explained below.

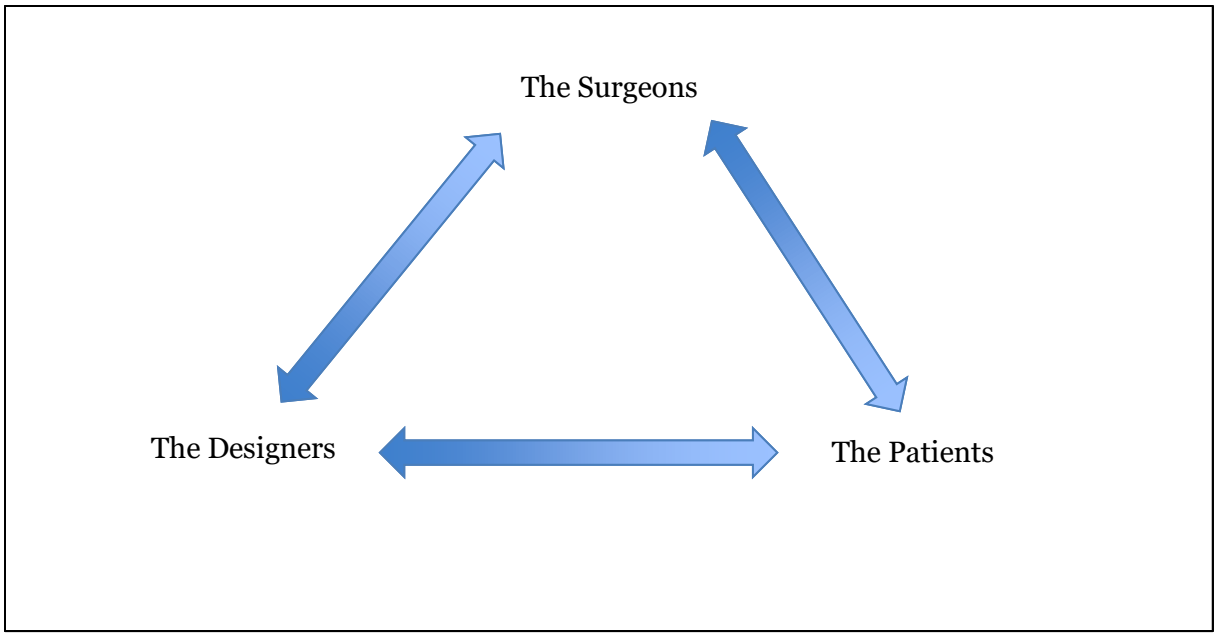

Figure 10. Main Project Stakeholders

3.2.1. The Surgeons

There are many clients that must be considered when developing an engineering project. In this project the surgeons were considered to be the primary clients. They are the ultimate decision maker in the process of UCL care. No matter what another stakeholder believes, if the surgeon refuses to do an operation then it will not happen. They also are generally in charge of informing the patient of his or her options. Dr. Magit explained that when a surgeon is going to use a new procedure or device it is best if that procedure or device is similar to an existing solution. Something drastically different would require extensive training to use. The surgeon needs a solution that fixes the problem, does not require a great deal of training to learn, and makes the patient happy.

3.2.2. The Designers

The role of the designers is to create a viable design that is both desired by and beneficial to the other stakeholders. In the project the design team consists of Matthew Cannata, Giulio Cataldo, Dr. David Magit, Cullen McCarthy, and Professor George Pins. The designers have a

great deal of limitations to consider. First is time. The device must be designed and ready to be tested approximately six months from the beginning of the process. Cost is also a major factor, with only a $750 budget available for designing, prototyping, and testing. COVID-19 has also resulted in a variety of major limitations, including shortening the timeline and the ability of the designers to acquire materials.

3.2.3. The Patients

In this project the patients were considered to be the ultimate users of the design. Patients are critical to the stakeholder analysis. These are the individuals who are afflicted with the partial tear of their UCL. The patients have a great deal of choice in the matter. If a patient fails to see the value in an intervention and chooses not to have it, then it does not happen. Patients also carry a great deal of the burden after surgery. They may be paying for the procedure. The patient is the one who deals with post-surgical pain. The patient is the one who does preoperative and postoperative physical therapy. Whatever solution is found must be sure to address the concerns that a patient has during the entire operative course.

3.3. Initial Objectives

After meeting with the client Dr. Magit, the design team came up with a list of primary objectives that the design must meet to fulfil the basic desires of the client. These primary objectives were: *Biofunctionality, Surgical Integration, Recovery, Versatility and Cost*. A short description of these objectives can be found in the Table 1 below.

Table 1. Primary Objectives with definition

Objective	Definition
Biofunctionality	Mechanical and material properties conducive to surgical implantation
Surgical Integration	Ability to incorporate into current surgical practice
Recovery	The patient's ability to heal effectively
Versatility	The implant can be adapted to many different functions
Cost	Market value should outweigh costs

3.4. Constraints

After meeting with Dr. Magit, and developing a list of initial objectives, a list of constraints was established. A summary of the compiled constraints can be found in Table 2 below.

Table 2. Design constraints developed with Dr. Magit

Constraints	Definition
Return to Pre-injury Strength	Implant allows performance at the pre-injury level
Return to Pre-injury Range of Motion	Implant allows the patient to maintain full range of motion
No Immunorejection	Implant does not illicit a foreign body immune response
No disease transmission	Implant has a limited risk of causing infection
Decreases Operative Promorbidities	Implant does not violate native tissue and forgoes the need to use a graft
Single Surgery Site	Procedure does not require multiple incision sites

3.5. Final Objectives

After the establishment of the primary objective, the design team developed a series of secondary and tertiary objectives to define a better understanding of the project goals. From this

an objective tree was created to better visualize the concepts and their relation to each other. The tree can be found in Figure 11 below.

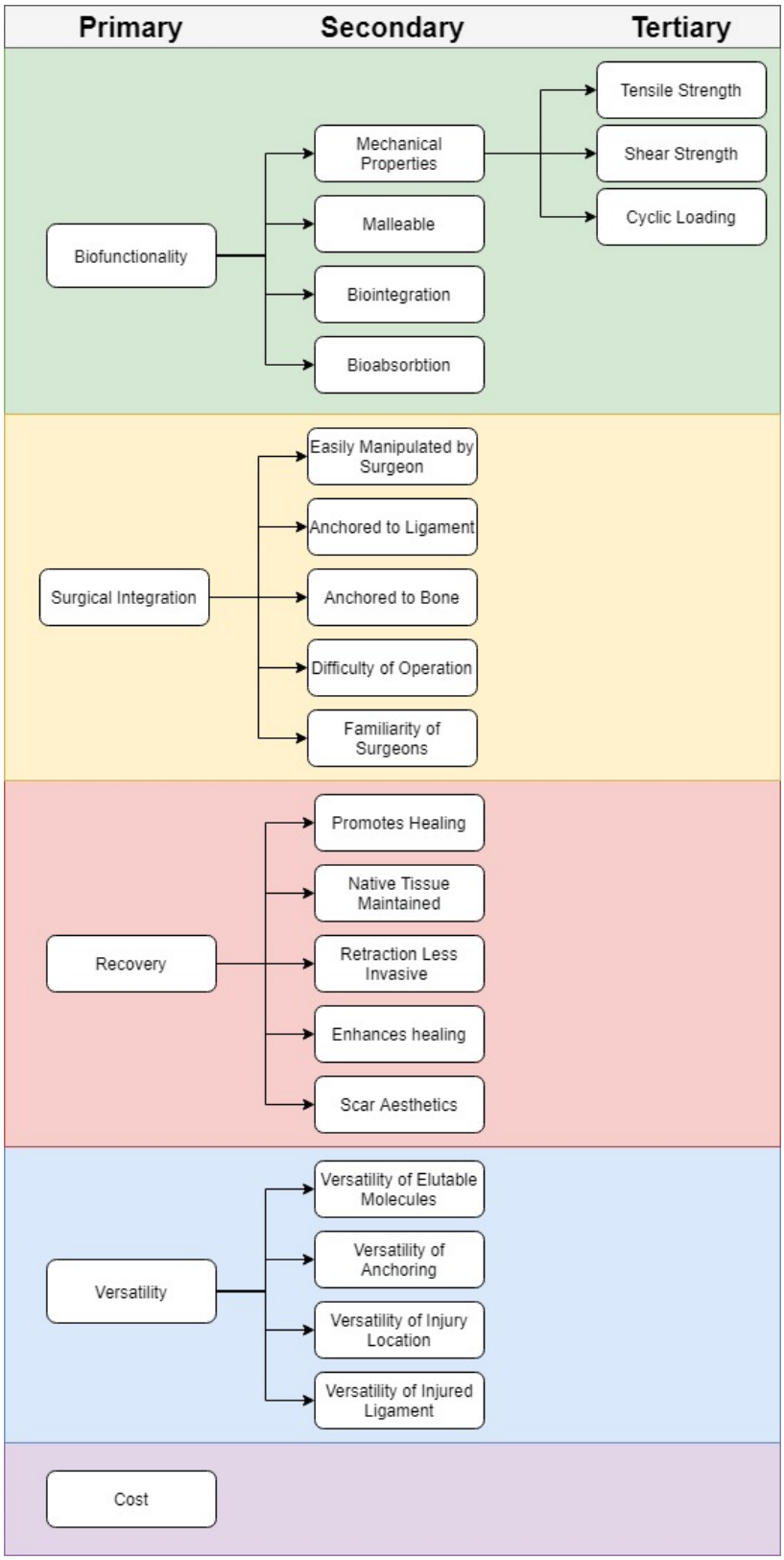

Figure 11. Objective Tree

The primary objectives were rated using a pairwise comparison chart (PCC), this allows a quantitative representation of their relative importance. Each objective was given a score based on this. In a PCC there are three possible scores; 1, 2, or 3. A score of "1" indicates that it is less important than compared objective, "2" indicates they are equally important, "3" indicates that it is more important than compared objective. The total score is a summation of each comparison. Final scores were established by the design team and the advisors. The adjusted weight factor was created by dividing the objectives score by the sum of all the scores. A summary of the final scores from the PCC can be found in Table 3 below, the full table can be found in Appendix C.

Table 3. Results of Pairwise Comparison of Primary Objectives

Primary Objective	**Score**
Biofunctionality	0.300
Surgical Integration	0.200
Recovery	0.250
Versatility	0.150
Cost	0.100

The design team indicated that of the primary objectives, biofunctionality was the most important. It was a high priority that the final design had mechanical and material properties that would allow for an optimal implant. This was followed by recovery; our devices main objective is the promotion of healing to return the injured ligament to pre-injury performance. The design team then considered the importance of surgical integration. It was vital to ensure that any procedure that we developed could be easily adopted into current practice with little technical challenge. The designed implant also needed to be versatile, it should be able to be

comfortably applied to all patients and be fined tuned in order to meet individual patient needs. Cost was the least important aspect of our design, though it is important that the relative pricing is competitive with currently used techniques, if the device is viable for the intended application there should be limited opposition to a fair price point.

After the PCC was established for the primary objectives, the same process was done to the secondary objectives in each subcategory of the primary objectives. Definitions for each secondary objective can be found in the Tables 4,5,6 and 7 below.

Table 4. Description of secondary objectives for Biofunctionality

Biofunctionality	
Secondary Objective	*Description*
Mechanical Properties	Implant has properties that allow it to be manipulated and function without compromising integrity
Malleable	Implant can be manipulated to fit injury site of native tissue
Biointegration	Implant is comprised of materials that are unreactive in the body
Bioabsorbtion	Implant is comprised of materials that are readily degradable in the body

Table 5. Description of secondary objectives for Surgical integration

Surgical Integration	
Secondary Objective	*Description*
Easily Manipulated	Implant is flexible enough for the surgeon to use properly without difficulty
Anchored to Ligament	Implant allows for attachment to the native ligament
Anchored to Bone	Implant allows for attachment to bone with proper tensioning
Difficulty of Operation	Accompanying surgical procedure is not more complex or intricate than what a typical physician is accustomed to in the OR
Familiarity of Surgeons	Does not change operation approach in accordance with muscle planes

Table 6. Description of secondary objectives for Recovery

Recovery	
Secondary Objective	*Description*
Promotes Healing	Native functional tissue (not scar tissue) grows at injury site
Native Tissue Maintained	Ligament is repaired and functions as needed
Retraction less invasive	Procedure is less invasive and less damaging to surrounding tissue and less manipulation if the ulnar nerve
Scar Aesthetics	Small, thin scar; the less visible the better when compared with standard scar left from Jobe/Docking technique
Enhances Healing	Implant allows for improved recovery rates and overall regeneration

Table 7. Description of secondary objectives for Versatility

Versatility	
Secondary Objective	*Description*
Versatility of Elutable Molecules	Implant can elute a desired molecule
Versatility of Anchoring Mechanism	Procedure can be anchored in a variety of ways depending on surgeon preference
Versatility of Injury Location	Implant can repair proximal, distal, or midsubstance injuries
Versatility of Injured Ligament	Implant is not limited to only UCL repair

The pairwise comparison summaries for these secondary objectives can be found in Tables 8,9,10 and 11 below. The complete PCC for each individual objective group can be found in Appendix D.

Table 8. Results of PCC of secondary objectives for Biofunctionality

Biofunctionality	
Secondary Objective	*Score*
Mechanical Properties	.250
Malleable	.250
Biointegration	.250
Bioabsorbtion	.250

The design team decided that each secondary objective for biofunctionality was deemed to be equally important. The design must have material and mechanical properties conducive for repair. The mechanical properties will specifically help ensure that the implant will allow for proper implementation, allowing it to perform as desired. The bioabsorbtion and biointegration aspects will allow for the tissue to maintain its native morphology and promote proper degradation. The device also needs to be malleable; this will allow for the proper contact with the injury site to increase the overall healing of the ligament.

Table 9. Results of PCC of secondary objectives for Surgical integration

Surgical Integration	
Secondary Objective	*Score*
Easily Manipulated	0.250
Anchored to Ligament	0.250
Anchored to Bone	0.250
Difficulty of Operation	0.150
Familiarity of Surgeons	0.100

The design team decided that it was important that the design be easily manipulated by the surgeon. This is important as the surgeon must be able to manipulate the implant so that it is oriented properly to administer to the ligament. Every patient is different, and the design needs to take that into account. It was equally important that the design can be properly anchored to

both the ligament itself and the bone. If the design is not able to be anchored than the ligament will not be able to be under the proper static loading, which is important for ligament function. It was also deemed that difficulty of the operation is important, however, if the design is promising surgeons are willing to attempt a more tasking procedure. This was similar in the familiarity of surgeons, it is important to develop a procedure that is intuitive, but they will be willing to adopt a new procedure if it is viable.

Table 10. Results of PCC of secondary objectives for Recovery

Recovery	
Secondary Objective	*Score*
Promotes Healing	0.250
Native Tissue Maintained	0.300
Retraction less invasive	0.200
Scar Aesthetics	0.100
Enhances Healing	0.150

The design team decided that the most important aspect of recovery is maintaining the native tissue. This is the novelty of the design; it is extremely vital to design process. The design also needed to include an aspect that promotes the healing process of the ligament. This can allow for an improved recovery when compared to current techniques. The designed procedure should also aim to reduce the invasiveness of current techniques. There is a risk of damaging surrounding tissue and aggravating the ulnar nerve, therefore caution must be taking when developing the approach. Additionally, the team wanted the implant to enhance healing, not only should it facilitate healthy ligament regeneration, but induce the tissue to propagate growth to increase the efficiency of the healing process. The team also considered the scar aesthetics after implantation, it was decided that care should be taken to minimize the visible scar, however, it was not important to the final design.

Table 11. Results of PCC of secondary objectives for Versatility

Versatility	
Secondary Objective	*Score*
Versatility of Elutable Molecules	0.208
Versatility of Anchoring Mechanism	0.292
Versatility of Injury Location	0.375
Versatility of Injured Ligament	0.125

The design team wanted to create a device that could be easily adapted to the patient. Therefore, it was important that the device can be easily augmented to fine-tune the response. Most importantly the design must we applicable to all UCL partial tears regardless of the injury location on the ligament. From there the design should be adaptable to many anchoring techniques. Fixing the implant to the ligament needs to be intuitive and fixing the device to the bone is necessary. Surgeons often have a preferred anchoring method, so the design team wanted to ensure that the final design can be adaptable and function in conjunction to the preferred anchoring type. It was also important that the design can elute an arsenal of therapeutic molecules. This can be used to help expedite the healing cascade from multiple inputs. The team also considered designing the implant to be adaptable to other similar soft tissue injuries, such as in the rotator cuff. This was deemed important for future iterations; however, it was not vital to the initial design.

After the PCC was established for the secondary objectives, the same process was done to the tertiary objectives in each subcategory of the secondary objectives. Definitions for each tertiary objective can be found in Tables 12 below.

Table 12. Results of Description of tertiary objectives for Mechanical Properties

Biofunctionality	
Tertiary Objective	*Description*
Tensile Strength	Implant has tensile properties that allow it to be manipulated and function without compromising integrity
Shear Strength	Implant has tensile properties that allow it to be manipulated and function without compromising integrity
Cyclic Loading	Implant has tensile properties that allow it to be manipulated and function without compromising integrity

The pairwise comparison summaries for these tertiary objectives can be found in Table 13 below. The complete PCC can be found in Appendix E.

Table 13. Results of Description of Tertiary objectives for Scaffold Mechanical Properties

Biofunctionality	
Tertiary Objective	*Description*
Tensile Strength	0.333
Shear Strength	0.333
Cyclic Loading	0.333

The design team decided that all mechanical properties related to the final design were of equal importance. The implant must have optimal strength for its intended application without losing its integrity.

3.6. Revised Client Statement

After the analysis of the objectives was established, accompanied by further research, and extensive discussion, the team proposed a revised client statement. It is the following:

Design, develop, and characterize an implantable scaffold to improve surgical outcomes for Grade II UCL repair procedures in a reproducible manner. The implantation should be easily integrated into surgical practice, and the scaffold should promote healing of the ligament through directional support of the scaffold and the controlled elution of 1.5 ng of FGF-2 over a 3-week period. After 6-8 weeks, the scaffold should degrade as the native tissue regenerates.

The design team believes that this revised client statement better represents the most important objectives evaluated, and their relation to the design itself.

3.7. Project Approach

In order to ensure the completion of the design within the given time, the project team developed a plan to organize the major components of the process. The following section describes the various approaches used to keep progress in line with the desired timeline. Each was used to organize and prepare specific objectives.

3.7.1. Management Approach

The design team implemented a management plan in order to ensure proper progress of the project is maintained.

To ensure that the goal of the project aligns with the desires of the client, weekly meetings were established. This allows for an environment of collaboration and communication between the major stakeholders in the project. In preparation for each meeting, an agenda was sent out to ensure the meetings stay on task and maintain efficiency. During these meetings the design team presented presentations related to the research and findings of the previous week. The project team itself also meet multiple times weekly to discuss research and formulate the approach for the project.

3.7.2. Design Approach

After outlining the objectives and utilizing PCC to determine the level of importance of each grouping, the design process began. With these established criteria, the major components of the design can be factored into brainstorming sessions. The brainstorming sessions have occurred briefly, however analysis of each potential idea will not be performed until saturation of ideas is believed to be met. After that proper analysis of concepts will be conducted in relation to how much each design meets the defined objectives. After the design has been finalized and prototyped, materials will be ordered for the creation of the functioning device. It is expected that the initial design will be modified as the testing process occurs.

3.7.3. Financial Approach

The design team was granted a total of $750 by Worcester Polytechnic Institute in order to complete the project. Knowing the budget is limited, the design team focused on the most effective use of the capital and how the money should be allocated. A list of potential materials and their relative costs has not been created but will be completed along with the initial design phase.

4. Design Process

The following chapter contains a detailed discussion of the major objectives, constraints, functions, and specification that the design team developed throughout the project.

4.1. Needs Analysis

In collaboration with the clients, the needs and wants of the design were established in line with the objectives of the project. A list was compiled of aspects that fell into these categories. The objectives were established thorough discussion with the client. The design team defined a need as something the solution must have to work; without it the design would not succeed. A want is desirable that could benefit the design but is not necessary for the desired outcome. The list of wants and needs along with their definition in relation to the design can be found in Table 14.

Table 14. List of design needs

Needs	**Definition**
Mechanical properties conducive to regular manipulation in a surgical setting	Implant has tensile, shear, compressive, and cyclic loading properties that allow it to be manipulated without compromising integrity
Malleable	Implant can be manipulated to fit injury site of native tissue
Biointegration	Implant is comprised of materials that are unreactive in the body
Bioabsorbtion	Implant is comprised of materials that are readily degradable in the body
Easily Manipulated by Surgeon	Implant is flexible enough for the surgeon to use properly without difficulty
Can be Anchored to Ligament	Implant allows for proper attachment to the native ligament
Can be Anchored to Bone	Implant allows for attachment to bone with proper tensioning
Promotes Healing	Native functional tissue (not scar tissue) grows at injury site
Native Tissue Maintained	Ligament is repaired and functions as needed
Versatility of injury location	Implant can repair proximal, distal, or midsubstance injuries
Want	**Definition**
Difficulty of Operation	Accompanying surgical procedure is not more complex or intricate than what a typical physician is accustomed to in the OR
Familiarity of Surgeons	Does not change operation approach in accordance with muscle planes
Retraction less invasive to surrounding tissue	Procedure is less invasive and less damaging to surrounding tissue and less manipulation if the ulnar nerve
Scar Aesthetics	Small, thin scar; the less visible the better when compared with standard scar left from Jobe/Docking technique
Enhances Healing	Implant allows for improved recovery rates and overall regeneration
Versatility of Elutable Molecules	Implant can elute a desired molecule
Versatility of anchoring mechanisms used	Procedure can be anchored in a variety of ways depending on surgeon preference
Versatility of injured ligament	Implant is not limited to only UCL repair
Cost	Overall Cost is competitive with current techniques

4.1.1. Design Needs

Design needs were determined based upon the aspects that received higher scores in the PCCs. These were to be included in the final design and are crucial to the implant's efficacy in practice.

The most important aspect of the design is that native tissue is maintained, this aspect allows for the procedure to be biological and maintain the anatomy of the patient. Ligament tears very greatly between individuals. To address this the design team needed to create a device that can be utilized regardless of the location of the tear on the ligament. It is also important that the design possesses mechanical properties conducive to regular manipulation in a surgical setting. This allows it to be manipulated and secured without losing its integrity. The goal for the device is that it is completely integrated and absorbed into the native tissue, therefore it was important that the design was composed of materials that would allow for proper biointegration and bioabsorbtion. To ensure surgical ease the device needs to be malleable. This allows for the surgeon to apply and contour the implant to the injury site as needed. For proper ligament restoration, a certain level of static tension is needed. With that in mind it is critical that the implant can be secured to the ligament and the bone and allow for proper tensioning. Additionally, the goal of this device is to restore a partially torn ligament to pre-injury performance. In order to achieve this the device must promotes the healing of damaged tissue.

These aspects were determined to be requirements for a functional device. Their inclusion is vital to the performance of the implant.

4.1.2. Design Wants

Design aspects that received lower scores in the PCCs were not considered crucial to the final design through the discussion process. There were to be included if possible when creating a

final design. Many of these would be beneficial to include in the design, but ultimately can be excluded if necessary.

If the difficulty of the procedure was minimized, it would be optimal to make it as relatively easy as possible to encourage surgeons to adopt it into their practice. The new approach was also aimed to be similar to existing techniques. This would be beneficial to surgeons because if the technique utilizes tools that are already in their arsenal, it would be easier to adopt into their practice. If the same equipment, such as drill packs, drill guides, suture packs, etc. are used then it decreases the cost barrier of adopting a new technique. Care was taken to develop an approach that requires less invasive retraction of surrounding tissue. This was done to limit the damage that surrounding tissue would receive as a result of the procedure. This will help the recovery, but as long as the procedure uses a similar incision approach to current practice it is unnecessary. This will also affect the size of the scar after the procedure is completed. Though it is desirable to leave the smallest possible scar, it will not compromise the effectiveness of the implant. It is also ideal to improve recovery rates of the patient through the enhancement of healing, however, if the recovery rates are comparable to that of current techniques it should not hinder the appeal to potential patients. The team wanted to develop a device that was versatile and easily augmented to best address the patient's needs. This includes being able to elute various therapeutic molecules, an aspect that can be beneficial but not necessary. Similarly, the design is aimed to be anchorable with varying methods, however, if it is only possible through a certain approach it will not greatly hinder the design. Looking to the future, it would be beneficial to create a design that can be used in similar soft tissue injuries. This would greatly expand the market segment of the device; however, it is not necessary for the intended application. It was also important to consider the cost of the deployment. The overall approach should be competitive with currently accepted techniques. Though this is important, as long as the cost is not egregious it should not deter patients from requesting the treatment.

These aspects are not requirements of the final design, may be beneficial in future iteration. Overall, they will help increase the appeal of the technique to potential patients and make it more marketable as a result.

4.1.3. Needs and Wants Design Matrix

A design matrix was established to match design considerations with their influence on the overall objectives. It allows a relation between the design aspect and how it related to the needs and wants of the result. If a design consideration is marked with an X, then it is being influenced by and therefore has relation to the objective. The matrix allows for the visualization of the link between design and objectives, and how they will affect the product. The design matrix can be found in the Table 15 below**.**

Table 15. Preliminary Needs Wants Matrix

Needs	Mechanical Properties	Malleable	Biointegration	Bioabsorbtion	Easily Manipulated	Anchored to Ligament	Anchored to Bone	Promotes Healing	Native Tissue Maintained	Versatility of Injury Location	**Wants**	Difficulty of Operation	Familiarity of Surgeons	Retraction less invasive	Scar Aesthetics	Enhances healing	Versatility of Elutable Molecules	Versatility of Anchoring	Versatility of Injured Ligament	Cost
Implant Materials	X	X	X	X				X	X											X
Collagen Threads	X							X								X				
Collagen Film	X	X			X			X								X	X			
Collagen Matrix Configuration	X	X			X			X	X							X	X			
Implant Size						X	X	X		X		X	X					X	X	
Implantation Procedure						X	X		X	X		X	X	X	X			X	X	

4.2. Functions and Specifications

In order to better design in accordance with the needs, specifications were developed. This allowed for quantitative and qualitative benchmarks that are to be incorporated into the final design. It was determined that based on the literature and similar applications that the implant should have properties like that of native tissue (Magit, 2019). By creating an implant with similar structure to native tissue there will be an increased promotion of integration and it will aid in maintaining the injured tissue's morphology (Chvapil et al., 1993). It was also found that the device should have an ultimate tensile strength of similar magnitude to 2.4 MPa (Kato and Silver, 1990). This will allow for the implant to be properly anchored without losing its structural integrity, while still being malleable. For proper categorization of elutables, FGF-2 was used as a baseline therapeutic. This was due to FGF-2 being well categorized in the literature and an important component of the healing cascade. The literature was used to determine that an appropriate release profile for this growth factor was 1.5 ng over a 3-week period (Cornwell, 2007). It was also determined that the implant should ultimately degrade after 6-8 weeks, leaving a healed ligament (Laitinen, 1992). A compilation of the desired specifications can be found in Table 16.

Table 16. List of specifications derived from needs

Needs	**Specification**
Mechanical properties	UTS of at least 2.4$\pm$0.46 MPa
Malleable	Malleable when handled
Biointegration	Structurally similar to native tissue
Bioabsorbtion	Degrade in 6-8 weeks
Easily Manipulated by Surgeon	Malleable when handled
Can be Anchored to Ligament	Suture allows for anchoring
Can be Anchored to Bone	Suture allows for anchoring
Promotes Healing	1.5 ng of FGF-2 over a 3-week period
Native Tissue Maintained	Anatomy is maintained

4.2.1. Size

The size of the anterior bundle of the UCL varies from patient to patient based on height, arm length, bone structure, and other anatomical variability. Studies have found an average length from origin to insertion to be between 21.1mm and 31.4mm (Labott, Aibinder, Dines, & Camp, 2018). It should be noted that the ligament also is able to adopt an axial strain of 18%, changing in length by up to 2.8mm to 4.8mm under normal flexion and extension motions (Labott, Aibinder, Dines, & Camp, 2018). The width along the anterior bundle has been found to be between 4.0mm and 7.6mm (Labott, Aibinder, Dines, & Camp, 2018). There is some variability among studies with regards to the size dimensions of the ligament. Much of the variability can be attributed to differences in the methods the authors use to measure the ligaments and where they define origin and insertion points of the ligament.

The literature was further validated after exploring a cadaver elbow with Dr. Magit; processed images can be found in figure 12 below. This image depicts the length of the ligament as being 25.77 mm and the width as being 8. 44mm. The measurements we gathered are slightly larger than the data found in literature, but this is due to the specimen being especially large. We believe the metrics above develop a realistic size specification for our design

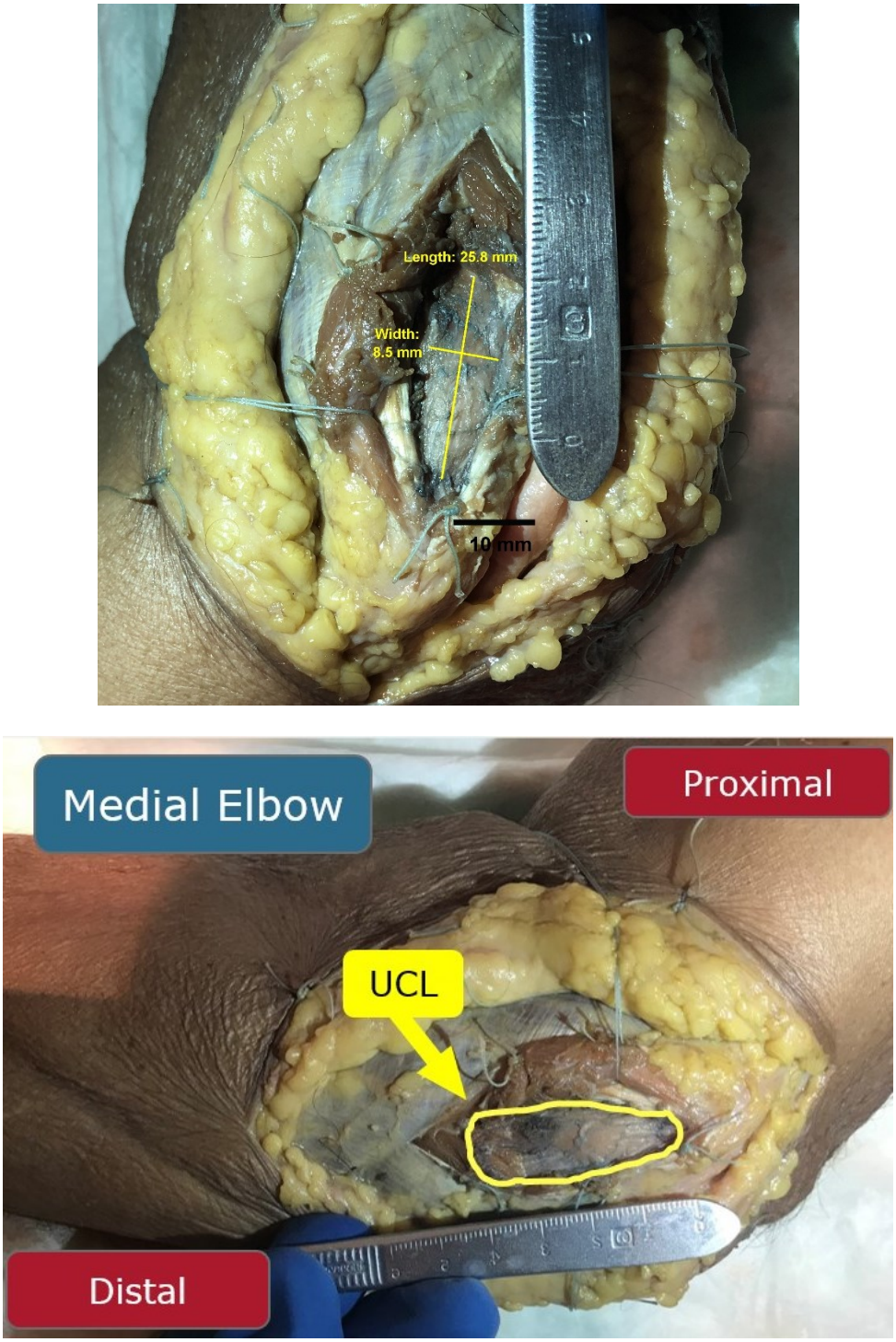

Figure 12. UCL image processed with ImageJ, all lengths are in millimeters

4.2.2. Strength

The internal strength of the ligament also plays an important role in the function of the elbow. In elite overhead throwing athletes, the anterior bundle of the UCL can be regularly subjected to valgus torques (also referred to as valgus stress in literature) of 64 Nm (Labott, Aibinder, Dines, & Camp, 2018). The ultimate tensile strength of the anterior bundle is also categorized in this study at a value of 260.9N (Labott, Aibinder, Dines, & Camp, 2018). Since the design is primarily for drug elution and aid in healing, and not for supporting loads during throwing, the implant does not necessarily need to be able to withstand the same forces and torques as the ligament itself.

4.2.3. Flexibility

The elbow joint's function is largely attributed to its degree of flexibility and multidirectional range of motion. Studies have characterized the degree of flexion at the elbow joint to be 0 degrees to 140 degrees with a more constricted minimal range for everyday function of 30 degrees to 130 degrees (Karbach & Elfar, 2017). The elbow must also allow the radius and ulna to rotate in tandem to at least 50 degrees of pronation and 50 degrees of supination in order to maintain good function (Karbach & Elfar, 2017).

4.2.4. Translating Measurements to Specifications

Based on the reported data surrounding the anterior bundle of the UCL, our design should fit within a length of 21mm to 31mm and should be able to accommodate specimens with an approximate width from 4.0mm to 7.6mm. It should also be able to take on regular axial strains of up to 18%. The design must not inhibit the normal flexion of the elbow, at least 30 degrees to 130 degrees from full extension. It must also not inhibit the pronation or supination of the radius and ulna. At a minimum, 50 degrees of both pronation and supination must be maintained.

4.3. Conceptual Design Phase

After the design team compiled the desired needs and functions of the final device, the brainstorming process began. In collaboration with the clients, the team underwent a brainstorming session to thoroughly visualize how the functions and desired outcomes can incorporated into a design. Following the secondary design phase, pros and cons lists were created with each of the conceptualized designs. After analysis, a matrix using the weighted design criteria was used to rank each idea. Utilizing this process, a final design was established.

4.3.1. Initial Brainstorming of Collagen Implant Designs

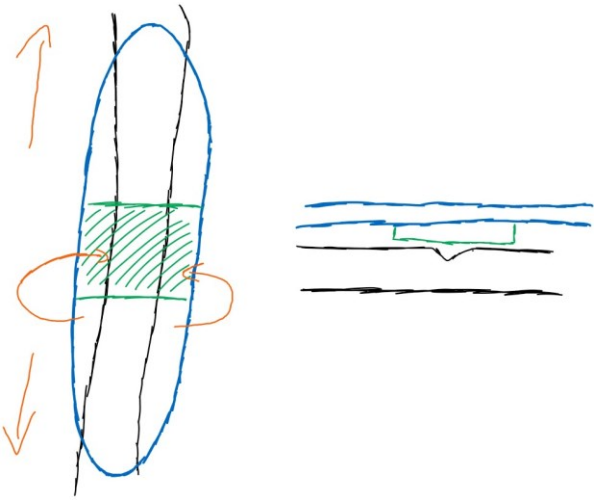

Figure 13. CIGAR

Figure 13 shows the CIGAR design. It would be a tensioned collagen blanket system. It would use strong sutures or wire to attach the two ends of the blanket to bone to provide tension. Attached to those wires would be a collagen blanket, represented in blue. A small piece of that blanket, represented in green, would have a type 1 collagen sponge that has growth factors, PRP, or other desirable compounds. That thick piece would be targeted to lay on top of that partial tear site. The edges of the blanket could be wrapped over the ligament and sutured in on the edges to ensure that it remains on the ligament.

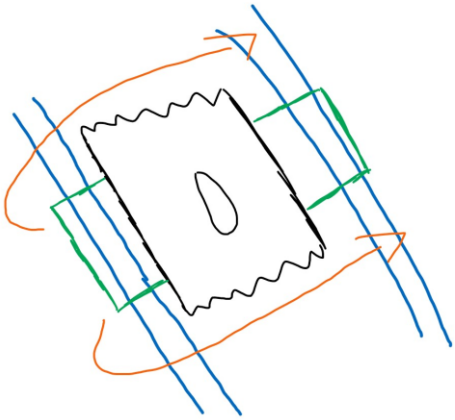

Figure 14. TACOS

Figure 14 shows the TACOS design. This approach would be a collagen film sleeve, represented in green, that could be wrapped around the partially torn ligament. The sleeve would then be whip stitched around the injured ligament. This would tubularize the native tissue and add supplemental collagen to the injury site. The ends of the device could potentially be anchored to bone.

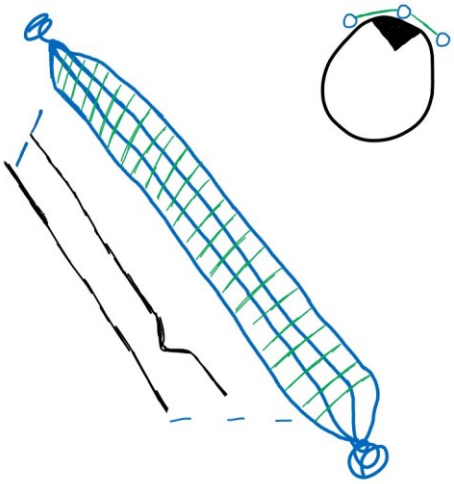

Figure 15. SHADOW

Figure 15 shows the SHADOW design. This approach is comprised of 3 fiber wires that run the length of a partially torn ligament, represented in blue. They are connected through a type I collagen sponge matrix, represented in green, that is supported with a fiber wire mesh. The matrix is then impregnated with growth factors, such as PRP, that will elute after implantation. The device is along the tear and then anchored alongside the insertion and origin points of the injured ligament. Then tension of the system and the proximity to the injury site can be adjusted to the likeness of the surgeon. This device does not need to enclose the entire ligament but is fixed to the injured side. This is beneficial when applied to ligaments that are not fully exposed and isolating them would damage the surrounding tissue. It is an alternative to methods that need to surround the injured ligament. This device provides the structural support necessary to function similarly to normal conditions, in addition to this the elution of growth factors will improve the healing of the injury site. It functions both as a support system and a growth factor delivery device.

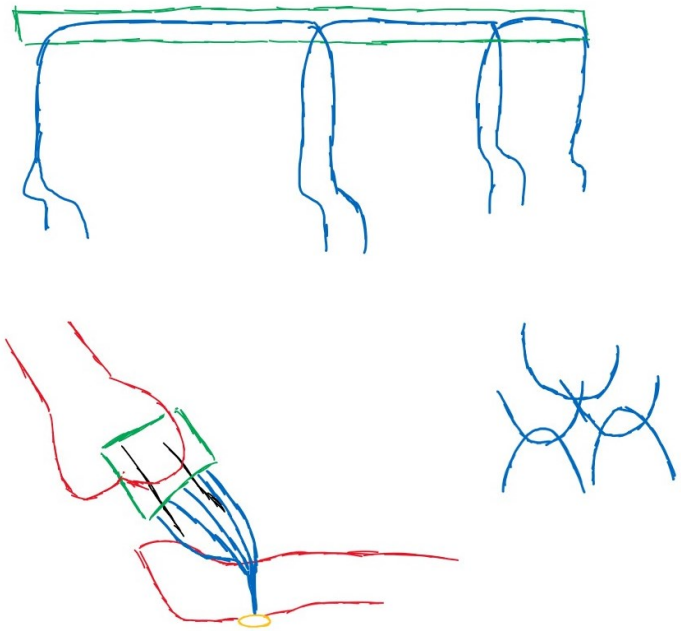

Figure 16. COZY

Figure 16 shows the COZY design. This approach is comprised of a Type I collagen film, impregnated with a fiber wire mesh system. A woven fiber wire mesh ensures the device possesses sufficient tensile strength just as the healthy native ligament does. The ends of the individual fiber wires in the mesh system pass through the film and can be manipulated. This allows the fiber wire ends to be sewn into the damaged ligament and then anchored to either the medial epicondyle of the humerus or the sublime tubercle of the ulna depending on the location of the injury. Therapeutic biologics such as PRP, certain growth factors, and fibrocytes can be incorporated into the collagen membrane to help facilitate ligament healing.

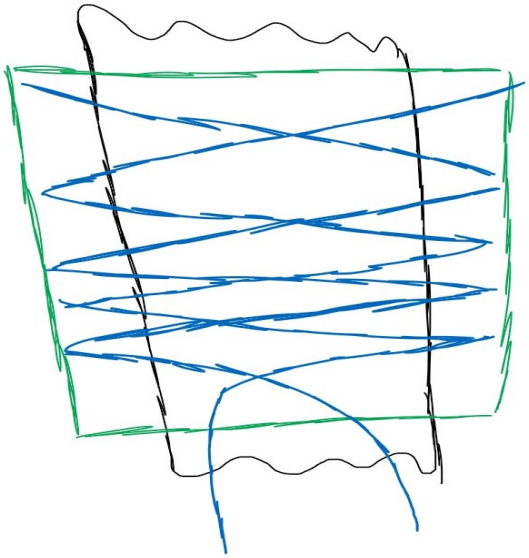

Figure 17. Top view of SIDEWINDER

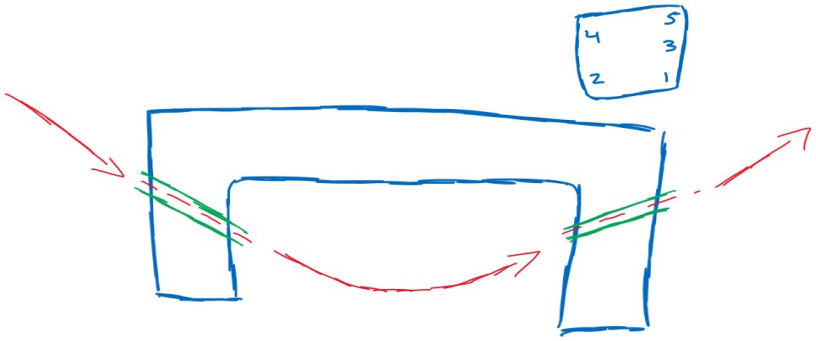

Figure 18. Side view of SIDEWINDER

Figures 17 and 18 show the SIDEWINDER design. This approach utilizes an external open box or bridge structure device that temporarily squishes the damaged ligament into a uniform, workable shape. The box provides numbered guide slots for the surgeon to pass sutures through in a modified whipstitch pattern through the ligament at and around the injury site. Lining the box device is a separate Type I collagen-based film. This film is to be fitted directly onto the injury site. It can be impregnated with biological treatments such as PRP, growth factors, and/or fibrocytes depending on physician preferences. The box is then removed, and the suture tails are anchored to bone at either the medial epicondyle of the humerus or sublime tubercle of the ulna, depending on the location of the injury. This provides tension necessary for optimal function to the ligament while the modified whipstitch and collagen film provide some structure and support along with regenerative properties to benefit the native tissue.

4.3.2. Secondary Brainstorming of Collagen Implant Designs

After further consideration with the major stakeholders, a second iteration of brainstorming began. While many of the initial designs had promise, the team changed the focus of the project. Less stress was put on designing an implant that mimicked the mechanical properties of native tissue, and more stress was put on drug elution and healing promotion. Thus, a second round of

designs took place.

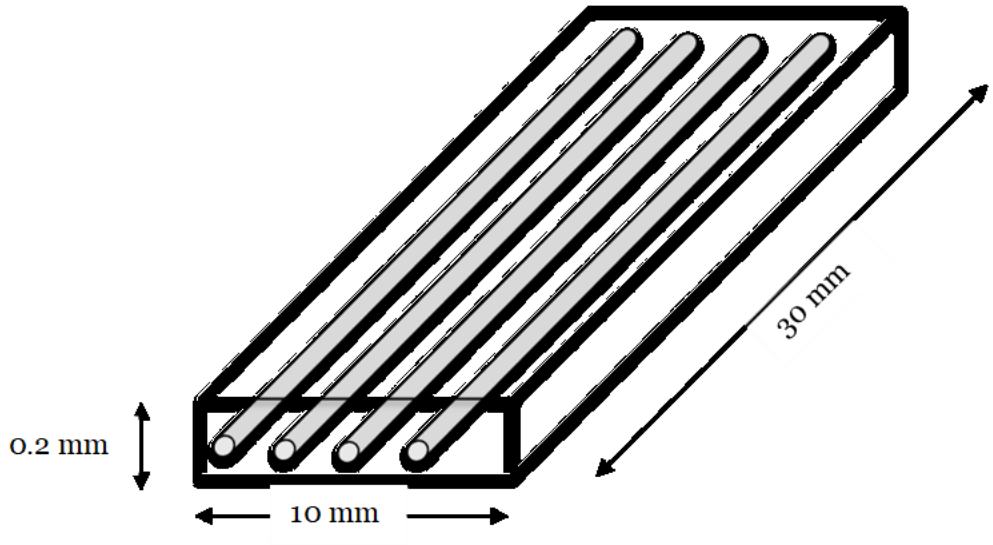

Figure 19. Schematic of Film with Threads

Figure 19 shows the schematic for a composite consisting of a collagen film impregnated with collagen threads. All threads were placed parallel to each other, mimicking the fibrous composition of the native ligament. Threads add a unique ability to promote directional healing along with axial strength in a secondary capacity, while films allow for a malleable, flexible, and handleable quality. This design incorporated growth factors to further promote healing. These can be loaded into both the film component and the thread component of the composite. Doing so allows for the instantaneous bolus of growth factor, as well as a sustained release over time as the scaffold degrades. This is beneficial to the healing process and is the desired release profile of orthopedic surgeons. Growth factor loading can be accomplished during the manufacturing process by adding it to the collagen slurry to integrate it into the film, and via post-process physisorption to the surface of the composite.

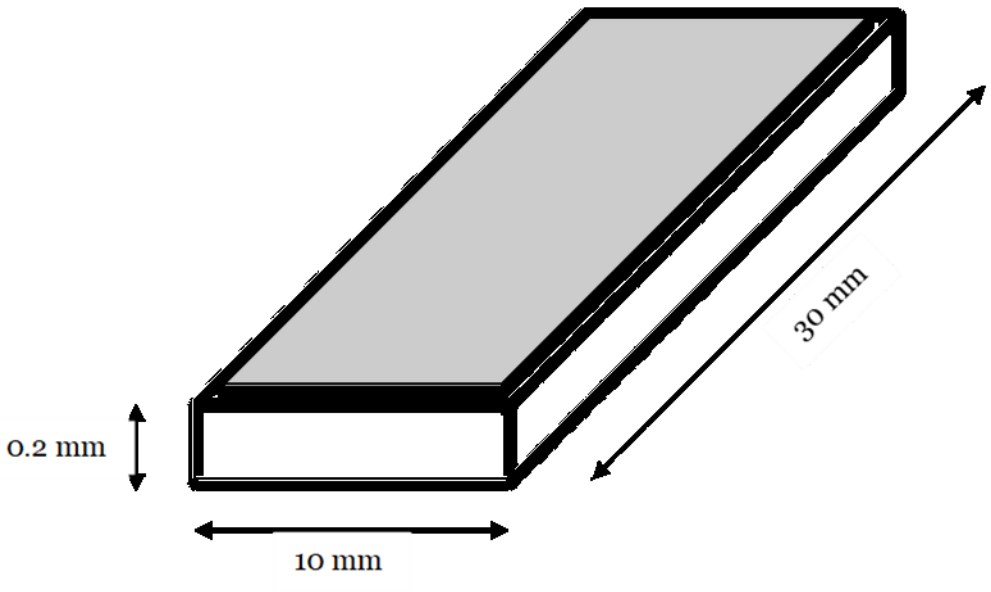

Figure 20. Schematic of Film with Sponge

Figure 20 shows the schematic for a composite consisting of a collagen film attached to a collagen sponge. The sponge is made of lyophilized collagen, pore density can be controlled through the lyophilization process. The sponge adds the unique ability to absorb and elute large amounts of growth factors, while films allow for a malleable, flexible, and handleable quality. These growth factors can be loaded into both the film component and the sponge component of the composite. Doing so allows for the instantaneous bolus of growth factor, as well as a sustained release over time. This is beneficial to the healing process and is the desired release profile of orthopedic surgeons. Growth factor loading to the film can be accomplished during the manufacturing process by adding it to the collagen slurry to integrate it into the film, and via post-process physisorption to the surface of the composite.

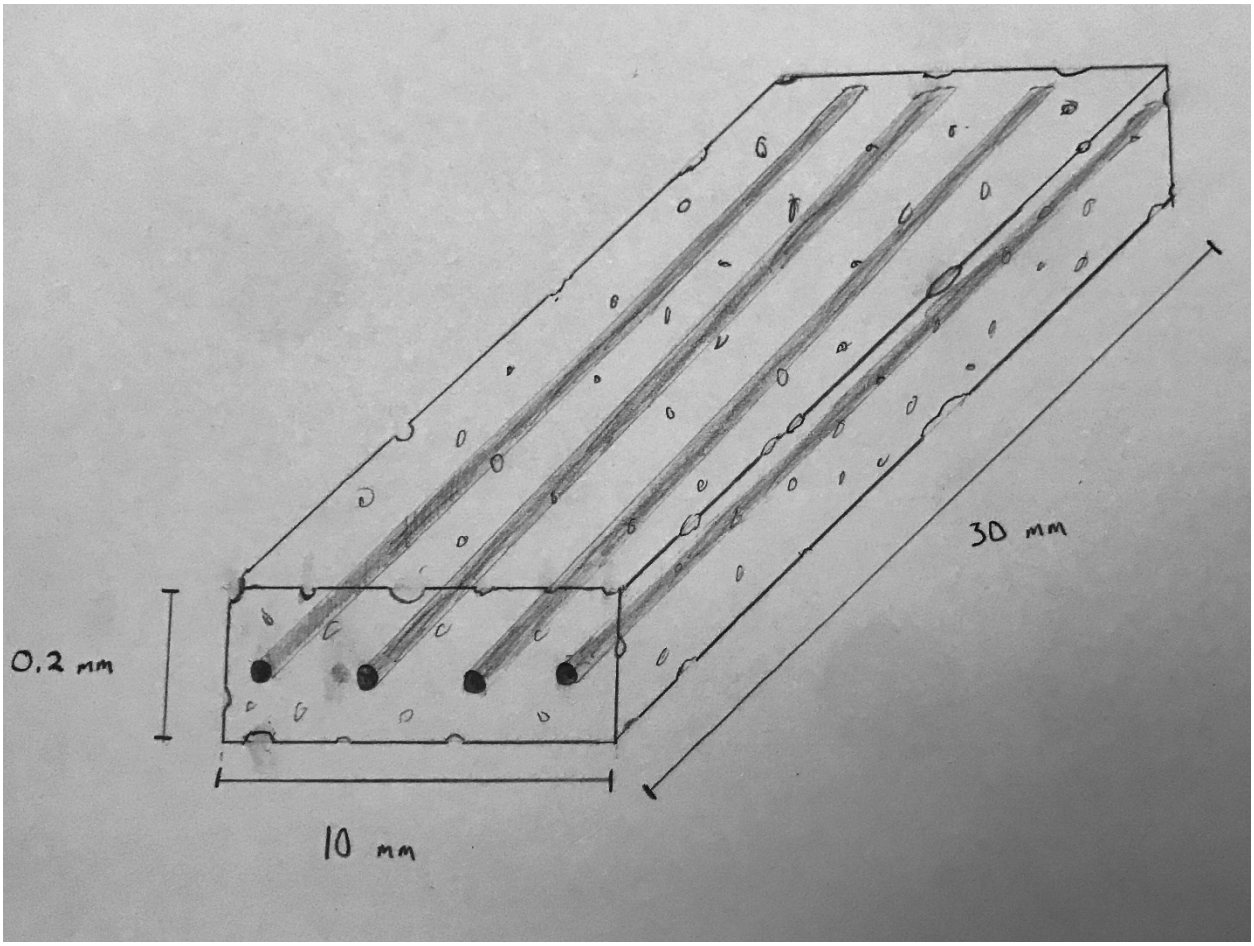

Figure 21. Schematic of Sponge with Threads

Figure 21 shows the schematic for a composite consisting of a collagen sponge impregnated with collagen threads. All threads were placed parallel to each other, mimicking the fibrotic composition of the native ligament. Threads add a unique ability to promote directional healing along with axial strength in a secondary capacity, while the sponge allow for a malleable, flexible, and handleable quality. The sponge also adds the ability to absorb and elute large amounts of growth factors to further promote healing. These can be loaded into both the sponge component and the thread component of the composite. Doing so allows for the instantaneous bolus of growth factor, as well as a sustained release over time. This is beneficial to the healing process and is the desired release profile of orthopedic surgeons. Growth factor loading can be

accomplished during the manufacturing process by adding it to the collagen slurry to integrate it into the threads, and they will absorb into the pores of the sponge.

4.3.3. Evaluation of Composite of Film with Threads

Incorporating collagen threads into a film creates an implantable device that serves to meet many of the design criteria. The formed composite will have mechanical properties that can be varied by adjusting the thread count. The threads provide directional mechanical strength that the film alone does not possess. This does not compromise the malleability of the composite; it will still be easily manipulated by the surgeon. The process of creating these composites is easily reproducible in the laboratory, which is beneficial to the manufacturing process. The composite can be impregnated with growth factors that can be released as the device degrades.

Though the process is reproducible, at its current state manufacturing is small scale. It is a difficult time-consuming process to complete on the bench top using standard laboratory equipment. Tubularization of the ligament will be limited as the surgeon will physically tubularize it with the device. The collagen that is being utilized is based on an acidic solution. This could prove to have negative consequences when impregnating with growth factors (Narla, 2020). This version of the composite will have a limited amount of growth factor, as the film cannot absorb excessively large amounts. There is also no literature that characterizes the degradation of a composite of this type. The pros and cons are summarized in Table 17 below.

Table 17. Composite of Film with Threads Pros and Cons

Composite of Film with Threads	
Pros	**Cons**
Biocompatible	Limited in amount of growth factor impregnation
Easily reproducible	Small scale manufacturing and processing
Threads provide mechanical strength	Limited ability to tubularize
Thread count can change mechanical properties	Not well characterized degradation
Ability to incorporate threads of varied treatments	Currently based on acidic collagen solution
Ability to elute growth factors	
Malleable and easy to manipulate by surgeon	
Novel application	

4.3.4. Evaluation of Composite of Film with Sponge

The formed composite will be malleable; it will still be easily manipulated by the surgeon. The composite can be impregnated with growth factors that can be released as the device degrades. By utilizing the sponge, a larger ratio of growth factors can be impregnated into the device. The spongy component will also be able to be loaded with, and systematically elute PRP, derived from the patient.

This process requires that the sponges be lyophilized, which needs specific equipment. Tubularization of the ligament will be limited as the surgeon will physically tubularize it with the device. The collagen that is being utilized is dissolved in an acidic solution. This could prove to have negative consequences when impregnating with growth factors. The film and sponge also have limited mechanical strength between them, which will constrain the applications in ligament reconstruction. The pros and cons are summarized in Table 18 below.

Table 18. Composite of Film with Sponge Pros and Cons

Composite of Film with Sponge	
Pros	**Cons**
Biocompatible	Small scale manufacturing and processing
Ability to elute growth factors	Difficult to reproduce
Ability to elute PRP	Limited ability to tubularize
Sponge can absorb large amounts of growth factors	Currently based on acidic collagen solution
Malleable and easy to manipulate by surgeon	Film has little mechanical strength
	Sponge has little mechanical strength
	Sponge becomes weak after wetting
	Needs access to lyophilizer

4.3.5. Evaluation of Composite of Sponge with Threads

The formed composite will have mechanical properties that can be varied by adjusting the thread count. The threads provide directional mechanical strength that the film alone does not possess. This does not compromise the malleability of the composite; it will still be easily manipulated by the surgeon. The process of creating these composites is easily reproduceable in the laboratory, which is beneficial to the manufacturing process. The composite can be impregnated with growth factors that can be released as the device degrades. By utilizing the sponge, a larger ratio of growth factors can be impregnated into the device. The spongy component will also be able to be loaded with, and systematically elute PRP, derived from the patient.

This process requires that the sponges be lyophilized, which needs specific equipment. Tubularization of the ligament will be limited as the surgeon will physically tubularize it with the device. The collagen that is being utilized is based on an acidic solution. This could prove to have negative consequences when impregnating with growth factors. This concept has already

been developed in previous works (Flemming et al.,2010). This approach does not create a novel application. The pros and cons are summarized in Table 19 below.

Table 19. Composite of Sponge with Threads Pros and Cons

Composite of Sponge with Threads	
Pros	**Cons**
Biocompatible	Small scale manufacturing and processing
Threads provide mechanical strength	Difficult to reproduce
Thread count can change mechanical properties	Limited ability to tubularize
Ability to incorporate threads of varied treatments	Currently based on acidic collagen solution
Ability to elute growth factors	Sponge has little mechanical strength
Sponge can absorb large amounts of growth factors	Sponge has little mechanical strength
Malleable and easy to manipulate by surgeon	Sponge becomes weak after wetting
	Needs access to lyophilizer
	Not a novel application

4.3.6. Quantitative Assessment of Design Elements

To quantitatively assess the design elements, the scores for each objective was adjusted to represent the weight that each aspect will have in the final design. The weighting system was established in a hierarchical fashion based on the scores derived in the PCC. The weight factor is the score derived from the PCC itself, it was adjusted by multiplying by the weight factor of the objective it is nested within. This gives the relative weight based on the total score. The breakdown of scores can be found in Table 20 below.

Table 20. Final Design Criteria with weight factors

Primary	WF	Secondary	WF	Adjusted	Tertiary	WF	Adjusted
Biofunctionality	0.300	Mechanical Properties	0.250	0.075	Tensile Strength	0.333	***0.025***
					Shear Strength	0.333	***0.025***
					Cyclic Loading	0.333	***0.025***
		Malleable	0.250	***0.075***			
		Biointegration	0.250	***0.075***			
		Bioabsorbtion	0.250	***0.075***			
Surgical Integration	0.200	Easily Manipulated	0.250	***0.050***			
		Anchored to Ligament	0.250	***0.050***			
		Anchored to Bone	0.250	***0.050***			
		Difficulty of Operation	0.150	***0.030***			
		Familiarity of Surgeons	0.100	***0.020***			
Recovery	0.250	Promotes Healing	0.250	***0.063***			
		Native Tissue Maintained	0.300	***0.075***			
		Retraction less invasive	0.200	***0.050***			
		Scar Aesthetics	0.100	***0.025***			
		Enhances Healing	0.150	***0.038***			
Versatility	0.150	Versatility of Elutable Molecules	0.208	***0.031***			
		Versatility of Anchoring	0.292	***0.044***			
		Versatility of Injury Location	0.375	***0.056***			
		Versatility of Injured Ligament	0.125	***0.019***			
Cost	***0.100***						

Figure 22 below depicts the specific breakdown of the final design criteria.

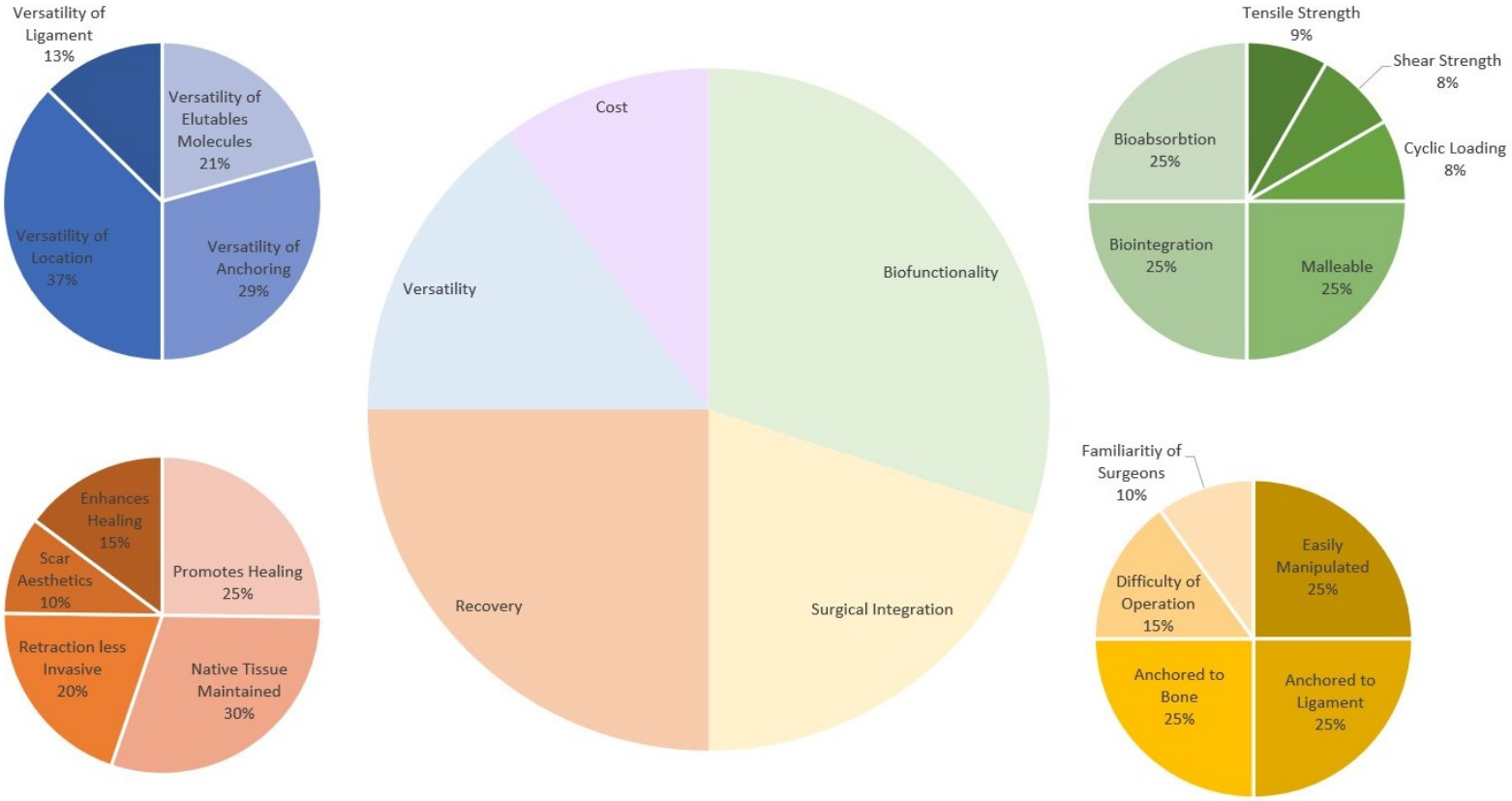

Figure 22. Breakdown of Design Criteria

Utilizing this quantitative assessment of the design criteria, a Pugh analysis was performed to determine the foundation for the final design. Ratings were given to each design based on the literature, the summary of which can be found in design evaluation chapter (3.5). In the case of the Pugh analysis, a rating system follows (-1,0,1). Where each criterion is evaluated with respect to a baseline. A score of 1 means it is better than the standard, 0 is equivalent to the standard, -1 is worse than the standard. This analysis can be seen in Table 21 below.

Table 21. Pugh Analysis of Conceptual Designs

	GRAFT		Film w/Threads		Film w/Sponge		Sponge w/Threads	
Objective	**Weight Factor**	**Baseline**	**Rating**	**Adjusted**	**Rating**	**Adjusted**	**Rating**	**Adjusted**
Tensile Strength	*0.025*	0	1	0.025	-1	-0.025	1	0.025
Shear Strength	*0.025*	0	1	0.025	-1	-0.025	-1	-0.025
Cyclic Loading	*0.025*	0	1	0.025	-1	-0.025	-1	-0.025
Malleable	*0.075*	0	1	0.075	1	0.075	1	0.075
Biointegration	*0.075*	0	1	0.075	1	0.075	1	0.075
Bioabsorbtion	*0.075*	0	1	0.075	1	0.075	1	0.075
Easily Manipulated	*0.050*	0	1	0.050	1	0.050	1	0.050
Anchored to Ligament	*0.050*	0	1	0.050	1	0.050	1	0.050
Anchored to Bone	*0.050*	0	1	0.050	1	0.050	1	0.050
Difficulty of Operation	*0.030*	0	0	0.000	0	0.000	0	0.000
Familiarity of Surgeons	*0.020*	0	0	0.000	0	0.000	0	0.000
Promotes Healing	*0.063*	0	1	0.063	1	0.063	1	0.063
Native Tissue Maintained	*0.075*	0	1	0.075	1	0.075	1	0.075
Retraction less invasive	*0.050*	0	0	0.000	0	0.000	0	0.000
Scar Aesthetics	*0.025*	0	0	0.000	0	0.000	0	0.000
Enhances Healing	*0.038*	0	1	0.038	1	0.038	1	0.038
Versatility of Elutable Molecules	*0.031*	0	1	0.031	1	0.031	1	0.031
Versatility of Anchoring	*0.044*	0	1	0.044	1	0.044	1	0.044
Versatility of Injury Location	*0.056*	0	1	0.056	1	0.056	1	0.056
Versatility of Injured Ligament	*0.019*	0	1	0.019	1	0.019	1	0.019
Competitive Pricing	*0.100*	0	0	0.000	0	0.000	0	0.000
	1.000	0		0.775		0.625		0.675

5. Development and Verification of Final Design

Utilizing the results of the quantitative assessment, the team moved forward with the collagen film-thread composite. Our solution involves a novel collagen film/microthread composite material. The team specifically used insoluble self-assembling bovine type I collagen. This was used to create threads and films. Collagen microthreads were placed onto a 7.5 cm by 12.5 cm polydimethylsiloxane (PDMS) mold. The threads were placed parallel to each other, mimicking the fibrous composition of the native ligament. The collagen film is made from a slurry of type I collagen in 10mN HCl at pH 2.0. 40 mL of the slurry was added to the mold to incorporate the threads into a film. This was left to air-dry under controlled conditions. The dried composite sheets were hydrated in Dulbecco's phosphate-buffered saline (dPBS) and cut to 1 cm by 3 cm sizes to mimic native ligament dimensions. Growth factor loading can be accomplished during the manufacturing process by adding it to the collagen slurry to integrate it into the film and/or via post-process physisorption to the surface of the composite (Cornwell, 2017).

The design incorporates collagen threads imbedded in a collagen film. This provides directional healing along with structural and mechanical support. The collagen will be impregnated with growth factors in order to promote the healing of the injured ligament. Figure 23 represents a schematic of device deployment.

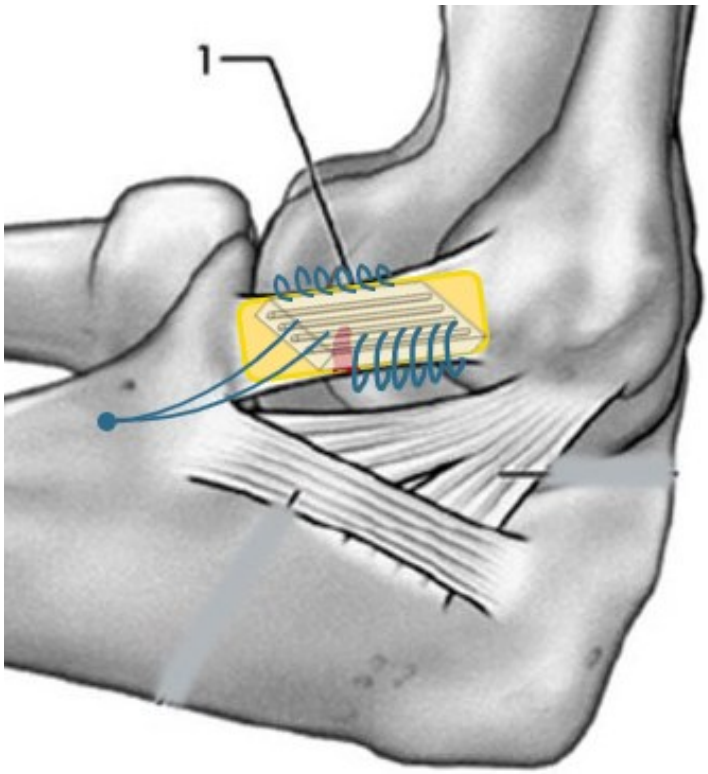

Figure 23. Schematic of final design administered to a damaged UCL

The device is aimed to have a straightforward deployment. The surgeon exposes the elbow in the method he or she chooses, revealing the partially torn ligament under layers of skin, subcutaneous fat, and muscle. Our malleable device would be placed directly atop the ligament at the deformity/injury site, with the threads running in the same directions of the ligament fibers. The device would be sutured in on both sides. The injured ligament loses some of its tensile strength upon injury (Magit, 2019). Thus, the sutures that run through the device and ligament are pulled tightly, following the same orientation as the native ligament, to put it back under tension. A tunnel is drilled into the patient's bone, and the tensioned suture is anchored to it. The device can be anchored using the surgeon's preferred anchoring method, such as a button anchor or an interference screw, to either the sublime tubercle of the ulna or the medial epicondyle of the humerus (Magit, 2019).

5.1. Collagen Treatments

Collagen can be treated in a variety of ways in order to modulate its overall properties. Treatments such as ultraviolet crosslinking (UV XL) can be used to increase the ultimate tensile stress of collagen threads (Cornwell, 2007). The support of the composite can be altered through increasing thread density (O'Brien et al., 2016). This can be done physically during the manufacturing of the composite or through electrochemical alignment (Kishore et al., 2012). Altering these aspects of the composite will help increase the ultimate tensile stress and maximize the structural support of the imbedded threads.

Methods such as encapsulation and surface absorption can be used to load therapeutics onto the components of the final composite. Encapsulation is used when the desired therapeutic release profile can be related to the degradation of the composite (Wang et al., 2017). This can be used to deliver small quantities of therapeutic over a prolonged period. Surface absorption is used to fix therapeutics to the exterior of the composite, this method will provide an instantaneous bolus (Cornwell, 2007). This can be used when instantaneous application of therapeutics is desired.

For the remainder of this paper the design team focused on UV XL and therapeutic loading as the main treatments for the collagen composites. This was due to their desired effects on the collagen being conducive to our application. These methods are well categorized and can be done efficiently with the lab equipment available. A compilation of the researched treatment options can be found in Table 22 below.

Table 22. List of Collagen Treatments

Treatment	**Effects**
UV Crosslinking	Increase UTS (Cornwell, 2007).
Increasing thread density	Improve directional support (O'Brien et al., 2016).
Electrochemical alignment	Greater packing density (Kishore et al., 2012)
Encapsulation of therapeutics	Loads collagen with therapeutic molecules (Wang et al., 2017)

Surface absorption	Loads threads with therapeutic molecules (Cornwell, 2007)

5.2. Tensile Testing

In order to categorize the material properties of the collagen composites, tensile testing was performed. Tensile testing was conducted in an effort to better understand the effects of UV crosslinking treatments on collagen films and composites. The results of this testing could also confirm that the tensile properties of our scaffold are similar to other collagen-based scaffolds demonstrated in the literature (Kato and Silver, 1990) with an ultimate tensile strength of 2.4 MPa. Additionally, the testing protocol is modeled after the Food and Drug Administration guidance document for the preparation of knee ligament devices (US FDA, 2019). The mechanical characterization of our product would be an important data set required by the FDA to gain their approval.

Our testing protocol was designed to be compatible with a BlueHill 3 tension testing method written by the team for uniaxial tension testing. The method utilizes a strain rate of 50% per minute and specimen dimensional parameter inputs set to 1 cm in width by 3 cm in length. The gauge length for the specimens was kept at 3 cm for each test conducted and was insured manually by the team member operating the machine. The program did not include an automated stop function, as the team stopped each test manually when full rupture of the specimen was observed. Our testing method was written to report both load and extension continuously for the duration of each test. Following the completion of our data collection, load values were converted to stress values based on our device's cross-sectional area of 2.0 mm^2 and extension values were converted to strain values based on our 3 cm gauge length. These conversions were achieved using a Microsoft Excel spreadsheet. We used an Instron Electropuls E1000 coupled with a 50N load cell (50 N Static Load Cell, no. 2530-50N, Instron) and for each test. A generalized schematic of our experimental set-up can be seen below in Figure 24.

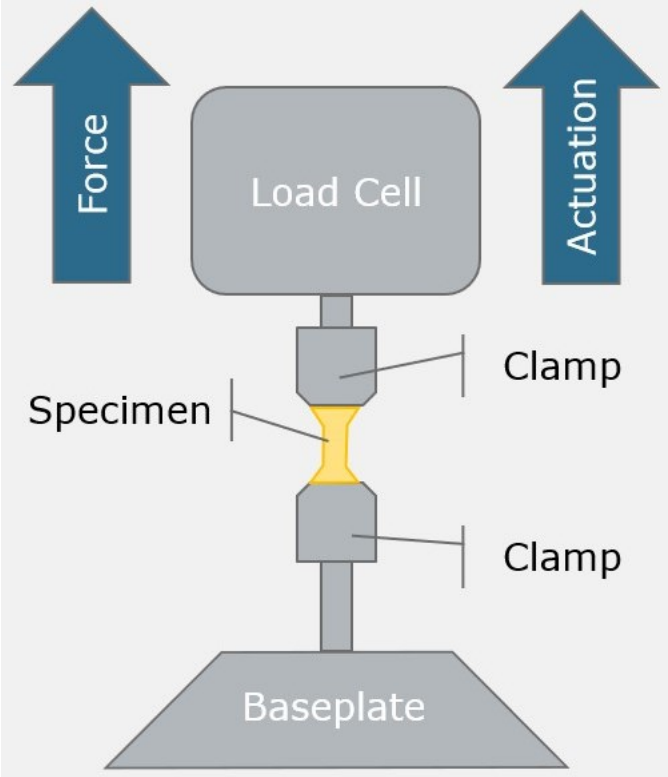

Figure 24. Instron Setup Schematic

Individual films were cut to 1 cm by 3 cm dimensions, hydrated in Dulbecco's phosphate-buffered saline (dPBS) for at least 30 minutes, and glued to velum frames with medical grade adhesive. Each sample had a thickness of 0.2 mm and a cross-sectional area of 2.0 mm^2 The frames, with samples attached, were fastened to the grips (Lever Action Grips, no. 2711-006, Instron) of the Instron by placing the ends of the frame in the grips and then engaging the spring loaded mechanism to secure it into place. Then, the sides of the velum frames were separated with scissors. The grip models and fixation methods are slightly different for the UV Crosslinked tests and are outlined accordingly in the appropriate section. All tests were run until the sample demonstrated a full-thickness tear, denoting failure. Our general set-up is pictured below in Figure 25, both during testing and at failure.

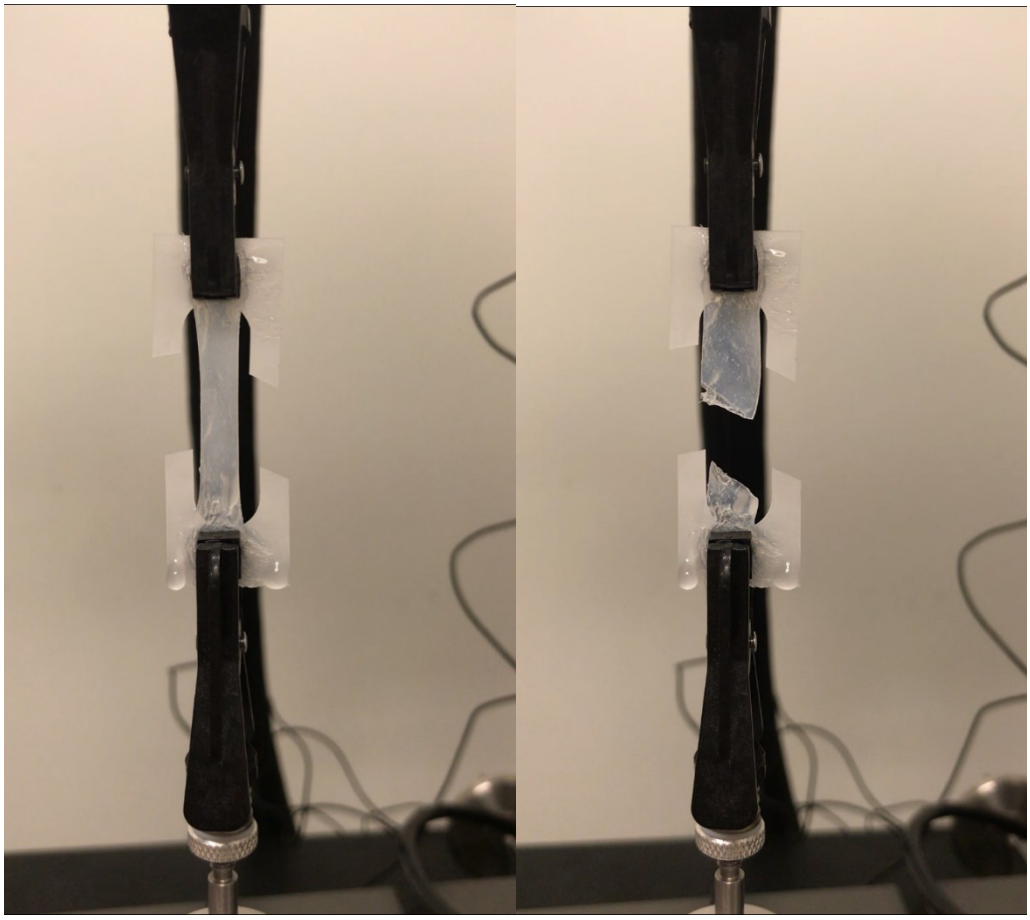

Figure 25. Instron Set up for Tensile Testing

5.2.1. Uncrosslinked Film

Tensile testing was performed on the uncrosslinked (UNX) films to determine the load, stress, and strain at failure. For our uncrosslinked samples, no additional treatment was administered to the collagen after its formation into films. These are the most basic samples we made; they do not include the incorporation of threads and they act as a comparative control for samples treated differently. Figure 26 below shows the stress versus the strain of the 6 samples. This data shows a repeated failure at similar stresses. The bulk of this sample set demonstrated failure between 0.50 MPa and 1.00 MPa. Specimen 6, which is noted by the green load/extension curve, slipped out from the grips prior to tearing, resulting in a curved peak and more gradual load drop compared to the other specimens in the sample. The films also tend to be ductile based on the strain endured before failure. The values for ultimate tensile stress and

strain at failure of each specimen can be found in Figures 27 and 28. The results of this are summarized in Table 23.

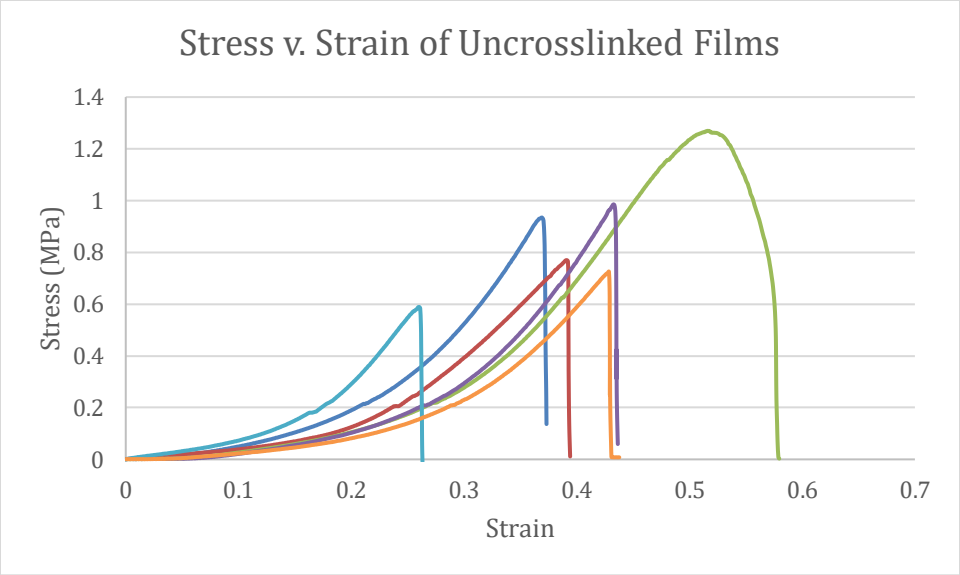

Figure 26. UNX Films Stress vs. Strain

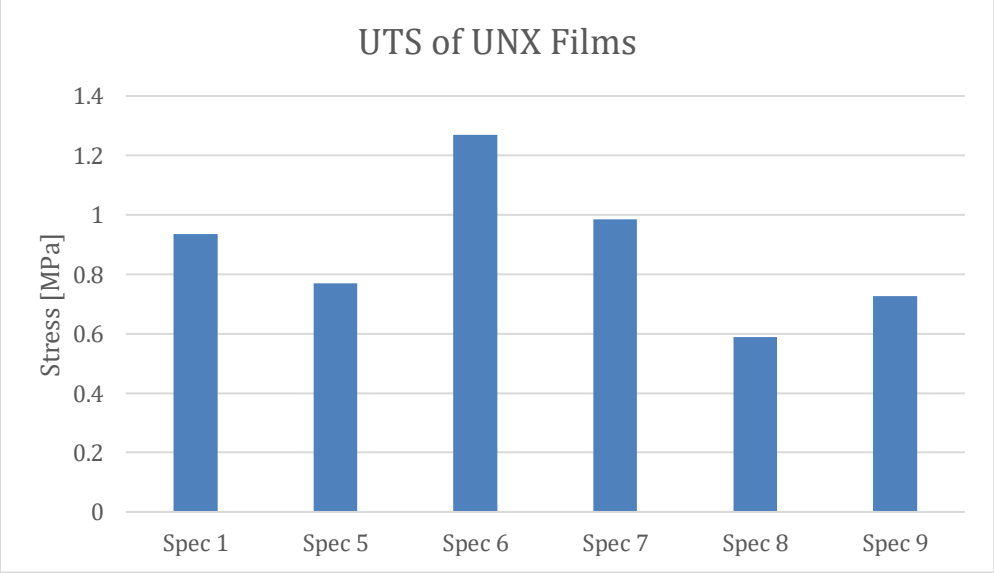

Figure 27. UNX Film UTS

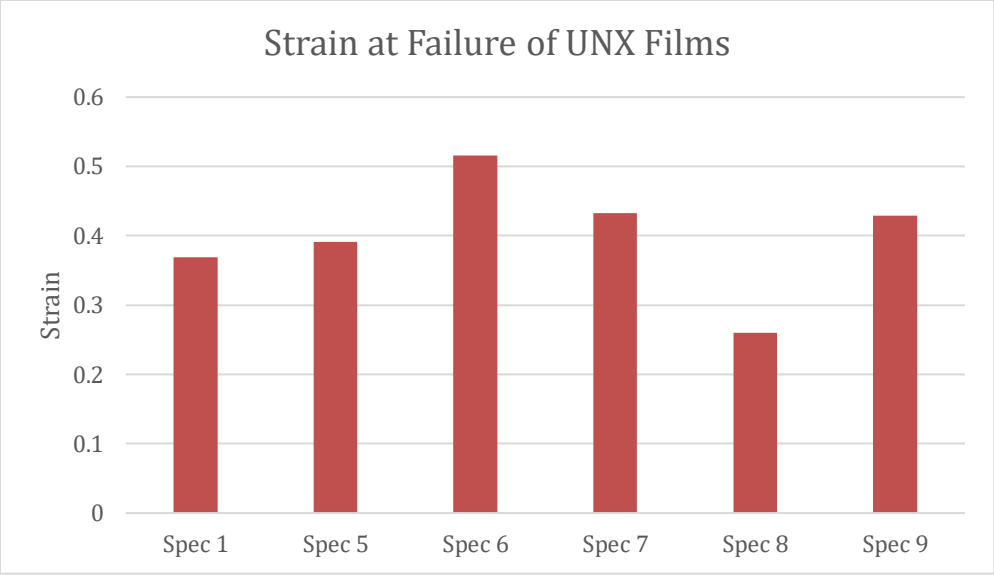

Figure 28. UNX Strain at Failure

Table 23. Results of UNX Film Tensile Testing

n= 6	UTS (MPa)	Strain at Failure
Average	0.879	0.400
STDV	0.240	0.085
Median	0.852	0.410

Based upon this sample data, the UNX films have an average UTS of 0.879 and strain of 0.400 or 40% before failure. The standard deviation of this sample is high, so in the future more testing of UNX films is planned to reduce this It would be beneficial to increase the sample size to reduce the variability of our data.

5.2.2. UV Crosslinked Film

Tensile testing was performed on the UV crosslinked films to determine the load, stress, and strain at failure. These films were crosslinked by ultraviolet light for 15 minutes at a wavelength of 254 nm using a UVP CL-1000 benchtop crosslinker in accordance with the protocol found in the literature (Cornwell et al., 2007). These samples were fixed directly to the grips of the Instron, without the use of a velum frame, by tightening the pads of both grips (Advanced Screw Side Action Tensile Grips, no. 2710-100, Instron) at the ends of the film until they were firmly pressed against one another. These tests were conducted before all other tensile testing, and the

experimental set-up and fixture development was still in the process of being optimized. Future tests should be conducted with samples attached to a velum frame as all other sample types were. Figure 29 below shows the stress versus the strain of the 11 samples. This data shows a variable bimodal peak load for the samples. The cause of the data variability remains undetermined; however, the group has postulated that the grips used in this experiment were not designed to handle sufficient loads experienced by the film specimens. As a result, some specimens may have slipped at the grips or the grips may have been over tightened in response to slipping, causing some samples to rupture at the grips as opposed to midsubstance. The bulk of the specimens which did not appear to slip demonstrated ultimate tensile strengths between 3.65 MPa and 4.72 MPa, including the upper limit specimen. The values for UTS and strain at failure of each specimen can be found in Figure 30 and 31. The results of this are summarized in Table 24.

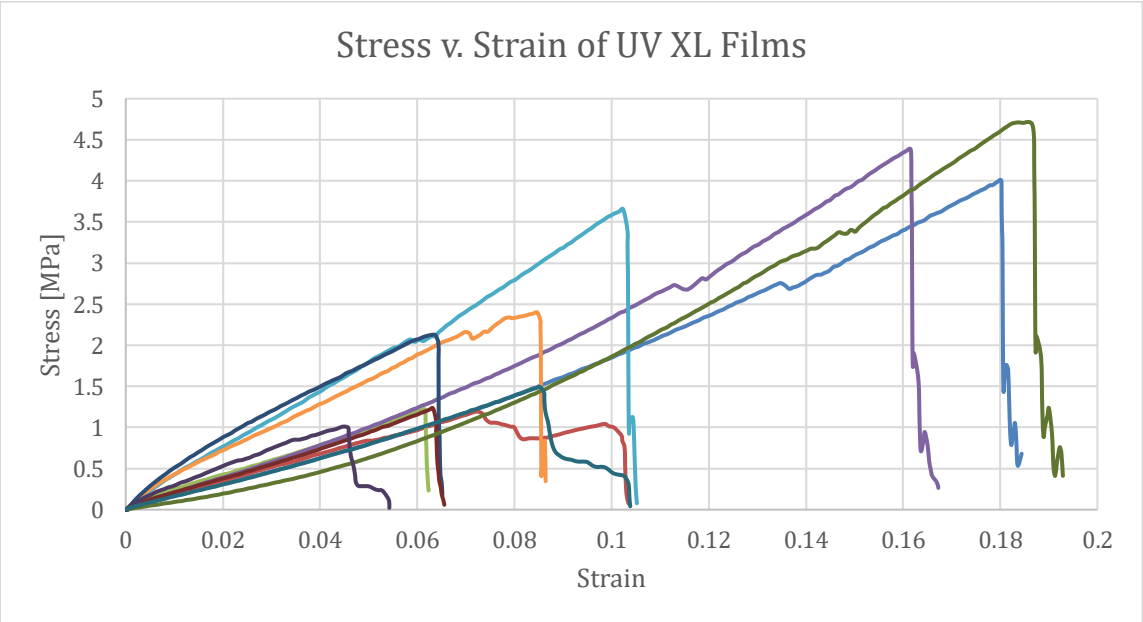

Figure 29. UV XL Films Stress vs. Strain

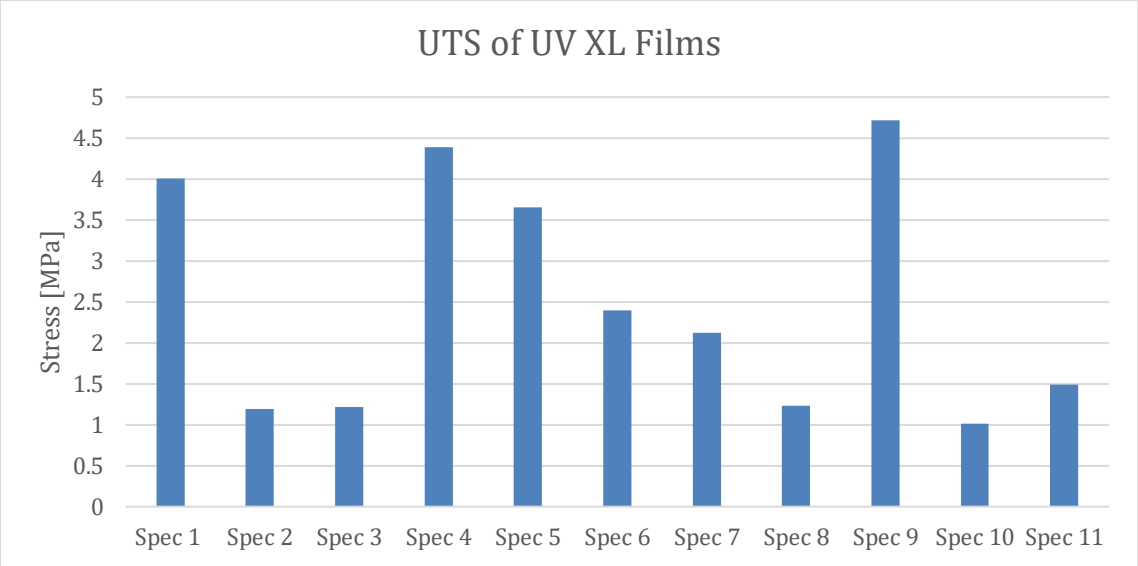

Figure 30. UV XL UTS

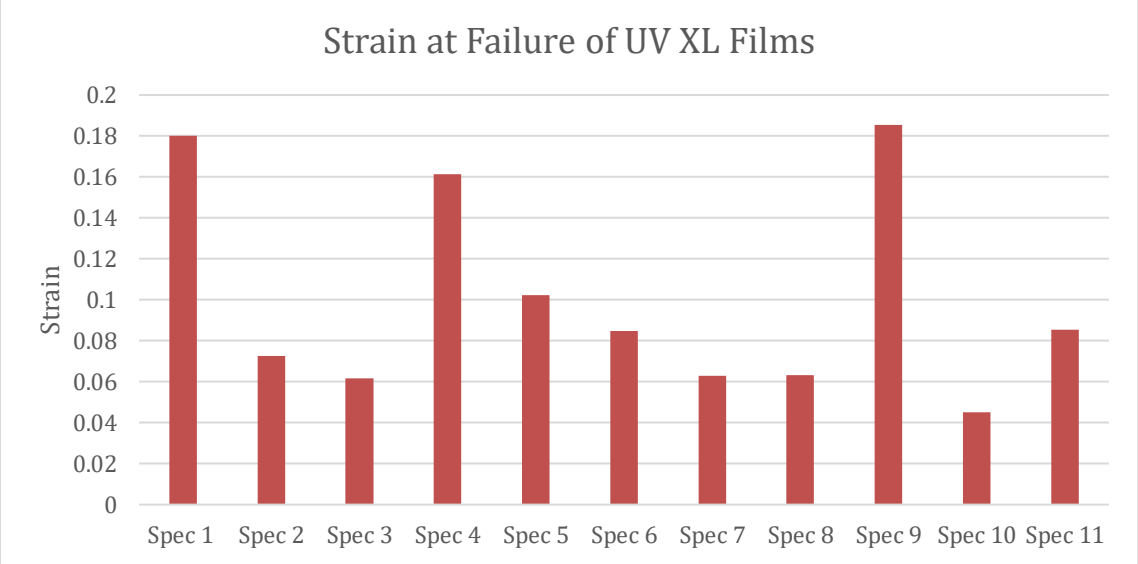

Figure 31. UV XL Strain at Failure

Table 24. Results of UV XL Film Tensile Testing

n= 11	UTS (MPa)	Strain at Failure
Average	2.49	0.100
STDV	1.44	0.051
Median	2.13	0.085

The average UTS of the UV XL films was recorded at 2.49 MPa and the average strain at failure was determined to be 0.100 or 10%. The standard deviation of this sample is very high, so in the future more testing of UV XL films is planned to reduce this.

5.2.3. Uncrosslinked Composite

Tensile testing was performed on the uncrosslinked composites to determine the load, stress, and strain at failure. These samples were fixed to vellum paper before testing in order to prevent slipping at the grips following the procedure outlined for the UNX Films. Figure 32 below shows the stress vs. strain of the 8 samples. The bulk of this sample set demonstrated failure between 0.60 MPa and 1.10 MPa, with an upper limit of 1.36 MPa. The values for UTS and strain at failure of each specimen can be found in the Figures 33 and 34 below. The results of this are summarized in Table 24.

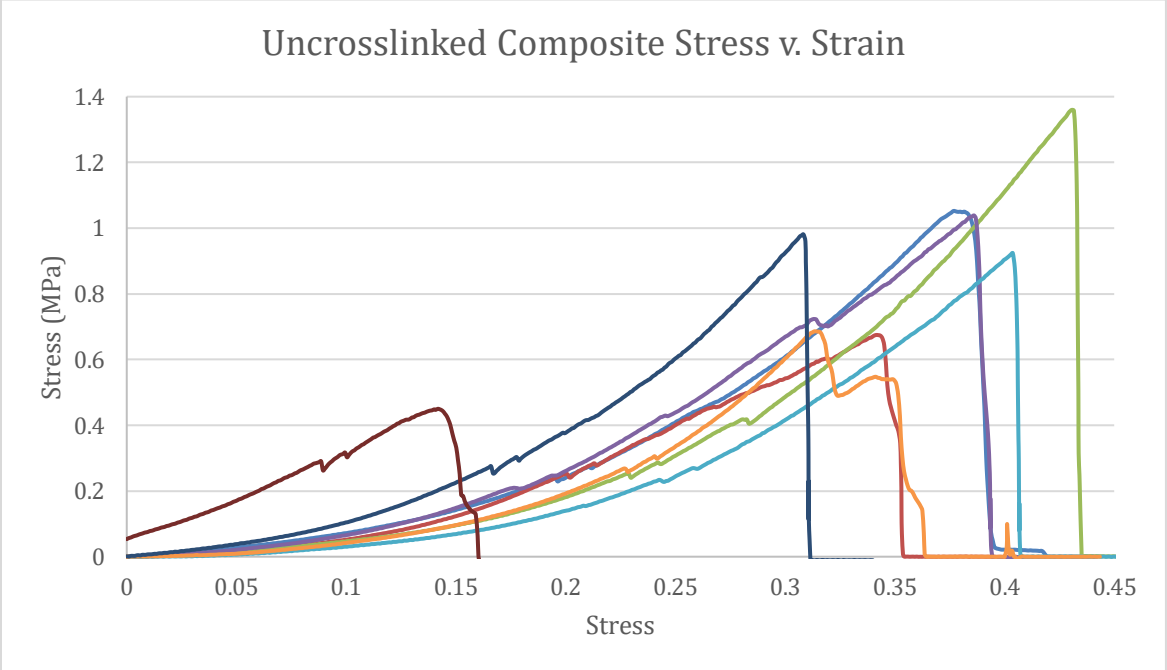

Figure 32. UNX Composites Stress vs. Strain

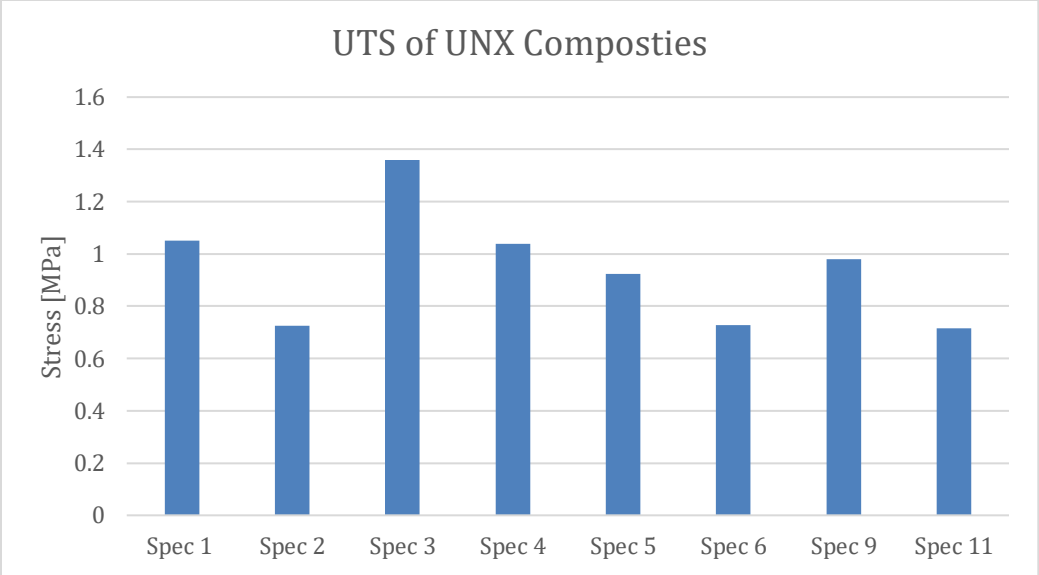

Figure 33. UNX Composite UTS

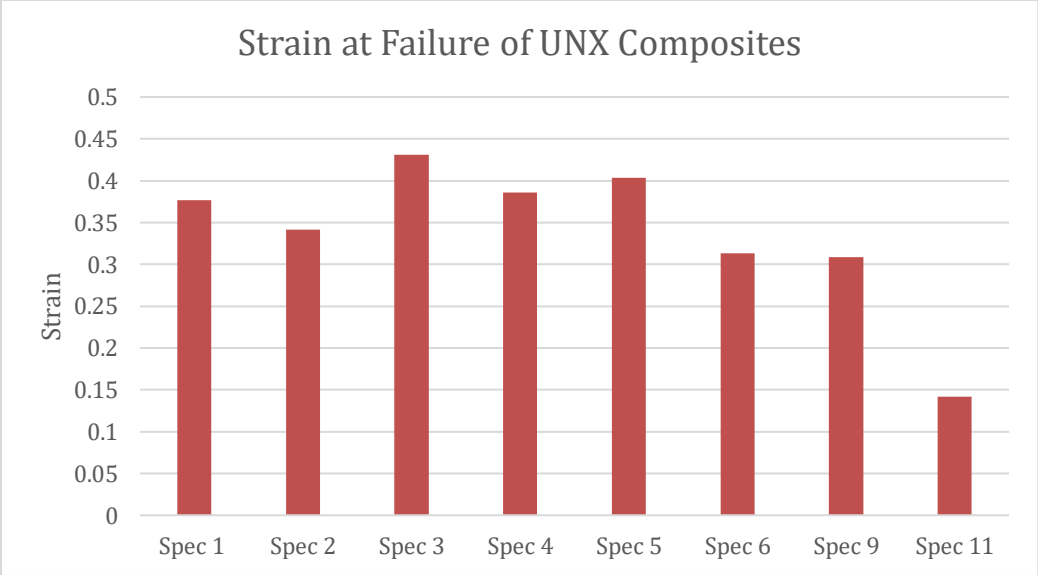

Figure 34. UNX Composite Strain at Failure

Table 25. Results of UNX Composite Tensile Testing

n= 8	UTS (MPa)	Strain at Failure
Average	0.996	0.338
STDV	0.283	0.090
Median	0.940	0.360

Based upon this sample data, the UNX composites have an average UTS of 0.996 MPa and strain of 0.338 or roughly 34% before failure. The standard deviation of this sample is high, so

in the future more testing of UNX film composites is planned to reduce this. It would be beneficial to increase the sample size to reduce the variability of our data.

5.2.4. UV Crosslinked Composite

Unfortunately, due to constraints with laboratory access because of COVID-19, we were unable to obtain data for UV crosslinked films composites. We anticipate the results of this test, however, to demonstrate the highest UTS and lowest strain to failure measurements of any of our testing cohorts. We believe the combined comparative strength of a UV XL film with the directional support of embedded threads should yield increased tensile strength when compared to both UNX and UV XL films, and UNX composites.

6. Future Device Validation

Unfortunately, due to constraints with laboratory access because of COVID-19, we were unable to obtain data for validation results. Therefore, planning for verification testing is outlined below.

6.1. Mechanical Testing

The FDA requires that implantable materials be well categorized before they can be reviewed for approval. In order to properly record the mechanical properties of the design the design team outlined future testing that should be conducted.

6.1.1. Uniaxial Tensile Testing

The uniaxial tensile testing conducted, as described in chapter 5, provided some useful data. In the future it is important that this testing be replicated. A proper statistical analysis should be performed until statistical significance has been reached.

6.1.2. Suture Testing

Suture testing must be performed on the composited to quantify the pull-out strength required for failure. Proper testing methods for these experiments may be adapted from *ISO 7198:2016 Cardiovascular Implants and Extracorporeal Systems – Vascular Prostheses – Tubular Vascular Grafts and Vascular Patches*. Suture pull out methods outlined in this standard are likely transferable to our purpose regardless of their indication for cardiovascular implantation use. This is used to determine where the suture can used and how long it is intended to remain there. Prior to testing information should be gathered from surgeons to determine the size of the suture needle to be used. Once this is determined, suture of different gauges should be tested to determine how the suture size effects the integrity of the composite. Testing should be done until statistical significance has been reached.

6.1.3. Cyclic Loading

Cyclic loading testing should be performed to determine the effects of repeated stress on the structural integrity of the composite. *ASTM F2150-19 Standard Guide for Characterization and Testing of Biomaterial Scaffolds used in Regenerative Medicine and Tissue Engineered Medical Products* should be used to adopt the appropriate testing methods into the scope of this project. Care should be taken to emulate the stresses on the native UCL during restricted motion. Immediately following the procedure, the range of motion and load on the UCL is restricted (Magit, 2019). The composite will be degraded before the UCL will be experiencing normal loads and rotation. Therefore, the cyclic loading should try to simulate the post-surgery forces experienced in the UCL. Testing should be done until statistical significance has been reached.

6.2. Degradation Testing

Our composite was designed specifically to degrade over time in a controlled manner. Other devices on market such as the Arthrex Internal Brace system do not degrade at all and thus potentially pose a serious foreign body burden on the patient's immune system (*Arthrex - UCL InternalBrace™ Ligament Augmentation Repair*, n.d.). In order to eliminate the concern for any prolonged foreign body response at the implantation site, our device must be completely bioabsorbable as outlined in our objectives. We can use an *in vitro* degradation profile of our device as evidence that the collagen scaffold should be broken down appropriately *in vivo*. This testing acts as our way to mimic body conditions so that we can better model how our composite would degrade at the surgical site.

After identifying our optimal degradation profile of 6-8 weeks from the time of implantation to full degradation, we could begin testing different formulations of our composite (Laitinen, 1992). We intended to test all the same treatments expressed in our tensile testing experiments.

These would include, but are not limited to, an UNX Film control group, an UNX composite group, a UV XL film group, and a UV XL composite group. The goal of this testing is to best match the degradation profile of our composite formulations to that which has been stated in the literature and adopted into our own goals (6-8 weeks).

Though time and resource constraints restricted our abilities to conduct this testing, we were still able to develop a protocol. The procedure was adapted from a degradation assay of collagen threads to better categorize the in vivo characterization of the implant (Cornwell et al., 2007). We believe that this procedure will transition well from thread applications to testing a composite with few augmentations. The full protocol can be seen in Appendix F.

6.3. Drug Elution

To promote the healing of the native ligament the collagen composite will be impregnated with growth factors. The ability to elute drugs directly to the wound site would set this device apart from the currently available techniques, as none of them have this ability currently. Due to the COVID-19 pandemic, the laboratory was closed, and the scheduled drug elution studies became impossible to complete.

Initially, it was hoped that this device could elute platelet rich plasma (PRP). When the switch to only using pure growth factors was made, it had to be decided which specific growth factors would be tested. Fibroblast Growth Factor 2 (FGF-2) is a growth factor that has been extensively studied in the literature (Cornwell, 2007), and is a major component in PRP (Krüger, 2013). Using PRP as a basis for dosage, it was determined that a normal PRP dose for an UCL injury would result in 1.5 ng of FGF-2 (Kwapisz, 2018; Krüger, 2013). Thus, this 1.5 ng amount was determined to be the target amount of FGF-2 to deliver. There is a large amount of FGF-2 present in a wound site to help rebuild vasculature and to heal tissue. This amount is

elevated for three weeks, and thus it was decided that this device would aim to deliver its 1.5 ng of FGF-2 for 3 weeks (Cornwell, 2007).

In the literature there are many methods mentioned for how to incorporate drugs into an implantable device (Wang, 2017). The two methods that Wang, 2017 mentions that are most promising for this application are encapsulation and surface absorption. Encapsulation would have consisted in us adding the desired amount of growth factor directly into the collagen slurry that is cast to become the film portion of the composite. Surface absorption involves making the composite, and then placing it in a solution containing the growth factor, that allows the factor to absorb directly into the surface of the composite.

Both methods come with benefits and drawbacks. Encapsulation won't work if the acidic slurry damages the growth factor. Encapsulated FGF-2 would also have to endure the drying process and possible UV crosslinking. The literature does not explain if it should be expected that these treatments damage the growth factor or not. In fact, we reached out to Sigma Aldrich, a supplier of these growth factors, and they did not know if the factors would survive the process or not. Therefore, experimental testing would need to be performed to find out if this is a viable method. Surface absorbed growth factors, on the other hand, does not endure the processing steps that encapsulated factors do. That being said, surface absorption could potentially lead to a massive initial bolus without providing the desired sustained release. There could also be difficulty in measuring the amount of growth factor in the device, as it is possible that not all of the growth factor will be absorbed into the composite. It may also be possible to load a sample with both methods to provide a large initial bolus and a long-term sustained release.

Once the growth factors have been loaded, the collagen will be degraded following the collagen degradation methods explained in section 5.3. The only difference is that instead of

measuring the optical density of the solution, an ELISA kit will be used to measure presence of FGF-2. The ELISA kit will be used according to manufacturer's instructions.

6.4. *In Vivo* Testing

According the FDA guidelines, all novel implantable devices require testing in an animal model to verify their safety in a living system. The team is confident that in vivo testing will validate the concept of native tissue regeneration at the injury site. These tests will allow us to observe direct tissue response at a cellular level in the context of living systems. Implanting the device in a living system will also demonstrate any generalized negative reactions, be they unforeseen inflammatory responses or improper tissue ingrowth. Characterizing these results will be vitally important to fine tuning our device formulation to correct these issues before human trials. It is also important to note that our product may perform differently in animals than it does in humans, even in mammalian animal subjects. This may be due to differences in anatomy and physiologic processes. There are no well-defined, readily accessible animal models that possess both a similar elbow structure and joint activity pattern to humans. Therefore, the team has identified Merino sheep subjects as a potential large animal models, given its well documented use in ACL orthopedics research (Madry et al., 2015). Due to known time and money constraints, it was determined at the beginning of this project that *in vivo* testing would not be done during this year. It is still an important device validation study and it should be conducted by the future team.

7. Discussion

While the design team may not have been able to conduct the full battery of validation tests, the data gathered still managed to prove valuable. With a critical eye, existing data can be examined to iterate on the present design, and it can be used to plan future testing.

7.1. Comparison of Tensile Results

Figure 35 below plots representative stress vs. strain curves for each of the three treatment groups that underwent uniaxial tensile testing. Figures 36 and 37 below were compiled to easily compare the average stress and strains at failure for each treatment, respectively. Some specimens clearly slipped prematurely, and these data were eliminated from calculation. That being said, some samples may have slipped slightly in ways undetectable to the experimenters. It is suggested that future teams consider using a new set of tensile tests on a fresh set of samples. Table 26 puts all the average data into one centralized location for ease of access. As indicated by the data, we observed a dramatic increase in ultimate tensile strength in the UV XL films treatment group when compared to both the UNX film and UNX composite groups. Additionally, the average strain to failure was greatly reduced from almost 40% in UNX groups, to 10% in the UV XL group. These results confirm our design's mechanical properties are easily tunable via our UV crosslinking method. More studies could be conducted to explore the effects of other crosslinking methods on our device. Some crosslinking methods may change the mechanical properties more dramatically or they could offer more precise control of property modification compared to UV crosslinking, but further experimentation would be required.

While our crosslinking process produced an increase in ultimate tensile strength, we also observed an attenuation of strain to failure. As shown, the average strain to failure of this group was 10%. This could cause some degree of concern because the native ligament must be capable of regular strains up to 18% (Labott, Aibinder, Dines, & Camp, 2018). The movement of the native ligament will be tightly regulated throughout the healing process of any surgical

procedure, so the implant impinging on full range of motion once healed is of little or no concern. However, the stress and strain shielding phenomenon at the interface of our device and the native tissue during the healing process should be considered, given the disparity in strain properties (Korabi et al., 2017). While we may not know how the effects will manifest without *in vivo* studies, it is important to consider this difference from the native tissue and how it may affect tissue remodeling.

The data trends also suggest our production techniques can yield films and composites with similar ultimate tensile strength characteristics to other collagen-based scaffolds found in the literature. Kato and Silver's collagen fiber scaffold demonstrated tensile strengths of 2.4 ± 0.46 MPa (Kato and Silver, 1990). Using their benchmark data, we found that our films and composites may not align perfectly with their recorded UTS values. We showed that the UTS of our composite devices is easily tunable and further experimentation should bring us closer to the desired value outlined in our objectives.

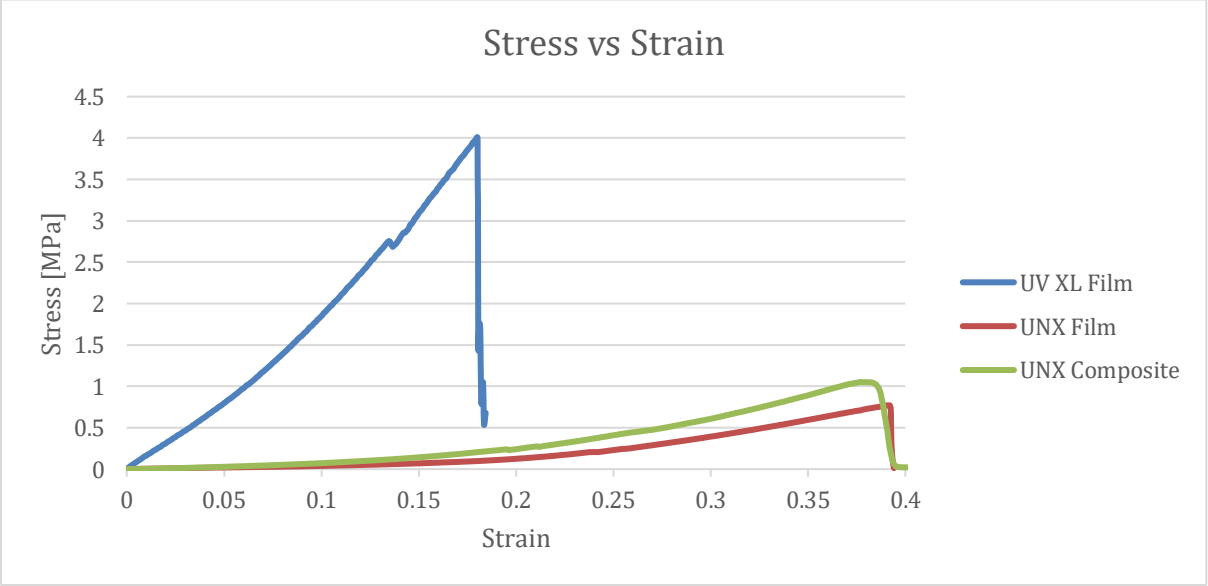

Figure 35. Representative Stress vs Strain

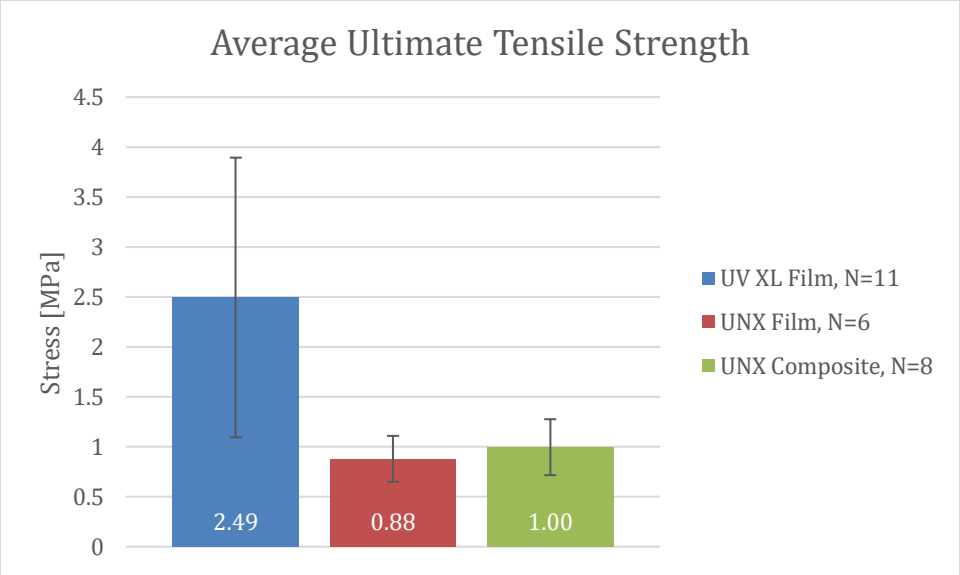

Figure 36. Average UTS

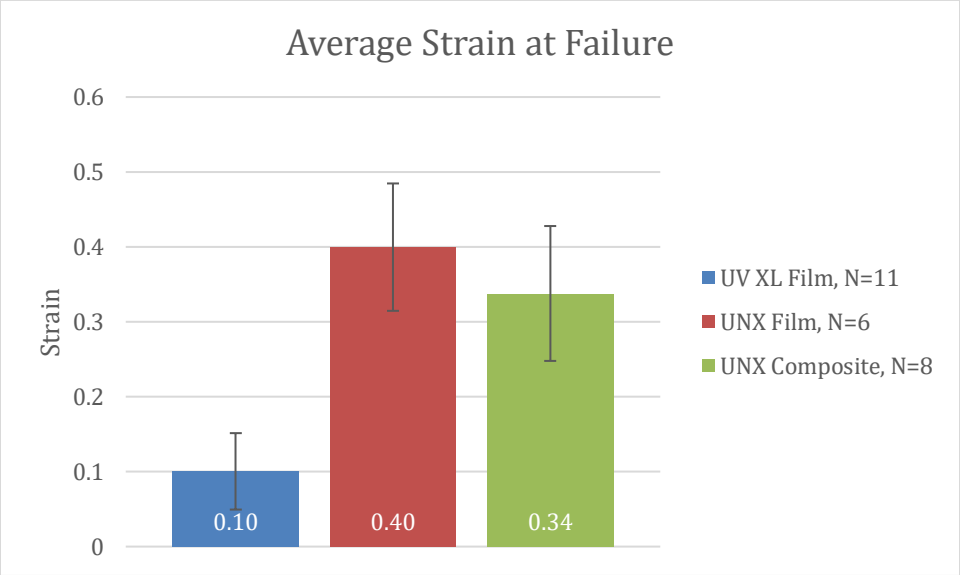

Figure 37. Average Strain at Failure

Table 26. Average Results of Tensile Testing

	UTS (MPa)	STDV	Strain at Failure	STDV
UV XL Film	2.49	1.44	0.10	0.051
UNX Film	0.88	0.24	0.40	0.085
UNX Composite	1.00	0.28	0.34	0.090

In order to understand the significance of the effects of the different treatments, statistical analysis was performed. Based on the different sample sizes, the team decided to perform t-Test comparing the UV XL films and UNX composites to the UNX film, our control group. Therefore,

a Two-Sample t-Test was run assuming unequal variances for each comparison group. Tests were run for both UTS and strain at failure. The null hypothesis for each group assumed that the UTS or strain values are equal, the alternative hypothesis assumed that the values were not equal. The two-tail p value and a significance level $\alpha = 0.05$ was selected for the tests. A compilation of t-Tests can be found in Appendix G.

For the comparison of UNX composites to UNX films, no statistical significance was established. When comparing UTS, a p value of 0.635 was obtained. This value is greater than the significance level, and therefore we cannot reject the null hypothesis. The strain at failure t-Test resulted in a p value of 0.215. This value is greater than the significance level, and therefore we cannot reject the null hypothesis. Based on this analysis, the addition of threads to form a composite did not affect the UTS or strain at failure of the UNX collagen films. Anecdotally however, we observed differences between in UTS values between the UNX film and UNX composite groups. The team intends to further explore this notion by replicating this study and testing again for statistical significance.

For the comparison of UV XL to UNX films, some claims can be made. When comparing UTS, a p value of 0.00379 was obtained. This value is less than the significance level, and therefore we can reject the null hypothesis. The strain at failure t-Test resulted in a p value of 9.84E-05. This value is less than the significance level, and therefore we can reject the null hypothesis. Based on this analysis, the UV crosslinking of the collagen has an effect on both the UTS and the strain at failure of collagen films.

7.2. Impact Analysis

The development of our composite along with its potential deployment into the orthopedic medicine field opens the door for a wide range of considerations. The design and manufacturing of any product needs to consider the ramifications of upscaling beyond the effect to the design team and target market. It is important to focus not only internally, but also more broadly on the economic, environmental, and political impacts, among others.

7.2.1. Economic Impact

Baseball is big business. The annual revenue for Major League Baseball (MLB) is over ten billion dollars (Brown, 2020). MLB pitchers cost one and a half billion dollars annually (Frank, 2016). When a third of pitchers, the billion-dollar commodity, have had had UCL reconstruction (Carroll, 2013), it is clear that a great deal of money is being lost to injury. If this device can reduce recovery time then astounding amounts of money can be saved by players and teams, as players will be able to return to play much faster.

For an individual athlete, a UCL reconstruction costs between $10,000-$26,000 (MedRepublic, 2020). It is impossible to predict exactly what this device will cost, but there are no components that are particularly costly. This $10,000-$26,000 figure is a useful benchmark and in the future the device and its deployment should aim to cost less than that amount.

This device was designed specifically with the UCLs of elite athletes in mind, however, the device may also be used in other spaces. One possible application is in the repair of rotator cuffs (Magit, 2019). This is a massive patient population, with 250,000 rotator cuff repairs performed in the United States annually (Rahman et al., 2017). If this device can expand into the rotator cuff market, and other soft tissue orthopedic applications, then it could potentially go from a niche elbow device to a mass market device.

7.2.2. Environmental Impact

The chemicals used in the purification process of collagen from bovine hide need to be disposed of with care and can be considered harsh. There should be limited environmental impact derived from the manufacturing process of the designed implant. Excess collagen left over from the manufacturing when cutting to size does produce biological waste. Additionally, there are large quantities of chemicals and buffers needed to make collagen scaffolds. In the future, thought must be taken when choosing the sterilization process, as many could prove to

have environmental impacts. It does not consume large amounts of energy when compared to general lab consumption. We do not foresee any large environmental impacts.

7.2.3. Societal Influence

Our device will allow for an approach aimed specifically at restoring partially torn UCLs to pre-injury condition and performance. The applications of this device will be brought to public attention as it becomes validated as a revolutionary method of healing. Initially it will be seen primarily through the vector of the MLB. The device has the potential to mirror the rise in popularity of the Jobe technique and surpass it as its efficacy is proven. As it is expanded to other soft tissue injuries, it will become a stimulating agent for research. This will affect the direction of biomedical research towards developing scaffolds for other applications. Using a device such as ours, there will be a decrease in excessive surgeries. There will be no need for a patient to undergo complete reconstruction for a less demanding injury. This will allow for more appropriate interventions in the future.

7.2.4. Political Ramifications

Major league baseball is a 10 billion dollar a year business that many people across the globe take note of (Brown, 2020). While pitchers are a large part of the game, there are a great many factors that determine the sport's global popularity beyond the health of a pitcher's elbow. It's impossible to perfectly predict the political ramifications of this device, but we expect that they are likely negligible.

7.2.5. Ethical Concerns

The ethical aspects of this device center around the misuse of its applications and misunderstanding of its results. There has been a rise in youth receiving the Jobe technique (Watson, 2014). This has caused an increase in misconception surrounding its effects. Athletes are attempting to get the surgery done preemptively, believing that it will make them a better player (Magit, 2019). This is a false belief; the reconstruction aims to return the torn UCL to pre-

injury conditions. Most of these cases are turned away, however, there are some athletes who still receive it (Hamley, 2015). By extension it can be believed that similar circumstances may arise in the use of this device. It is important that patients are well informed and not given incorrect or misconstrued information. There is also an ethical consideration on the obtaining of collagen. Currently it is obtained from a variety of cadaver animals, primarily cows. This process can be considered unethical by certain demographics. In the future *in vivo* testing must be done for validation before introduction into human medicine, this presents ethical issues with the use of laboratory experimentation on animals.

7.2.6. Health and Safety Issues

The device is an implantable design and therefore it is important that it remains sterile throughout the manufacturing, delivering, and surgical process. There are risks of disease transmission and contamination that could be potentially harmful to the patient. It is important that the manufacturing and packaging process is created in such a way that the risk of contamination is limited. This will reduce any potential danger of harmful transmission. There is also a possibility for a patient to be allergic to the bovine sourced components of the device. In this case it is important that the patient is aware of the components of the implant before surgery to discuss a different treatment option and avoid any reaction. We have no reason to believe our device will impart any additional risk when compared to the current operative standard of care.

7.2.7. Manufacturability

The cost of manufacturing of this device was considered. An objective was to create a device that would not be expensive for use. A material breakdown and associated costs can be found in Appendix H. It was determined that the approximate cost of the device is $1.00. This was based off the yield from the creation of films and threads from a collagen slurry. We determined that following the thread extrusion protocol, enough threads to create 3 composites can be obtained

per milliliter of collagen suspension. Through the film protocol, there is enough material to make 11 film samples from 40 mL of collagen suspension. These metrics were used to calculate the material cost of $1.00/composite. This price does not account for labor, time, or equipment cost. As the design is moved to bulk manufacturing, the initial cost per unit will be significantly increased to cover the overhead fees associated with large scale manufacturing. The design team believes that the current manufacturing method can be scaled up with limited difficulties. Doing so should allow for the production unit cost to decrease when accounting for the costs of manufacturing excluding material price.

7.2.8. Sustainability

The production of the implant will have little impact on global sustainability. Currently collagen is obtained from bovine hides. There is research suggesting that yeast can be used as alternative source for the production of type I collagen (Nokelainen, 2001). The process of deriving collagen from the yeast is difficult and requires a lot of resources. In the future if it is possible to adopt into practice this will allow for a more sustainable method of obtaining collagen than the current practice.

7.2.9. Industry Standards

Various guidelines from the FDA were followed during this project. Standards considered by the design team for guidance included *ASTM F2212-19 Standard Guide for Characterization of Type I Collagen as Starting Material for Surgical Implants and Substrates for Tissue Engineered Medical Products (TEMPs)* and *ASTM F2150-19 Standard Guide for Characterization and Testing of Biomaterial Scaffolds used in Regenerative Medicine and Tissue Engineered Medical Products*. These guidelines helped determine the proper testing necessary for proper categorization. Future testing and development will also follow these standards. This will help to ensure that our product is safe and well characterized on a broad spectrum of properties outlined previously, and that all the data gathered on the product is

reproducible in future tests. The current design team fully intends to adhere to the appropriate standards going forward.

8. Conclusions and Recommendations

Year after year, athletes with partial tears continue to choose between options that fail to provide a solution that focuses on repairing and regenerating native tissue. This device serves to fill that need.

The team was able to design and produce a prototype collagen scaffold for grade II ulnar collateral ligament repair. Along with that, the team was able to demonstrate that each component of the composite can be changed independently. These small independent changes come together to allow for the final device to be fine-tuned to desired overall properties. The current composite design can be modified to control the elution profiles of loaded molecules.

Unfortunately, due to the COVID-19 pandemic, the team was unable to complete its full battery of validation testing. Next year's team will be able to perform the degradation and drug elution studies outlined in this paper. After that, *in vivo* testing would help aid in verifying the safety and efficacy of the device. The device can also be further modulated, such as including a sponge in the next iteration. The sponge would make it possible to elute platelet rich plasma. On top of PRP, other pure growth factors involved in the healing cascade could be incorporated, such as platelet derived growth factor (PDGF) or transforming growth factor β, (TGF- β).

One of the hopes is that once this device is used in ulnar collateral ligaments in athletes that is can be tested in other orthopedic soft tissue applications, such as healing patients with rotator cuff injuries, labrum injuries, or injuries of the many ligaments of the knee. It could even potentially be used within veterinary medicine.

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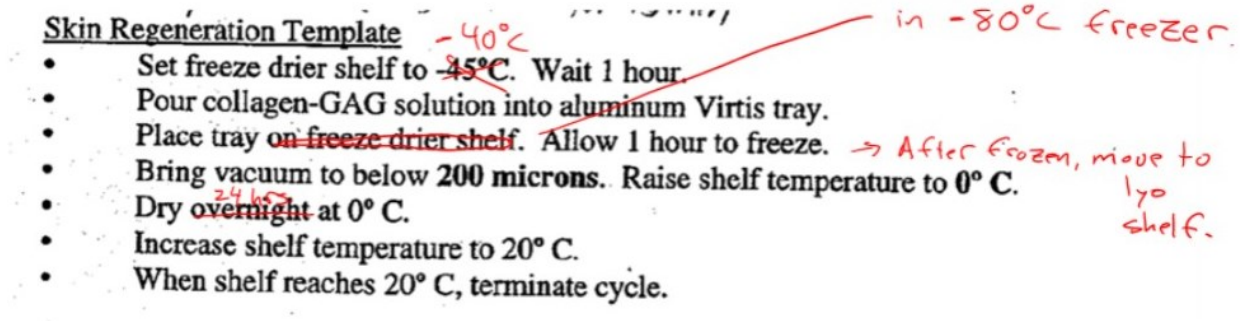
Appendix

Appendix A: Lyophilizing Protocol



Skin Regeneration Template

- Set freeze drier shelf to ~~-45°C~~ -40°C. Wait 1 hour.
- Pour collagen-GAG solution into aluminum Virtis tray.
- Place tray ~~on freeze drier shelf~~ in -80°C freezer. Allow 1 hour to freeze. → After frozen, move to lyo shelf.
- Bring vacuum to below **200 microns**. Raise shelf temperature to **0° C**.
- Dry ~~overnight~~ 24 hrs at 0° C.
- Increase shelf temperature to 20° C.
- When shelf reaches 20° C, terminate cycle.

Appendix B: Collagen Film Protocol

Collagen-GAG Suspension

Materials

1. 625 mls of 0.05M Acetic Acid
    a. 1000 mls of dH_2O + 2.9 mls AA – glacial
2. 3 g SEMED-S (Kensey nash)
3. 137.5 mg Chondroitin (Sigma)

Procedure

1. Chill blender to 4C by hooking water cooler through blender.
2. Place 500 mls of AA and 3 g of SEMED-S into blender. Make sure there is a tight seal. Run blender 18000 rpm for 90 minutes
3. Stop blender and set up dripping mechanism. To drip 40 ml/5 minutes = 8 ml/minute.
4. Place 137.5 mg of Chondroitin and 125 ml of AA into beaker.
5. Remove 100 ml of the Chondroitin and AA solution and place in another beaker. This is what you will drip into the blender.
6. Once dripping mechanism is set up, turn on blender for another 90 minutes.
7. Pour collagen-GAG suspension into two separate containers making sure they have equal amounts (balanced!) Suspension should be homogenously mixed.
8. Centrifuge both containers at 3000 RPM for 15 minutes to remove air bubbles.

Collagen-GAG Membranes

Materials

1. PDMS membrane
2. 70% Etoh
3. Sterile water
4. Pipette box that PDMS membrane fits securely in! (area = 148.5 cm^2)
5. Collagen-GAG suspension

Procedure:

1. Clean PDMS membrane and pipette box with 70% Etoh. Place PDMS membrane in box. Rinse with sterile water and air dry in laminar flow hood. (isn't fully sterile – however helps to keep clean!)
2. Make sure PDMS membrane is secure in pipette box.
3. Pour 40.35 ml of Collagen-GAG suspension making sure nothing leaks under the PDMS. Remove all air bubbles.
4. Allow to air dry for 48 hrs in laminar flow hood.
5. Remove and place in tin foil. Store in desiccator.

Appendix C: Results of Pairwise Comparison from Primary Objectives

Table 27. PCC of Primary Objectives

Objective	Biofunctionality	Surgical Integration	Recovery	Versatility	Cost	Total	Adjusted
Biofunctionality	-	3	3	3	3	12	0.300
Surgical Integration	1	-	1	3	3	8	0.200
Recovery	1	3	-	3	3	10	0.250
Versatility	1	1	1	-	3	6	0.150
Cost	1	1	1	1	-	4	0.100
						40	1.000

Appendix D: Compilation of Pairwise Comparisons from Secondary Objectives

Table 28. PCC of Secondary Objectives for Biofunctionality

Biofunctionality						
Objective	Mechanical Properties	Malleable	Biointegration	Bioabsorbtion	Total	Adjusted
Mechanical Properties	-	2	2	2	6	0.250
Malleable	2	-	2	2	6	0.250
Biointegration	2	2	-	2	6	0.250
Bioabsorbtion	2	2	2	-	6	0.250
					24	1.000

Table 29. PCC of Secondary Objectives for Surgical integration

Surgical Integration							
Objective	Easily Manipulated	Anchored to Ligament	Anchored to Bone	Difficulty of Operation	Familiarity of Surgeons	Total	Adjusted
Easily Manipulated	-	2	2	3	3	10	0.250
Anchored to Ligament	2	-	2	3	3	10	0.250
Anchored to Bone	2	2	-	3	3	10	0.250
Difficulty of Operation	1	1	1	-	3	6	0.150
Familiarity of Surgeons	1	1	1	1	-	4	0.100
						40	1.000

Table 30. PCC of Secondary Objectives for Recovery

Recovery							
Objective	Promotes Healing	Native Tissue Maintained	Retraction less invasive	Scar Aesthetics	Enhances healing	Total	Adjusted
Promotes Healing	-	1	3	3	3	10	0.250
Native Tissue Maintained	3	-	3	3	3	12	0.300
Retraction less invasive	1	1	-	3	3	8	0.200
Scar Aesthetics	1	1	1	-	1	4	0.100
Enhances Healing	1	1	1	3	-	6	0.150
						40	1.000

Table 31. PCC of Secondary Objectives for Versatility

Versatility						
Objective	Versatility of Elutable Molecules	Versatility of Anchoring	Versatility of Injury Location	Versatility of Injured Ligament	Total	Adjusted
Versatility of Elutable Molecules	-	1	1	3	5	0.208
Versatility of Anchoring	3	-	1	3	7	0.292
Versatility of Injury Location	3	3	-	3	9	0.375
Versatility of Injured Ligament	1	1	1	-	3	0.125
					24	1.000

Appendix E: Compilation of Pairwise Comparisons from Tertiary Objectives

Table 32. PCC of Tertiary Objectives for Mechanical Properties

Biofunctionality					
Objective	Tensile Strength	Shear Strength	Cyclic Loading	Total	Adjusted
Tensile Strength	-	2	2	4	0.333
Shear Strength	2	-	2	4	0.333
Cyclic Loading	2	2	-	4	0.333
				12	1.000

Appendix F: Collagen Degradation Assay Protocol

Protocol adapted from Cornwell, 2007.

Enzymatic Degradation of Crosslinked Collagen Threads

Collagen thread degradation in collagenase was assayed for total protein content by ninhydrin reactivity. Two-inch segments of each type of crosslinked threads including uncrosslinked control threads were cut into 8 pieces and placed in a microcentrifuge tube. The samples were incubated at 37°C in 200 μL of 0.1M Tris-base, 0.25M CaCl2 solution (pH 7.4) containing 125 U/mL bacterial collagenase (Clostridium histolyticium, Calbiochem, Inc.) for either 4 or 24 hours. After incubation, the samples were centrifuged at 15,000 RCF for 10 minutes and the supernatant was reacted with 2% ninhydrin reagent (Sigma, St. Louis, MO) in boiling water for 10 minutes. The optical density was then measured at 570 nm in a spectrophotometer (SpectraMax, Molecular Devices, Sunnyvale, CA), and the relative optical density was calculated by subtracting the value of the background (collagenase only control) from the acquired optical density. The enzymatic degradation of each thread type was assayed in triplicate.

Appendix G: Statistical Analysis

μ_o: UNX Composite = UNX Film

μ_A: UNX Composite ≠ UNX Film

Table 33. t-Test UTS UNX Composite v. UNX Film

t-Test: Two-Sample Assuming Unequal Variances

UTS

α= 0.05	*UNX Composite*	*UNX Film*
Mean	0.940173125	0.878978
Variance	0.04896892	0.057416
Observations	8	6
Hypothesized Mean Difference	0	
df	10	
t Stat	0.488536014	
P(T<=t) one-tail	0.317852978	
t Critical one-tail	1.812461123	
P(T<=t) two-tail	0.635705955	
t Critical two-tail	2.228138852	

μ_o: UNX Composite = UNX Film

μ_A: UNX Composite ≠ UNX Film

Table 34. t-Test Strain UNX Composite v. UNX Film

t-Test: Two-Sample Assuming Unequal Variances

STRAIN

α= 0.05	*UNX Composite*	*UNX Film*
Mean	0.337826375	0.399657
Variance	0.008109575	0.007182
Observations	8	6
Hypothesized Mean Difference	0	
df	11	
t Stat	-1.31503305	
P(T<=t) one-tail	0.107626473	
t Critical one-tail	1.795884819	
P(T<=t) two-tail	0.215252946	
t Critical two-tail	2.20098516	

μ_o: XL Film = UNX Film

μ_A: XL Film ≠ UNX Film

Table 35. t-Test Strain XL Film v. UNX Film

t-Test: Two-Sample Assuming Unequal Variances

UTS

α= 0.05	*XL Film*	*UNX Film*
Mean	2.493980455	0.878978
Variance	2.042805412	0.057416
Observations	11	6
Hypothesized Mean Difference	0	
df	11	
t Stat	3.65464673	
P(T<=t) one-tail	0.001894925	
t Critical one-tail	1.795884819	
P(T<=t) two-tail	0.00378985	
t Critical two-tail	2.20098516	

μ_o: XL Film = UNX Film

μ_A: XL Film ≠ UNX Film

Table 36. t-Test UTS XL Film v. UNX Film

t-Test: Two-Sample Assuming Unequal Variances

STRAIN

α= 0.05	*XL Film*	*UNX Film*
Mean	0.100449061	0.399657
Variance	0.002596339	0.007182
Observations	11	6
Hypothesized Mean Difference	0	
df	7	
t Stat	-7.90398059	
P(T<=t) one-tail	4.92235E-05	
t Critical one-tail	1.894578605	
P(T<=t) two-tail	9.8447E-05	
t Critical two-tail	2.364624252	

Appendix H: Cost of Materials

Table 37. Material Cost

Material	Unit Cost	Amount Needed	Total
Glacial Acetic Acid	$43/L	2.9 mL	$0.12
Insoluble Type 1 Collagen	$53.8/g	3 g	$161.40
Chondroitin sulfate	$14.82/g	137.5 mg	$2.04
70% Ethanol (Sterilization)	$14.40/L	Negligible	$0.00
N-[Tris(hydroxymethyl)methyl]-2-aminoethanesulfonic acid	$2.33/g	12 g	$27.96
		Total Material Cost	$191.52
		Price/Composite	**$1.00**

* Materials listed is used to make 762.5 mL of collagen suspension
  64 mL is used to make threads
  698 mL is used for the creation of the film
  This can be used to create approximately 191 composites

Appendix I: Collagen Extraction Protocol

Pins Lab Biochemistry Protocol revised 11/1/19

Collagen Extraction Protocol

Materials:

- 13 rat tails
- ddH_2O
- 2 hemostats
- Scissors
- 4 pieces of gauze (unfolded)
- Funnel
- GSA rotor bottles
- ultracentrifuge
- 12-15kDa dialysis bags

- *SOLUTION 1:* 3% ACETIC ACID
  - 48mL glacial acetic acid
  - 1552mL ddH_2O

- *SOLUTION 2:* 30%NaCl
  - 96g NaCl
  - 320mL H_2O

- *SOLUTION 3:* 5%NaCl – 0.6%ACETIC ACID
  - 50g NaCl
  - 6.0mL glacial acetic acid
  - 1L H_2O

- *SOLUTION 4:* 0.6% ACETIC ACID
  - 2.4mL glacial acetic acid
  - 397.6mL ddH_2O

- *SOLUTION 5:* 1mN HCl
  - 5mL 1N HCl
  - 5L ddH_2O

Procedure:

- Thaw 13 rat tails in ddH_2O.
- Using two hemostats, dissect tendons from each tail by clamping each hemostat onto the tail, breaking the tail, and gently pulling the tendons out. Continue working your way down the tail by breaking through the vertebra every inch or inch and a half. Work from the tip of the tail to the base of the tail. Place tendon strands in 1% NaCl solution (10g/1.0 L diH_2O). Make sure each tendon is clean (any blood or tissue should be removed).
- After all strands have been extracted, rinse the tendons twice with 1% NaCl solution and once with ddH_2O.

- Put rinsed tendons into 1600mL of SOLUTION 1 [3% acetic acid (48mL acetic acid in 1552mL ddH_2O)] and stir **overnight** at 4°C. (**Day 1 ends here**)
- Using a funnel and four layers of cheese cloth or gauze, passively filter the solution into a two liter beaker to remove insoluble collagen fibers. (**optional step**)
- Pour filtrate into GSA rotor bottles and spin for 2 hours, 4°C, in RC5 centrifuge at 8590 RPM (12,800 G). Make sure bottles are balanced.
- Carefully decant supernatant into two liter beaker, discarding the pellet.
- At 4°C, using a separation filter or a buret, slowly drip 320mL (approximately 350mL/hr) of SOLUTION 2 [30% NaCl solution (96g/320mL)] into supernatant and allow to sit overnight. DO NOT STIR! (**Day 2 ends here**)
- Pour entire solution and precipitate into GSA rotor bottles and spin at 4960 RPM (4420 G), 4°C, for 30 minutes.
- Carefully decant supernatant and discard. Save any gelatinous material and any pellet. Rinse each rotor bottle clean with SOLUTION 3 [5% NaCl-0.6% acetic acid (50g NaCl and 6.0mL acetic/1L)] solution to ensure any remaining collagen which has adhered to the inside of the rotor bottle has been saved.
- Spin collagen mixture for a second time at 4960 RPM (4420 G), 4°C, for ten minutes. Again carefully discard supernatant and saving gelatinous collagen and any pellet. Rinse each rotor bottle with SOLUTION 3 [5%-0.6% solution] as necessary. (This step may not be necessary if collagen is not adhered to the bottles.)
- In a two liter beaker, resuspend pellets in 400mL of SOLUTION 4 [0.6% acetic acid (2.4mL acetic acid in 397.6mL ddH_2O)] and spin at **4°C overnight**, or as long as necessary to dissolve pellets. (**Day 3 ends here**)
- Place collagen solution into dialysis bags, MW cutoff less than 50kDa, (slightly larger than one foot long) and clip bags at both ends. In four or six liter Erlenmeyer flasks, dialyze collagen in SOLUTION 5 [1mN HCl (5mL 1N HCl/ 5L ddH_2O)] **five times** with a **minimum of four hours** between changing the dialysant. (**Note**: Continue until acetic acid smell is undetectable). (**Day 4-5**)
- Pour collagen solution into freeze dryer pan. Place in freeze dryer and freeze shelf, once collagen is frozen, start recipe #2 on freeze dryer. (This cycle may need to be run twice depending on the volume of collagen.) (See freeze dryer file for specs on recipe #2, briefly, freeze at -70°C under vacuum for 24 hours.) Store dry collagen in plastic bags at 4°C. (**Day 5-6**)
- To make collagen solutions, Lyophilized collagen can be re-suspended at a desired concentration in 10 mN HCl (10 ml/1000 mL; pH 2.0) at 4°C.
- To sterilize dilute solutions of collagen, add chloroform (at 300 ul/1000 ml collagen) and stir at 4°C for 48 hr in a sterilized bottle with the lid loosely capped to allow the chloroform to evaporate.

G. Pins, WPI, 11/1/19
A. Throm, Worcester Polytechnic Institute, 1/04 - Updated from K. Ham, Shriners Research Center, 1/97
Original Reference:
Elsdale, T., Bard, J., Collagen Substrata for Studies on Cell Behavior. The Journal of Cell Biology. V 54, (626-637).

Appendix J: Polydimethylsiloxane Protocol

PDMS Protocol

Materials:
SYLGARD brand 184 Silicone Elastomer Kit (Dow Corning, Midland, MI)
-Silicone Elastomer & Silicone Elastomer Curing Agent

Methods:

1. Prepare Silicone Elastomer according to manufacturer's instructions: Mix 10 parts of base (~30g) with 1 part of curing agent (~3g)
2. Vacuum off bubbles
3. Pour into molds
4. Let dry: (oven at 60C for ~2-3 hours; 37C ~overnight)

Yields 11.5cm x 8cm x 0.5cm piece of PDMS

Appendix K: Minutes from interviews with Dr. David Magit

The following information is a compilation of the annotated minutes from the design team's discussions with Dr. David Magit

Q: If an autograft or allograft is used in a reconstruction, is the native remaining ligament discarded or is the graft integrated into native tissue?

Magit: The native tissue is not removed. It is attached the graft, but it does not function as the normal ligament.

Q: Is there distinct differences with bone to ligament interface when compared to a post operation patient?

Magit: In the case of a reconstruction this interface is replaced with an anchor to bone interface. There is a problem with failing at this interface.

Q: Are there any modifications to the approach that you would like to see in a final design?

Magit: The change in anchoring system compared to current techniques. A smaller anchoring system will allow for less damage to surrounding tissue and less manipulation of the ulnar nerve. Converging bone tunnels can also be risky, if done incorrectly the integrity of the bones can be compromised.

Q: What timeline for intervention do you expect to give patients with partial tears?

Magit: This approach needs to be done immediately. After acute inflammatory stops, the application is limited as the injury goes to a chronic state.

Q: What therapeutics would be beneficial for the device to elute?

Magit: Platelet-rich plasma. It is a cocktail of growth factors that will be beneficial to healing. The individual growth factors such as FGF-2 or TGF-β can also be used if platelet-rich plasma cannot be used.

Q: Would the elution of NSAIDs be beneficial?

Magit: Including this as a potential is fine. But it would not be at the top of the desired elutables list. But including antibiotics could prove beneficial.

Q: Are there any properties that are essential to our design?

Magit: It would be ideal to decrease damage to surrounding tissue. It is important that the patient only undergoes a single surgery. These are not deal breakers, but they should be strived for. You must ensure that there is no disease transmission from the implant.

Q: What are your concerns with the internal brace approach?

Magit: It's not a biological solution. There is a large foreign body put into the elbow and it elicits a large immune response. It also does not restore the original anatomy of the ligament. There have not been any level 1 or 2 studies to look at outcomes.

Q: What is the traditional post operation guidelines for the reconstruction?

Magit: Generally speaking, initially the range of motion is limited from 30 to 90 degrees in a hinged brace. At 4 weeks it is extended to 15 to 115 degrees. At 6 weeks they are out of the brace. They go about 4 months without overhead motion. Then there is a period that focus on mechanics to rebuild strength. There is a goal of 12 months back to play

Q Do patients seek out the Jobe technique as a preemptive approach to a UCL injury?

Magit: There are people who try to get the surgery done before the injury occurs. These people believe that the surgery will allow them to throw harder and play better. This is false.