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ORTHO Regenerative Technologies Inc.

(CN.ORTH - CSE)

We Have the Technology to Rebuild

Based on our DCF model and a 15% discount rate, Ortho is valued at approximately $1.80 per share. Our model applies a 12% probability of ultimate approval and commercialization for the RESTORE platform in the rotator cuff and meniscus programs. The model includes contributions from US and global sources.

Current Price (11/20/2020)	$0.78
Valuation ($CAD)	**$1.80**

INITIATION

Ortho is developing its RESTORE platform that enables biologics and other regenerative medicines to be delivered to surgery sites in order to enhance healing and guide the regeneration of new tissue. The platform relies on a proprietary chitosan-based biopolymer matrix which is combined with platelet rich plasma (PRP) to improve the success rate of rotator cuff tear (RCT) and meniscus tear (MT) repair surgery. The company's sole product is Ortho-R.

Ortho's RCT program has completed its preclinical stage and is expected to enter clinical trials by early 2021 with IND efforts underway. The MT program is anticipated to enter the clinic in 2022. There is a substantial unmet need in both indications due to the high surgical failure rates that may be successfully improved with Ortho's products.

Approval for Ortho-R in RCT is expected in 2025 followed by MT in 2026. Partner-led commercialization is targeted for RCT in the US in 2025, followed by Canada & the EU the following year. Commercialization of MT is modeled one year behind the RCT program.

RESTORE may also address cartilage repair and improve the outcome of other musculoskeletal soft tissue repair conditions.

SUMMARY DATA

52-Week High	**0.99**
52-Week Low	**0.18**
One-Year Return (%)	**310**
Beta	**1.49**
Average Daily Volume (sh)	**61,492**
Shares Outstanding (mil)	**33.1**
Market Capitalization ($mil)	**25.8**
Short Interest Ratio (days)	**0.58**
Institutional Ownership (%)	**0.0**
Insider Ownership (%)	**31.7**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2020 Estimate	**N/A**
P/E using 2021 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of CAD)

	Q1 (Apr)	Q2 (Jul)	Q3 (Oct)	Q4 (Jan)	Year (Jan)
2020	$0.0 A	$0.0 A	$0.0 A	$0.0 A	$0.0 A
2021	$0.0 A	$0.0 A	$0.0 E	$0.0 E	$0.0 E
2022					$0.0 E
2023					$0.0 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
2020	-$0.02 A	-$0.03 A	-$0.03 A	-$0.02 A	-$0.10 A
2021	-$0.04 A	-$0.03 A	-$0.03 E	-$0.02 E	-$0.12 E
2022					-$0.13 E
2023					-$0.11 E

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INITIATION

We are initiating coverage of Ortho Regenerative Technologies Inc. (CNSX: ORTH.CN, OTCQB: ORTFI) with a current valuation of CAD$1.80[1] per share. This present value is based on our estimates for development of the company's sole product, Ortho R, for rotator cuff tear (RCT) repair and meniscus tear (MT) repair. The RCT project has substantially completed the preclinical work necessary to advance into human trials. The MT preclinical proof of concept has been successfully performed with IND-enabling preclinical work to take place in 2021. Ortho RTI has other programs that are in an earlier stage of development, which we anticipate will be advanced when specific funding is raised. We have allocated no value to these programs which represent further upside.

The company's platform is designated RESTORE and includes lead indications in RCT and MT, which are expected to be the subjects of Biologic License Applications (BLAs) in calendar year 2024 and 2025, respectively. Another program, at the early *in vivo* stage, targets osteoarthritis pain and function, while three other indications at the feasibility stage address articular cartilage, ligaments/tendons and nucleus pulposus.

Ortho RTI's technology combines its muco-adhesive, proprietary chitosan-based polymer matrix with platelet-rich plasma (PRP) or other biologics to rebuild damaged tissue and improve surgery outcomes in multiple indications. The primary material in the product, chitosan, is a polysaccharide originally derived from the chitin found in the exoskeleton of shellfish. The chitin is then purified and deacetylated to produce medical-grade chitosan. Chitosan is used in many applications including food manufacturing and production, as a pharmaceutical excipient and in surgeries. Chitosan helps blood to clot and is used as a hemostat to stop hemorrhage bleeding in wounded patients.

Ortho-R is designated as a device, drug and biologic combination product. Its approval process will be overseen by the FDA's Center for Biologics Evaluation and Research (CBER) and evaluated by the Office for Combination Products (OCP). Ortho is conducting investigational new drug (IND) enabling work and expects to launch a 75-patient Phase I/II study in the US. Following a successful early stage trial, two Phase III studies will be required and are planned to be run in parallel in both the US as well as EU and Canada, prior to the submission of a BLA in the United States, a Marketing Authorization Application (MAA) in Europe and a new drug submission in Canada which is anticipated in 2024.

Joint surgeries are frequent, and we estimate that there are over one million rotator cuff surgeries and over 500,000 meniscus tear surgeries in Ortho's target markets of US, EU and Canada, combined. The Ortho-R product is inexpensive to manufacture and is mixed with autologous platelet rich plasma (PRP) that is sourced from the patient minutes prior to surgery. Our literature review of both Ortho-sponsored and independent research finds evidence of a benefit from using PRP as a biologic, to improve structural integrity, decrease re-tear rates and accelerate healing. One of the shortcomings of current approaches incorporating PRP in rotator cuff repair is maintaining contact between the PRP and the surgically repaired tissue. Ortho-R seeks to address this through the development of a paste-like product that, once cured or clotted, is able to keep the PRP firmly in place allowing growth factors and cytokines to stimulate wound healing and tissue repair over an extended period of time of up to six weeks compared to less than one day for current techniques.

At the end of its second fiscal quarter ending July 31, 2020, Ortho held approximately $23,000 in cash that was augmented by another $2.6 million following the closing of two private placements finalized in early September. The company currently holds convertible debt with a face value of $3.2 million, which will mature in April 2022.

Ortho's approach to improving the healing and success rates of various types of joint surgery addresses many of the shortcomings faced by these procedures. The RESTORE technology and Ortho-R product has demonstrated its utility in large and small animal models supporting further advancement into human clinical trials. While the company is at an early stage of development, data generated to date is highly supportive of success of the biologic-chitosan combination to enhance and accelerate healing in joint surgery. With a large pool of surgeries that can benefit from the product, the company plans to pursue clinical trials and regulatory submission to obtain approval and ultimately sign licensing agreements or partnerships to commercialize products attached to the RESTORE platform.

[1] Share prices and financial statement items are denominated in Canadian Dollars.

Key reasons to own Ortho Regenerative Technologies shares:

- **Safe biopolymer combination product with favorable properties**
  - **Rapid coagulation**
  - **Avoids shrinkage**
  - **Adheres to soft tissues**
  - **Increases biologics residency time to augment and guide the regeneration of new tissue**
- **Demonstrated decreased tendon gap and improved bone structure in large animal RCT model**
- **No treatment-specific safety issues**
- **Sufficient capital raised to start phase I/II study in rotator cuff indication**
- **Unmet need in large markets with poor surgery success rates**
  - **About half of RCT surgeries fail**
  - **20% - 40% MT surgeries fail**
- **Chitin source material is abundant and inexpensive to procure**
- **Chitosan end product (Ortho-R) is inexpensive to manufacture**
- **Biologic product uses autologous PRP which can be sourced quickly and easily**
- **Lyophilized chitosan provides long shelf life**
- **Strong intellectual property protection in three patent families**
- **Clinical trials will include pharmacoeconomic benefit analysis**
- **Experienced management team and clinical advisory board**
- **Reputable CRO (MCRA) with orthopedics and biologics regulatory and clinical research expertise**

In the following sections we review the orthopedic space with a focus on the structure and common injuries of the tendon, meniscus and cartilage tissue. We further examine the prevalence of related joint disorders and discuss standard of care. The topic of our report then transitions to Ortho RTI's RESTORE technology and provides details regarding the sourcing of its components: chitosan and platelet rich plasma. We follow with a detailed review of the company's candidates, summarize preclinical research and review the regulatory path forward. An overview of the firm's intellectual property, risks, peers and competitors and leadership team is also provided. Finally, we discuss the assumptions in our appraisal and generate our valuation. Ortho's RESTORE platform is at an early stage of development generating proof of concept in preclinical studies supporting advancement into clinical trials. Ortho-R shows early promise to improve surgery success rates, improve availability of growth factors and other elements into damaged tissue and improve healing times at what we expect to be a reasonable cost. We initiate on Ortho Regenerative Technologies at $1.80 per share.

Orthopedics

Introduction

The word orthopedics is derived from the Greek words ὀρθός or "ortho" meaning straight and πεδ-ώ or "ped-o" correctly interpreted as to prevent a distortion. The specialty, orthopedics, is a categorization of medicine that addresses conditions of the musculoskeletal system. The earliest orthopedists corrected skeletal deformities with braces and other rehabilitative devices. Since then, the specialty has expanded to address a wide array of diseases and injuries including treatment of bones, joints, ligaments, tendons and muscles. It also includes cartilage and meniscus. Some of the most common orthopedic procedures today include joint replacements, spinal fusion, bone repair, treatment of Achilles tendon injuries, anterior cruciate ligament (ACL) surgery and arthroscopy. Orthopedics employs both the contributions of medical tools, devices, pharmaceuticals and biologics in the treatment of disease and injury. As the specialty continues to advance, new methods are being used that combine regenerative medicine with evolving surgical techniques, which hold promise to improve orthopedic surgical outcomes.

Exhibit I – Crooked Tree Braced to a Stake: Symbol of Orthopedics[2]



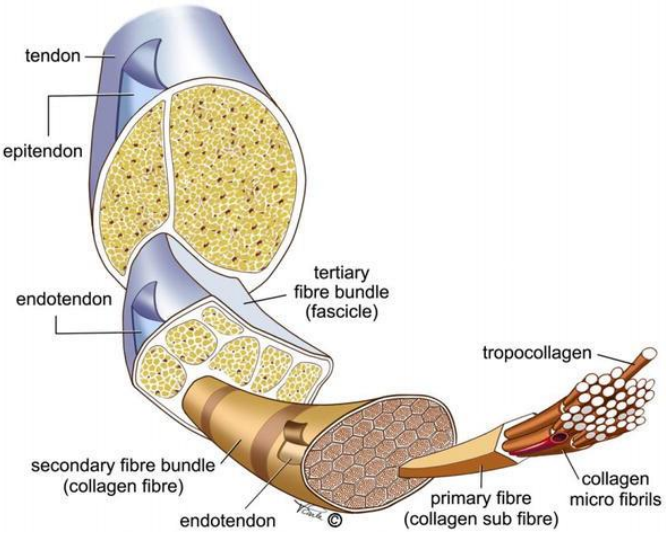
Tendons and Rotator Cuff Tears

A common orthopedic injury suffered by active individuals is tendon damage. This injury results from overuse, repetitive motion and is exacerbated by aging. Rotator cuff tears are a subset of tendon damage and have a high prevalence[3,4,5] in the general population at a rate correlated with age. Frequently, it is the tendon of the supraspinatus that tears in rotator cuff injury and while surgery can frequently correct the problem, failure rates in more complex tears are well above 50%.

[2] Source: shuterstock.com
[3] Minagawa, H. *et al.* Prevalence of symptomatic and asymptomatic rotator cuff tears in the general population: From mass-screening in one village. J Orthop. 2013 Mar; 10(1): 8–12.
[4] Tempelhof, S. *et al.* Age-related prevalence of rotator cuff tears in asymptomatic shoulders. Journal of Shoulder and Elbow Surgery Volume 8, Issue 4, July–August 1999, Pages 296-299.
[5] Sambandam, S.N. *et al*. Rotator cuff tears: An evidence based approach. World J Orthop. 2015 Dec 18; 6(11): 902–918.

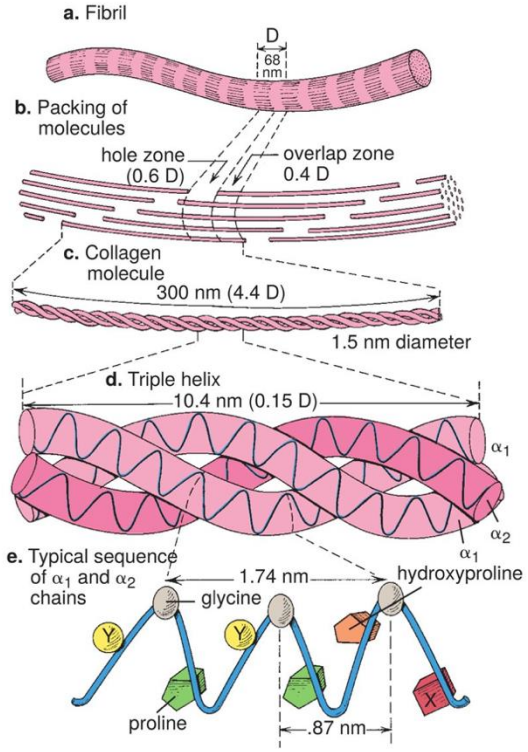
Tendons are a fibrous connective tissue with high tensile strength that are more elastic than ligaments. Tendons connect bone to muscle tissue whereas ligaments connect bones. Tendons derive their strength by bundling elongated proteins, much like rope or cable.

Exhibit II – Structure of Tendon[6]



The tendon is composed of tertiary fiber bundles that are made up of even finer fiber bundles. The fiber bundles comprise collagen fibers, which, themselves, are bundled collagen fibrils. While the fibrils are thin, they can span millimeters in length.[7] Interspersed between collagen units are non-collagenous matrix components including proteoglycans, glycoproteins and glycoconjugates. Between the collagen fibers are also tenocytes, or tendon cells, and associated progenitor (stem) cells.

Exhibit III – Collagen fiber structure[8]



[6] De Cassia Marqueti, R. *et al.* Exercise and Tendon Remodeling Mechanism. Interchopen, May 2019
[7] An estimate of the mean length of collagen fibrils in rat tail-tendon as a function of age. *Craig AS, Birtles MJ, Conway JF, Parry DA Connect Tissue Res. 1989; 19(1):51-62.*
[8] Computational Inelasticity of Fibrous Biological Tissues with a Focus on Viscoelasticity, Damage and Rupture - Scientific Figure on ResearchGate.

Tendon extracellular matrix

Of the tissues in the body, tendons have one of the highest ratios of extracellular matrix (ECM) to cells. Collagen, a primary structural element of ECM, makes up of 60-85% of the dry weight of a tendon.[9] The ECM is scaffolding where the cells reside to form higher order structures. The collagen in the ECM is 95% type I, with small amounts of other types.[10] Tendon tissue, like all connective tissue, has cells associated with its ECM performing various roles related to mechanical and biological maintenance. Tendon ECM homeostasis is dynamic and remodeling can occur in response to stimuli. Tendons can thicken and strengthen in response to use, although overuse and underuse, can lead to degeneration. Cell-matrix interactions are reciprocal; tendon cells manage the tendon matrix in response to mechanical and chemical stimuli and the stimuli transfer through the matrix. While understanding of the underlying mechanisms remains incomplete, the subject is central to the cell-matrix response to injury.

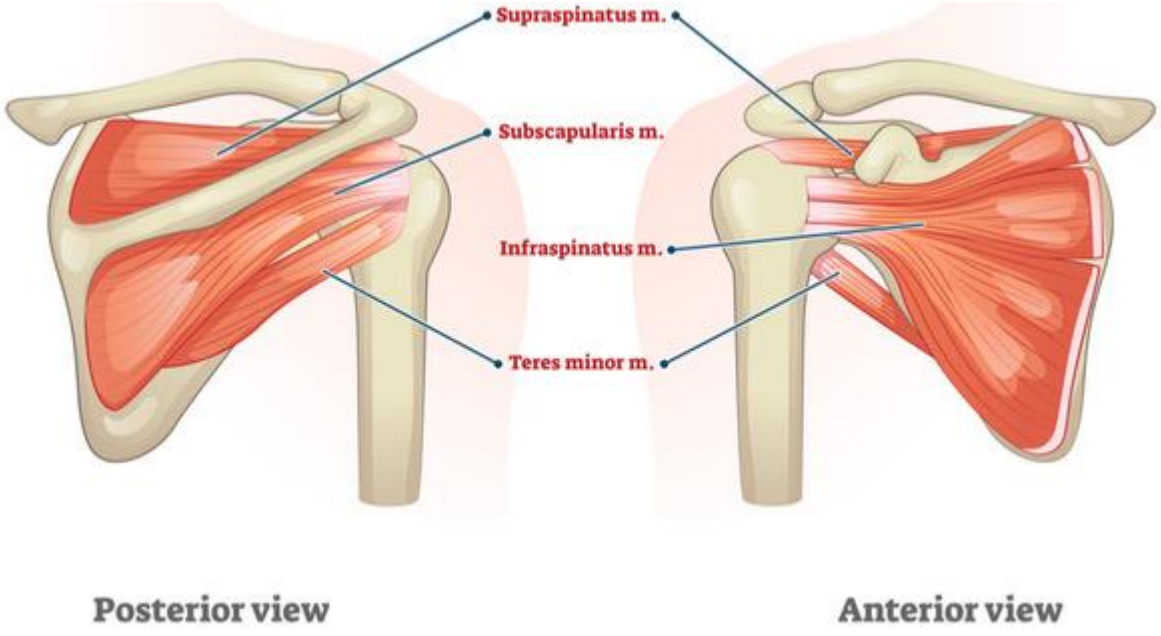
Tendon repair

The regeneration of tissue has long been a goal of medical science. Naturally occurring tissue repair and regeneration is an orchestration of multiple biological activities and is not completely understood. Tissue healing is thought to follow three independent and overlapping stages: inflammatory response, fibroblastic/proliferative and remodeling.[11] Fibrosis often precludes tissue regeneration. The evolution of scarring appears to be a tradeoff between guarding against infection at the expense of regeneration of tissue. Unfortunately, tendon tissue favors fibrotic healing through excessive and disorganized deposition of ECM that can reduce strength and leave it prone to re-injury. Regenerative approaches currently include cellular therapies, injections of platelet-rich hemoderivatives (PRHd) such as platelet-rich plasma (PRP), gene therapy and use of other biomaterials. The approaches attempt to promote regeneration while inhibiting peritendinous adhesion formation or bands of scar-like tissue that form between surfaces inside the body causing them to adhere, a common post-surgery complication.

Rotator cuff

The shoulder is a ball and socket joint stabilized by the rotator cuff. The rotator cuff comprises four muscles that control rotation of the humerus. Of the four muscles, the supraspinatus is the most commonly injured or torn. The supraspinatus inserts on the greater tubercle of the humerus and functions to abduct over a short range before the deltoids take over. Injuries of the rotator cuff range from tendinopathy to partial and full tears. Complete tears are especially serious, as the tear gap expands with time, minimizing the chances of repair. If completely torn, over time, the supraspinatus recedes to the point where even surgical intervention will struggle to achieve favorable outcomes. Tendon tissue lacks vasculature and instead relies on diffusion for nutrients, explaining the tendon tissue's limited ability for self-repair and also why tendon injury can progressively worsen as stress outpaces healing.

Exhibit IV – Rotator Cuff Muscle[12]



[9] The multicomposite structure of tendon. *Kastelic J, Galeski A, Baer E Connect Tissue Res. 1978; 6(1):11-23.*

[10] Screen, H. R., Berk, D. E., Kadler, K. E., Ramirez, F., & Young, M. F. (2015). Tendon functional extracellular matrix. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*, *33*(6), 793–799. https://doi.org/10.1002/jor.22818

[11] Costa-Almeida, R., Calejo, I., Gomes, ME. 2019. Mesenchymal Stem Cells Empowering Tendon Regenerative Therapies. Int. J. Mol. Sci.

[12] Source: shuterstock.com

Causes, Incidence and Prevalence

Rotator cuff injury is one of the most common tendon injuries seen and treated in adults and, in contrast to an acute injury such as one sustained in sports, age is the primary driving factor. Rotator cuff tear is typically a degenerative and progressive process. Acute, complete tears can occur as well and usually in younger patients, but it is the micro-trauma that causes tendon degeneration with insufficient healing that leads to degenerative tears later in life. As the tendon degenerates, less and less force is required to provoke a tear that becomes more and more likely. Potential causes include everyday accidents such as falling and lifting, sports such as pitching and swimming and occupations such as painting. Abnormalities in the rotator cuff ranged from 9.7% in those aged 20 and younger compared to 62% in patients 80 years old and older.[13] Unilateral pain increases the risk of a rotator cuff tear in the opposite shoulder. Beyond age 66, the likelihood of bilateral tears rises to 50%. Smoking is a known risk factor as is family history. Poor posture has also been shown to be a predictor of rotator cuff ailment. 65.8% of patients with kyphotic-lordotic postures, 54.3% with flat-back postures and 48.9% with sway-back postures had tears while only 2.9% of patients with ideal alignment had tears. Additional risk factors include trauma, hypercholesterolemia and occupations or activities with significant overhead activity.

Partial tears are a risk for further tears and are highly correlated with age, tear size and location. The larger the tear, the more susceptible it is to even greater separation and as tears enlarge, symptoms become worse. Symptoms include dull or deep ache in the shoulder, disturbed sleep, difficulty combing hair or reaching behind the back and arm weakness.[14] Anterior tears are more likely to progress.

The estimation of the prevalence of rotator cuff injury varies. A prospective study on 411 asymptomatic patients' shoulders found a 23% prevalence of tears with those in their 70s and 80s showing tears in 31% and 51% of evaluated patients, respectively.[15] An Austrian study[16] examining 212 asymptomatic individuals age 65 and older demonstrated 6% prevalence of full-thickness tears and a Norwegian study of 420 asymptomatic individuals age 50-79 found only 7.6% full thickness tears.[17] The estimates differ based on the severity of the tear. According to the US Census, there were approximately 73.4 million people in the US age 60 and older in 2019. Applying an estimated 30% prevalence, approximately at least 22 million people could suffer from tears, and 4.4 million with full thickness tears in the US, not counting younger populations. Approximately two million people per year visit their doctor in the US due to a rotator cuff problem.[18] In 2006, there were an estimated 272,148 rotator cuff repairs, an increase of 141% since 1996.[19] A simple linear extrapolation places the 2020 estimate at approximately 550,000. We examine additional sources such as Pearl Diver HealthCare Research that estimates 400,000 RCT surgeries per year and iData Research that finds 460,000 RCT surgeries per year.

Standard of Care

Treatment depends on age of patient, their functional demands of the rotator cuff and the disease's progression (acute vs chronic). Patients under 40 with complete tears are recommended surgery followed by rehabilitation. Arthroscopic or open surgery can be performed and aims to install anchors into the humerus, and suture the torn supraspinatus tendon to the anchor, placing the tendon in physical proximity to its original insertion site. Arthroscopic surgery, also known as 'keyhole surgery,' minimizes surgical damage to the tissue. Small incisions are made and through these openings, special rod-like cameras and tools enable the surgeon a view and work on the injury. The sutures are applied to the tear and if necessary, holes are drilled, and suture anchors are installed in the humerus. The sutures are looped through the anchors and through the tendon. After the procedure, the shoulder is placed in a sling. Patients typically return home on the same day of the surgery. Unfortunately, surgical repairs fail to heal in 20-95% of patients depending on age, tear size, smoking, time of repair, tendon quality, muscle quality, healing response and surgical treatments.[20] The greater the size of the tear, the greater the failure rate. This low rate of success highlights the need for continued research and development of new therapies to address this indication.

[13] Codding, J.L., Keener, J.D. Natural History of Degenerative Rotator Cuff Tears. Curr Rev Musculoskelet Med. 2018 Mar; 11(1): 77–85.
[14] https://www.mayoclinic.org/diseases-conditions/rotator-cuff-injury/symptoms-causes/syc-20350225
[15] Tempelhof S, Rupp S, Seil R. Age-related prevalence of rotator cuff tears in asymptomatic shoulders. J Shoulder Elbow Surg. 1999 Jul-Aug;8(4):296-9.
[16] Fehringer EV, Sun J, VanOeveren LS, Keller BK, Matsen FA. Full-thickness rotator cuff tear prevalence and correlation with function and co-morbidities in patients sixty-five years and older. J Shoulder Elbow Surg. 2008 Nov-Dec;17(6):881-5.
[17] Schibany N, Zehetgruber H, Kainberger F, Wurnig C, Ba-Ssalamah A, Herneth AM, Lang T, Gruber D, Breitenseher MJ. Rotator cuff tears in asymptomatic individuals: a clinical and ultrasonographic screening study. Eur J Radiol. 2004 Sep;51(3):263-8.
[18] https://orthoinfo.aaos.org/en/diseases--conditions/rotator-cuff-tears
[19] Colvin, A. C., Egorova, N., Harrison, A. K., Moskowitz, A., & Flatow, E. L. (2012). National trends in rotator cuff repair. *The Journal of bone and joint surgery. American volume*, *94*(3), 227–233. https://doi.org/10.2106/JBJS.J.00739
[20] This is according to Deprés-tremblay *et al.* 2016, work supported by Canadian Institutes of Helath Research and Ortho RTI.

Meniscus Tears

The meniscus is composed of cartilage shaped in the form of two facing Cs, designated the medial and lateral menisci. The articular cartilage covers the end of the femur and rests on top of the meniscus, forming a smooth and cushioned interface. During intense and sometimes normal athletic activity involving twisting and turning of the knee, the meniscus can tear with the risk of this outcome increasing with age.

Exhibit V – Top View of the Knee and Meniscus[21]

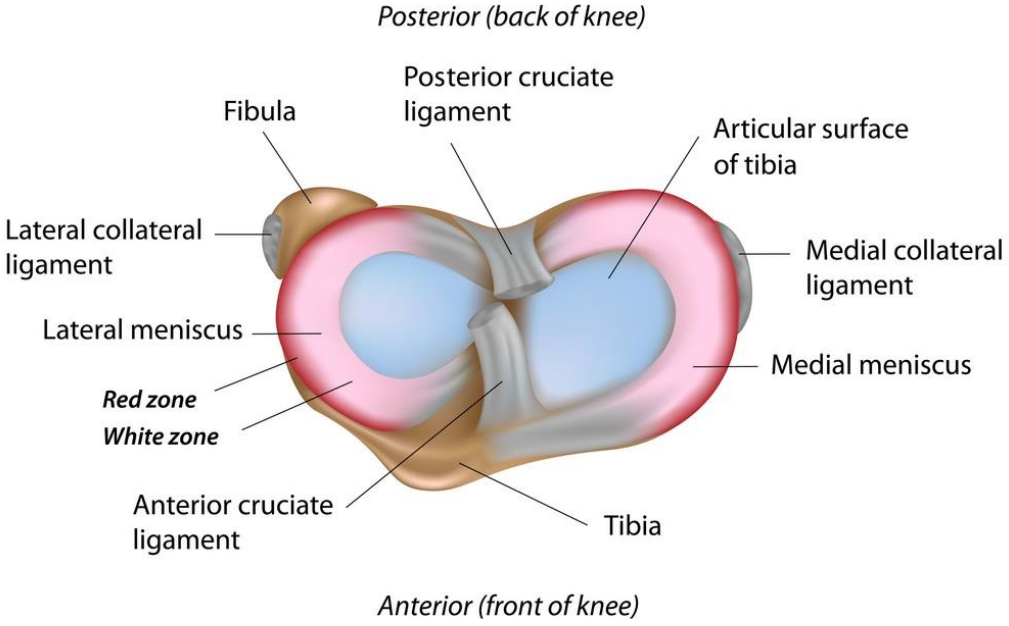
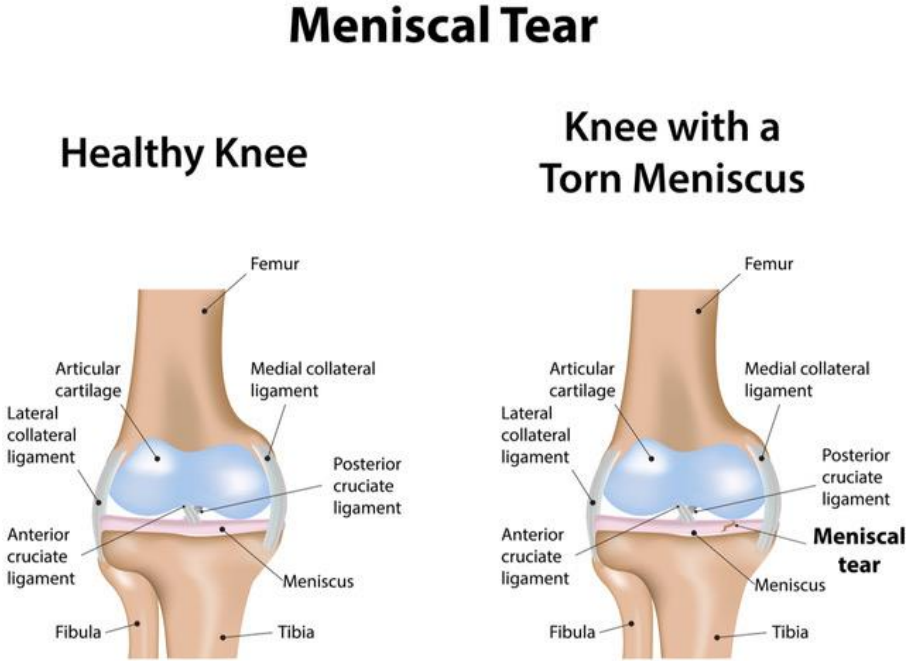


Exhibit VI – Meniscus and Tears[22]



The meniscus lines the top of the tibia where it articulates with the femur. The meniscus itself is fibrocartilaginous, unlike the articular/ hyaline cartilage that lines the femur. Together, the cartilage linings provide a smooth interface so that the femur and tibia do not grind and the knee bends fluidly. It also provides cushion for shock and stabilization for the joint. This joint receives the most extreme stresses in the human body and is susceptible to damage from overuse, twisting and injury. One of the most common orthopedic diagnoses for the meniscus is a tear and surgery for this defect makes up nearly half of the arthroscopic knee procedures performed in the US.[23] Partial meniscectomy is used when the meniscal tear is considered beyond repair. Most tears are not considered repairable. Some of the side effects of meniscectomy are a reduction in knee stability, increased contact stress on existing cartilage and an increase in the risk of osteoarthritis.

[21] Source: shutterstock.com
[22] Source: shutterstock.com
[23] Kim S, Bosque J, Meehan JP, et al. (2011) Increase in out- patient knee arthroscopy in the United States: a comparison of national surveys of ambulatory surgery, 1996 and 2006. J Bone Joint Surg Am 93: 994-1000.

The outer 10-30% of the meniscus is vascularized. The vascular and non-vascular portions are clinically differentiated. Vascularity of the meniscus is considered when evaluating whether a tear can be repaired. If the tear is in a vascularized region, the chances of repair are higher as there is blood flow of nutrients, oxygen and growth factors that help the tissue repair itself. However, if the tear is in an avascular zone, such as the inner meniscus, the ability for the tissue to repair is limited by the lack of blood flow.

Causes, incidence and prevalence
As shown in the exhibit above, the tears can occur in various parts of the meniscus. A torn meniscus is one of the most common knee injuries and can result from activities that may put rotational stress on the knee under load. Torn menisci cause pain, swelling and stiffness and patients may feel an obstruction to the movement of the knee. Other symptoms include popping sensation and pain in the knee under rotational stress. While most often associated with sports, such as tennis, basketball, even everyday activity such as kneeling, squatting or lifting can sometimes result in a meniscus tear. Degeneration in the knee can make the individual more prone to initial or further meniscus damage with age. Diagnosis begins with a physical examination, and can be further confirmed via MRI.

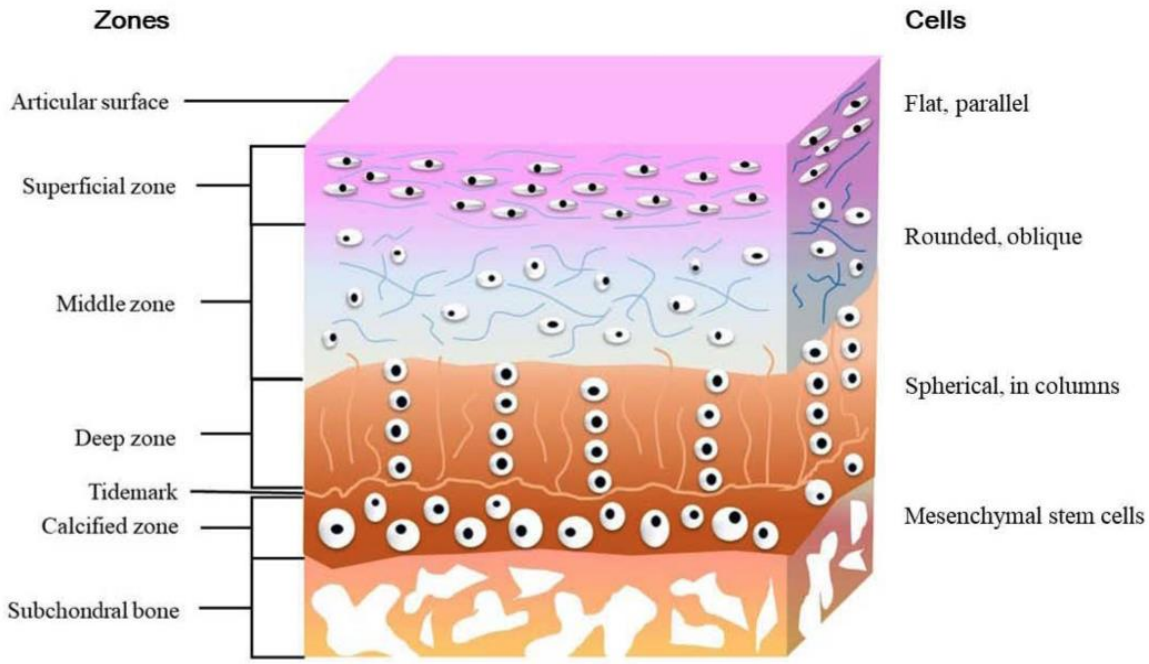
Standard of care
A conservative care regimen includes rest, ice and medication, allowing the meniscus to heal on its own, but as described before, the avascular nature of white meniscal tissue means that the healing will be slow and may be incomplete. Tears associated with arthritis often improve over time through treatment of the arthritis and surgery is not typically indicated.[24] Physical therapy may be able to compensate for the torn meniscus and stabilize the knee through muscular strengthening. When all else fails and symptoms are severe enough, arthroscopic surgery can be implemented to trim the meniscus using a minimally invasive approach.

Cartilage

Cartilage is connective tissue that is found in all parts of the body. There are three different types of cartilage: fibrous, hyaline and elastic. When hyaline cartilage lines the joints, it is known as articular cartilage forming a protective surface between articulating bones, providing a cushion and gliding surface.

The primary cell type in cartilage are chondrocytes. Chondrocytes begin as chondroblast cells that produce a collagen extracellular matrix (ECM). The ECM form lacunae, or spaces within the matrix, in which up to eight chondrocytes are caught and remain. Cartilage is avascular. As a result, chondrocytes rely on diffusion to receive nutrients, which contributes to cartilage's slow healing characteristics.

Exhibit VII – Cartilage Structure[25]



[24] https://www.mayoclinic.org/diseases-conditions/torn-meniscus/diagnosis-treatment/drc-20354823
[25] Ng HY, Alvin Lee KX, Shen YF (2017) Articular Cartilage: Structure, Composition, Injuries and Repair. JSM Bone and Joint Dis 1(2): 1010.

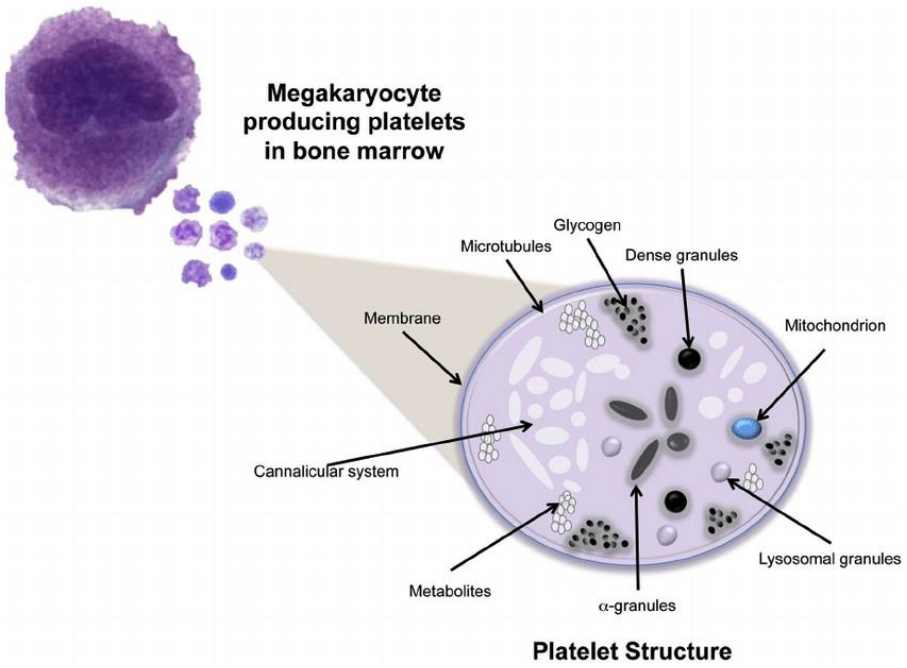
Platelets, Clotting and Platelet Rich Plasma

Platelet rich plasma (PRP) is plasma sourced from a patient's own blood that contains concentrated levels of platelets. Blood drawn from a patient is placed in a vial, then spun in a centrifuge to separate the fractions of blood. The yellow PRP sits on the top, a thin layer of white blood cells in the middle and red blood cells in the bottom portion of the column. Platelets are commonly associated with aggregation in response to vascular perforation and they contain growth factors which promote synthesis of extracellular matrix cell proliferation, chemotaxis, cell differentiation and angiogenesis to stimulate healing.[26] Modern understanding of platelets has expanded to include roles in intercellular communication, inflammation and immunomodulation.[27]

Platelets

Platelets are differentiated from megakaryocytes in the bone marrow primarily in response to thrombopoietin. Though without a nucleus, platelets retain many functioning organelles as well as a myriad of surface receptors and adhesion molecules. Platelets also contain many granules. There are also many preformed proteins inherited from megakaryocytes that can be released upon activation. Platelet activation is driven primarily by coagulation cascades.

Exhibit VIII – Platelet Structure[28]



Platelet Structure

Clotting

The first step in clotting is the adhesion of platelets to extracellular matrix. Von Willebrand factor (vWF), a blood glycoprotein involved in hemostasis, forms a bridge between the collagen and its glycoprotein receptor complex located on the membrane surface as well as other receptors, causing the platelet to change shape and release granule contents. Among the granule contents is calcium, necessary for the formation of thrombin. As the platelets form cross-links, the thrombus grows and stabilizes.

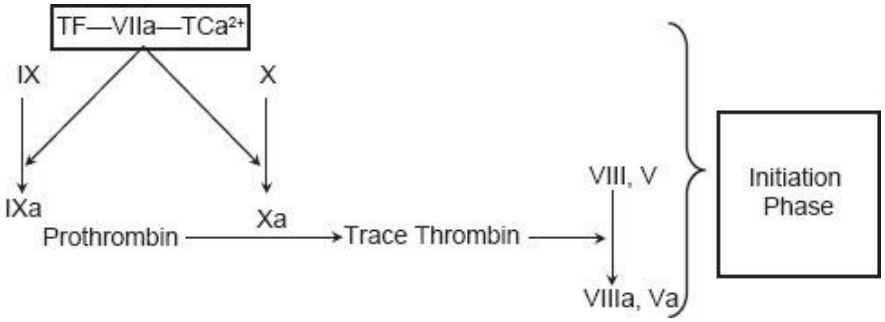
The calcium that is released in platelet degranulation is relevant to clotting factors. The majority of clotting factors are proteolytic enzyme precursors, or zymogens, that circulate in an inactive form. The zymogens undergo post translational modifications that enable them to bind calcium, as well as other divalent cations. As the zymogens bind to calcium, such as the $CaCl_2$ included as a clot activator in RESTORE, they become activated as part of the clotting cascade. The coagulation cascade centers around activated factor X. While thinking continues to evolve on the subject, it is believed that expression of tissue factor in damaged vessel (typical scenario for clotting) binds factor VIIa that activates factor IX and X. Factor Xa (activated) binds to factor II to form thrombin. The thrombin, alone, is not sufficient and relies on feedback loops to bind thrombin with platelets. The initially generated thrombin activates factor V and VIII, which, in acting as a cofactor for prothrombinase complex, accelerates the production of more IXa and Xa. Xa combines with cofactors factor V, tissue phospholipids, platelet phospholipids and calcium to form the prothrombinase complex that converts prothrombin to thrombin. The thrombin cleaves circulating fibrinogen to insoluble fibrin and activates factor XIII, which crosslinks fibrin stabilizing the clot.

[26] Mirzaya, R., *et al.* Rationale for Biologic Augmentation of Rotator Cuff Repairs. J Am Acad Orthop Surg 2019;27: 468-478

[27] Yun, S. H., Sim, E. H., Goh, R. Y., Park, J. I., & Han, J. Y. (2016). Platelet Activation: The Mechanisms and Potential Biomarkers. *BioMed research international*, *2016*, 9060143. https://doi.org/10.1155/2016/9060143

[28] Zapata, Juan & Cox, Dermot & Salvato, Maria. (2014). The Role of Platelets in the Pathogenesis of Viral Hemorrhagic Fevers. PLoS neglected tropical diseases. 8. e2858. 10.1371/journal.pntd.0002858.

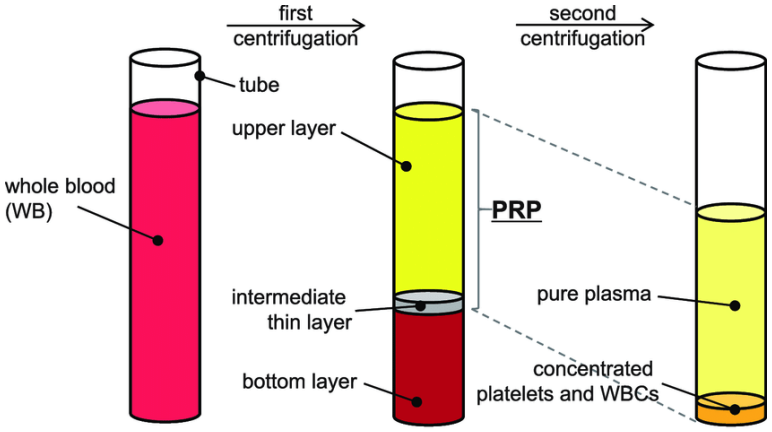
Exhibit IX – Coagulation Cascade Initiation[29]



Platelet Rich Plasma (PRP)

PRP is an autologous blood-derived product that contains a high concentration of platelets. PRP is thought to affect the healing process by supplying growth factors, cytokines, and other compounds that play roles in hemostasis, tissue repair and tissue remodeling.[30] PRP is safe, easily prepared and has minimal tissue rejection. PRP found its first applications in dentistry, oral and maxillofacial surgery to improve bone healing, and has since extended to treat orthopedic conditions including rotator cuff and meniscus tears and osteoarthritis. Ehrenfest *et al.* classified four families of PRP preparations including leukocyte-rich PRP, leukocyte-poor PRP, leukocyte-rich platelet rich fibrin and leukocyte-poor platelet-rich fibrin. In terms of therapeutic efficacy, platelet content, as well as erythrocyte and leukocyte concentration all play a role and differentiate the types of PRP.[31] The exact role of the cells in tissue repair is not fully understood. Leukocytes and leukocyte-rich preparations are thought to be proinflammatory, suggesting that leukocyte-reduced variants may be superior; however, *in vitro* investigation has shown that in fact the leukocyte-rich PRP has higher levels of platelet-derived growth factor, which could improve tissue repair, so it remains unclear which PRP preparation is superior for a specific condition.

Exhibit X – Production of PRP via Centrifugation[32]



Bone Marrow Aspirate Concentrate

Bone marrow aspirate concentrate is another autologous biologic that Ortho RTI may consider as a candidate in cartilage repair. However, due to the invasive nature of obtaining bone marrow aspirate and the success that has been observed so far with PRP, we do not expect much work to be done in this area.

Coagulation, Muco-adhesion and Residence Time

Once the chitosan biopolymer and the patient's PRP are combined, the mixture begins to coagulate. The paste-like mixture is applied to the tear and remains in place to assist the healing process. RESTORE can remain in place up to six weeks as compared to 24 hours for PRP alone. The formulation also resists platelet-mediated clot retraction or shrinkage which helps maintain contact between the PRP and healing tissue. RESTORE also has the property

[29] Palta, S., Saroa, R., & Palta, A. (2014). Overview of the coagulation system. *Indian journal of anaesthesia*, *58*(5), 515–523. https://doi.org/10.4103/0019-5049.144643

[30] Zadeh LG, *et al.* Multiple platelet-rich plasma preparations can solubilize freeze-dried chitosan formulations to form injectable implants for orthopedic indications. 2019 Bio-Medical Materials and Engineering 30 (2019) 349–364

[31] Dohan Ehrenfest, D. M., Andia, I., Zumstein, M. A., Zhang, C. Q., Pinto, N. R., & Bielecki, T. (2014). Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. *Muscles, ligaments and tendons journal*, *4*(1), 3–9.

[32] Piao, Linfeng & Park, Hyungmin & Jo, Chris. (2017). Theoretical prediction and validation of cell recovery rates in preparing platelet-rich plasma through a centrifugation. PLOS ONE. 12. e0187509. 10.1371/journal.pone.0187509.

of mucoadhesion, a type of bioadhesion that occurs between a mucosal surface and another material.[33] This bond, combined with a controlled degradation, allows the therapy to act for longer periods of time in a localized, targeted manner. The prolonged localized delivery is known as residence, as the implant remains in place and continues to provide therapeutic benefit. Mucoadhesive systems can deliver high molecular weight molecules such as peptides and oligonucleotides that may normally be digested if administered orally. Theories of forces driving mucoadhesion include wetting, electrostatic, diffusion, adsorption, and fracture theory.[34] While understanding of the mechanism of mucoadhesion continues to evolve, important factors driving it include hydrophilicity, molecular weight, cross linking, swelling and pH, among others.

The healing properties of chitosan and PRP have been discussed in depth.[35,36,37,38] Ortho has extended the effort into a proprietary combination product where the polymer is soluble in PRP, which is able to achieve the desired mechanical properties and consistency for administration.

RESTORE Technology

Ortho RTI's sole candidate, Ortho-R, is derived from Ortho RTI's RESTORE technology. While the company has highlighted other designations of Ortho-R that are intended for use in different sites, they are composed of the same proprietary biopolymer derived from chitosan. Ortho RTI's candidate can be applied to various common tear-injuries in the body such as those in the rotator cuff, meniscus, cartilage and joints affected by osteoarthritis. The product is a powder containing lyophilized chitosan, a lyoprotectant and clot activator. This powder is then mixed with a wet biologic, which is the patient's own PRP, which causes it to coagulate. The combination is shaken and the mixture applied by the surgeon on and around the repaired site. Within minutes, the implant takes on a thickened consistency and the surgeon can complete the operation.

The process of mixing and applying Ortho-R takes only minutes, does not interrupt surgery and has been shown effective in tissue repair *in vivo*. Surgery uses mechanical means of repairing the tissue, using sutures, anchors and/or staples. In the case of a rotator cuff tear, when the two halves of the tear are brought together by mechanical means, the body must complete the healing process by bridging the gap. RESTORE leverages biology to improve the healing process by combining a biocompatible polymer matrix with a regenerative factor to enhance healing. The Ortho-R material is thick by design, as the implant needs to remain localized to the injured tissue while it continues to supply growth factors critical to healing. Ortho RTI has developed and optimized the components of RESTORE to meet the specific therapeutic and material properties and has a shelf life of over two years. RESTORE has been optimized for solubility in the patient's PRP and has desirable mucoadhesive and residence properties. It is a combination of an implant and a drug and has been classified by the FDA as a drug/biologic that is delivered through an accessory device.

Chitosan

The basis of RESTORE is freeze-dried (lyophilized) chitosan. Chitosan is a biopolymer found in nature and is known to be beneficial for wound healing, having effects on blood clotting and recruitment of repair cells in wounds. Chitosan causes blood to rapidly clot, but also serves a role in stabilizing the blood clot mechanically, acting as a scaffold to maintain clot volume and increase clot adhesion to tissue. Researched applications are diverse and include chitosan employed as a biomaterial, in nanoparticles for gene and drug delivery and as an antimicrobial. It is the primary component in RESTORE, along with a lyoprotectant and a clot activator. Commercial chitosan is typically manufactured through the deacetylation of the parent polymer, chitin.[39]

[33] Shaikh, R., Raj Singh, T. R., Garland, M. J., Woolfson, A. D., & Donnelly, R. F. (2011). Mucoadhesive drug delivery systems. *Journal of pharmacy & bioallied sciences*, *3*(1), 89–100. https://doi.org/10.4103/0975-7406.76478

[34] Shaikh, R., Raj Singh, T. R., Garland, M. J., Woolfson, A. D., & Donnelly, R. F. (2011). Mucoadhesive drug delivery systems. *Journal of pharmacy & bioallied sciences*, *3*(1), 89–100. https://doi.org/10.4103/0975-7406.76478

[35] Mohammadi, R., *et al.* Effect of Platelet Rich Plasma Combined with Chitosan Biodegradable Film on Full-Thickness Wound Healing in Rat Model. Bull Emerg Trauma. 2016 Jan; 4(1): 29–37.

[36] Hattori, H., Ishihara, M. Feasibility of improving platelet-rich plasma therapy by using chitosan with high platelet activation ability. Exp Ther Med. 2017 Mar; 13(3): 1176–1180.

[37] Oktay, O.E., *et al.* Effects of Platelet-Rich Plasma and Chitosan Combination on Bone Regeneration in Experimental Cranial Defects. Journal of Oral Implantology, Vol. XXXVI/No. Three/2010

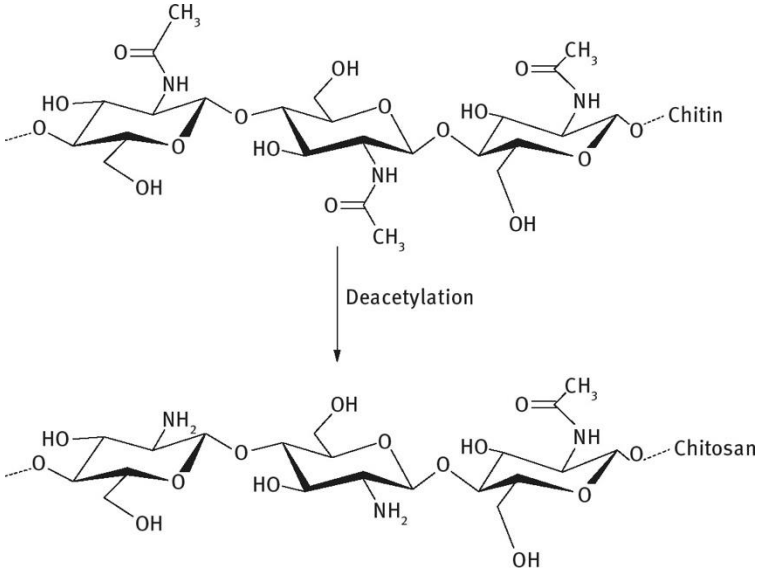
[38] Shimojo, A.A.M., *et al.* Performance of PRP Associated with Porous Chitosan as a Composite Scaffold for Regenerative Medicine. The Scientific World Journal. Volume 2015

[39] de Queiroz Antonino, R., Lia Fook, B., de Oliveira Lima, V. A., de Farias Rached, R. Í., Lima, E., da Silva Lima, R. J., Peniche Covas, C. A., & Lia Fook, M. V. (2017). Preparation and Characterization of Chitosan Obtained from Shells of Shrimp (Litopenaeus vannamei Boone). *Marine drugs*, *15*(5), 141. https://doi.org/10.3390/md15050141

Chitin is the second most abundant biopolymer in the world after cellulose. It is sourced from the exoskeletons of arthropods such as insects, crabs, lobsters, shrimp and other related animals. It can also be sourced from fungi which offers lower levels of inorganic materials and no requirement for demineralization treatment compared to crustacean sources.

Chitin is a polysaccharide composed of *N*-acetylated glucosamine (GlcNAc) and glucosamine (GlcN) subunits.[40] Chitin is further categorized into α-, β- and γ-types depending on layer arrangement, with α being the most common in nature. Chitin is most prevalent in the exoskeleton of arthropods but can also be found in fungi and mushrooms.[41] Chitin composition and content varies between species, with a primary source of chitin coming from crustaceans and the fishing industry. Chitin extraction requires acidic (1M HCl) and basic (1M NaOH) treatment for the removal of minerals and proteins, respectively. The NaOH treatment is also that which deacetylates the chitin, producing chitosan. GlcNAc conversion to GlcN is captured in a metric known as degree of deacetylation (DDA). The process can take 2-24 hours at 60-90 °C for each step, varying with specific sources. Bleaching with hydrogen peroxide can be used to further purify the chitosan. Recently developed biological methods of chitin purification, such as the use of protease, may also be used but lack the ability to separate chitin from catechols or amino acids directly attached to the polymer. Ortho sources its chitosan from a species of Northern shrimp named Pandalus borealis found in waters near Iceland.

Exhibit XI – Conversion of Chitin to Chitosan[42]



Lyophilization is freeze drying and greatly extends shelf life. After deacetylation, the chitosan is first frozen in solution with a lyoprotectant, a substance that allows the lyophilized chitosan to remain stable and preserve its activity. Without the lyoprotectant, the chitosan would continue to react and/or degrade. The process of lyophilization removes water via sublimation. Sublimation is the phase change between solid and gas, directly, without passing through the liquid phase, made possible through placing the frozen substance under strong vacuum, and then allowing the temperature of the frozen solid to rise. Ortho RTI has used the lyoprotectant trehalose, a natural glucose disaccharide synthesized by many species of plants and animals which protects cell membranes and labile proteins against desiccation.[43]

Calcium chloride ($CaCl_2$) is included in the powder mixture as a clot activator. It is widely available and used to activate PRP along with autologous thrombin or collagen type 1. Activation of PRP is necessary to initiate the platelet degranulation process that releases growth factors affecting cell division, angiogenesis, chondrogenesis and chemotaxis.

[40] Physical Sciences Reviews, Volume 1, Issue 9, 20160048, eISSN 2365-659X, ISSN 2365-6581, DOI: https://doi.org/10.1515/psr-2016-0048.
[41] Khousab F, Yamabhai M. Chitin research revisited, Mar. Drugs, 2010, 8, 1988–2012.
[42] Physical Sciences Reviews, Volume 1, Issue 9, 20160048, eISSN 2365-659X, ISSN 2365-6581, DOI: https://doi.org/10.1515/psr-2016-0048.
[43] Luyckx, J., & Baudouin, C. (2011). Trehalose: an intriguing disaccharide with potential for medical application in ophthalmology. *Clinical ophthalmology (Auckland, N.Z.)*, *5*, 577–581. https://doi.org/10.2147/OPTH.S18827

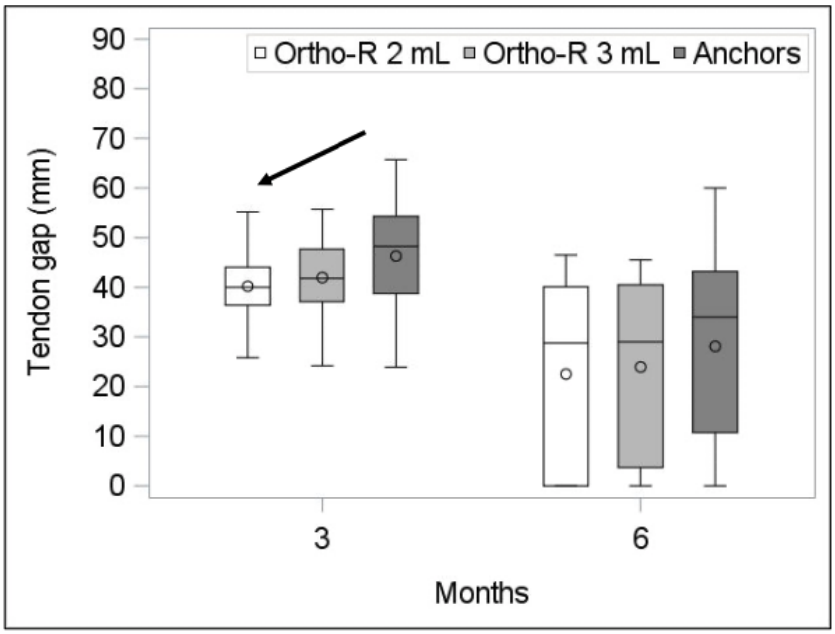
Candidates

Ortho RTI is targeting multiple indications with its RESTORE platform. Its lead candidate is Ortho-R, one of the multiple variants of the RESTORE platform, which is specifically designed to be used in rotator cuff tear (RCT) and meniscus tear (MT). It is expected to extend to applications in meniscal tear and possibly other areas. Preliminary work in spinal disc, articular cartilage, ACL repair, Achilles tendon and tennis elbow are also being explored through research at École Polytechnique in Montreal.

Preclinical Research, Rotator Cuff

On July 23. 2020, Ortho RTI released results from its pivotal preclinical ovine animal model rotator cuff tear study, MD-82. The study compared standard of care alone (control) with standard of care augmented with Ortho-R 2 mL and 3 mL treatment groups. The RCT repair pivotal study final results were generated from the statistical analysis of the histological data performed respectively by independent biostatisticians and licensed veterinarian pathologists blinded to treatment groups. Results from the study confirms evidence of better tendon and insertion site histology and overall repair in RCT treated with Ortho-R.

Exhibit XII – Tendon Gap, Ortho-R 2mL vs 3mL vs Anchors at 3 Months[44]



In the MD-82 pivotal preclinical study, 48 Dorset ewes were evaluated for standard of care, with and without the administration of Ortho-R. Analysis include between-group comparisons and dose response analyses of histological scores for infraspinatus tendon, infraspinatus enthesis[45] (infraspinatus tendon insertion site) and overall repair (infraspinatus pan-enthesis) groups.

The infraspinatus (ISP) was transected and repaired using four suture anchors. Ortho-R was solubilized in each ewe's PRP and implanted at the footprint and on top of the repaired site at 2 mL or 3 mL implant volume. Results showed that tendon gap decreased compared to standard of care alone at three months and histological appearance was improved at six months of tendon, tendon insertion site and overall repair. Results confirmed superiority in tendon and insertion site histology and overall repair in RCT treated with Ortho-R at six months post intervention. Histological scoring was performed by Biomedical Statistical Consulting and evaluated between groups and doses at the infraspinatus and its insertion site and overall repair. Overall repair analysis was more consistent with complete remodeling and healing for Ortho-R groups versus controls. Results also showed a dose dependent response, providing strong evidence for causality. Combined analyses showed a third of Ortho-R treated samples had complete healing with a smaller degree of remodeling while none of the control samples were so classified. In particular, Ortho-R 3 mL group showed more normal glycosaminoglycan (GAG) staining compared to controls; 100% of 3 mL group had normal GAG staining compared to 75% and 67% for 2 mL and controls, respectively. Safety was also promising with no treatment-specific findings across all measures such as clinical signs, hematology, clinical biochemistry, urinalysis and major organ histopathology.

For infraspinatus tendon measurements, data are consistent with less severe cellularity (cell accumulation), in Ortho-R treated groups, indicative of a more normal tissue ($p=0.031$, c-stat[46]$=0.625$). Moreover, no inflammatory cells were observed in Ortho-R treated tendon tissue, compared to 42% of controls having minimal to moderate inflammatory cell scores, indicating there was no observable inflammation in Ortho-R treated groups ($p=0.002$, c-stat$=0.708$). For ISP tendon insertion site measurements, the Ortho-R treated groups were associated with an increase in the proportion with no change or normal GAG staining compared to the controls ($p=0.071$, c-stat$=0.688$).

[44] Ortho RTI October 2020 Corporate Presentation
[45] Enthesis is the connective tissue between tendon or ligament and bone.
[46] The c-statistic provides an estimation of the effect size. In this study, c-stat from 0.6 – 0.7 and > 0.7 were considered as moderate and strong evidence of a relationship.

For infraspinatus pan-enthesis measurements (overall repair), evidence is consistent with more complete remodeling and healing within the Ortho-R treated groups compared to controls, as well as a dose-response association favoring improved remodeling and healing. In combined analyses, one-third (n=8/24) of Ortho-R treated samples had complete healing with a smaller degree of remodeling, whereas none of the control samples fell within this category or better (p = 0.019, c-stat = 0.726).[47] There was also evidence of more normal GAG staining compared to controls, particularly within the Ortho-R 3 mL group; 100% of the Ortho-RT 3 mL group had normal GAG staining (p = 0.016, c- stat = 0.774), whereas 75% were normal and 25% mild in the Ortho-R 2 mL group (p = 0.118, c-stat = 0.677) and 67% normal and 33.3% mild within controls.

The veterinarian pathologist histology report conclusion highlights *"The microscopic appearance of comprehensive ISP tendon enthesis healing (i.e. based on the overall quality of healing across the entire anatomic site), Ortho-R tended to have more complete healing of the enthesis site. This corresponded microscopically to an overall better structured, well-organized enthesis site, with distinct, regular well-organized tendon bundles, and fibrocartilage, generally combined with a lower score or magnitude of the bone remodeling."*, indicating that Ortho-R treated groups had structural organization closer to normal overall.

Preclinical Research, Meniscus

A pilot study for Ortho-M was performed in an ovine model.[48] Chitosan combined with PRP plus the lyoprotectant trehalose and calcium chloride ($CaCl_2$) as a clot activator was applied to surgically induced meniscus lacerations. In the first study, bilateral tears in seven ewes were treated by suturing, trephination and injecting chitosan (CS)-PRP or PRP alone into the tears. In the second study, unilateral tears in six ewes were treated by suturing, trephination, and CS-PRP injection, wrapping meniscus with collagen membrane and injecting CS-PRP under the wrap. CS-PRP implants were partly resident in the tears and trephination channels after one day and induced cell recruitment from vascularized periphery of the menisci. Complete repair and seamless repair tissue integration were observed in 25% of CS-PRP treated sites after three months in the first study and 50% of treated sites in the second study after six weeks. There was no healing in control sites treated with PRP or wrapping alone. The meniscus pilot study demonstrated the potential of the CS-PRP implant and has provided sufficient proof of concept to enter into a pivotal preclinical trial.

Clinical and Regulatory

Ortho plans to seek regulatory approval in the US as its first target market for Ortho-R. Ortho-R was designated as a device, drug and biologic combination product by the FDA and will be overseen by the Center for Biologics Evaluation and Research (CBER). The designation resolved a process begun on March 26, 2020 with an ongoing dialogue between the FDA and Ortho RTI for proper designation of the candidate. Discussions consisted of three rounds of questions and clarifications.

The FDA review determined that the Ortho-R product is considered a biologic as it incorporates autologous PRP. The syringes and dispensing pins required to administer Ortho-R justify the classification of the product as a device. The properties of chitosan and PRP based on research conducted by both Ortho and other independent researchers also played a role. Characteristics related to the electrostatic binding of the combination product, resulting modification of cell function, slowing of blood clot retraction and extended release of growth factors compared to PRP alone provided justification for classification of the product as a drug.

There are benefits and challenges associated with the designation as a combination product. Management has expressed that the potential benefits include a higher valuation for Ortho RTI, more attention from biopharma, regenerative medicine and orthopedic companies, a perception of higher therapeutic value, multiple mechanism of action labeling and higher reimbursement from payors. Potential challenges include the need for potency assay development, the need for two Phase III studies in multiple jurisdictions and more extensive efforts in negotiations with payors.

[47] A low p-value combined with a c-stat value > 0.6 indicates that statistical significance observed is due to moderate to large effect sizes.
[48] Ghazi ZL, Chevrier A, Hurtig MB, et al. (2017) Freeze-Dried Chitosan-PRP Injectable Surgical Implants for Meniscus Repair: Pilot Feasibility Studies in Ovine Models. Regen Med Ther 1(1):16-29

A US clinical trial is planned, structured as a randomized, controlled and blinded Phase I/II study with a primary endpoint of safety. Secondary endpoints include pain intensity using the visual analog scale (VAS), validated shoulder function score index, magnetic resonance imaging (MRI) for healing/structural and number of re-tears. Patients will be assessed to establish a baseline, and then at six weeks, then three, six and 12 months. Targeted enrollment is 75 patients with a 2:1 ratio of treated to standard of care. The trial is planned to take place at five clinical sites in the US. The protocol has been completed and CRO MCRA has been selected. The CRO is recognized for its expertise in orthopedics and has a regulatory arm which is expected to accelerate and smooth the path towards approval. Ortho plans its investigational new drug (IND) submission to take place in calendar 4Q:20. Other ongoing steps include completion of the investigator brochure, clinical site budget draft, site qualification and training for imaging and first patient enrollment targeted in 1Q:21. Ortho-R is being manufactured according to current good manufacturing practices (cGMP) and will be ready for first use in early 2021.

Competitors, Peers and Competing Therapies

The soft tissue orthopedic market is dominated by three companies, Arthrex, Smith & Nephew and DePuy Synthes, that control over 70% of revenues according to iData Research. Arthrex dominates in the rotator cuff, shoulder labrum repair, biceps tenodesis and ACL/PCL segments. Smith & Nephew is a leader in meniscal repair and hip arthroscopy, while DePuy holds second place in rotator cuff repair along with a broad portfolio addressing many sites in the orthopedic soft tissue market. Grandview Research estimates that the global orthopedic devices market was over $36 billion in 2017 growing at a 3% annual rate.

Ortho RTI uses its RESTORE technology to develop products used to repair hard to heal injuries in ligaments, tendons and other tissues. The company is pursuing treatments for several applications in the sports medicine and orthopedic spaces. Lead programs focus on rotator cuff and meniscal repair. Other programs treat damage to articular cartilage, the nucleus pulposus, osteoarthritis pain and other sites. There are a number of competitors that also provide orthopedic products in similar and adjacent spaces to Ortho. Companies such as Arthrex that provide allograft tissue, Johnson & Johnson's DePuy Synthes subsidiary competes with its TRUESPAN meniscal repair system and potentially with Novocart 3D, an in-development product from Aesculap Biologics that uses autologous chondrocytes to grow new cartilage. Smith & Nephew acquired BST-CarGel from Piramal Healthcare in 2016, which is a mixture of buffer, chitosan and patient's whole blood to create a bioscaffold to repair cartilage. The chitosan-based product has been approved in Australia, Canada and most of Europe.

Other competitors provide allogeneic fillers for musculoskeletal targets that promote healing using fusion grafts. Some, such as RTI Surgical, Conmed, JRF Ortho and Allosource provide a portfolio of allograft material for tendons, meniscus, bone and other structural components of the musculoskeletal system. One company, GreenBone Ortho, is even using wood to manufacture bone grafts. Organogenesis, Anika, Isto Biologics, Axiom Regenerative Therapies and Lipogems address joint pain and dysfunction with injections of regenerative medicines such as hyaluronic acid, collagen, PRP, adipose and placental tissue matrix. Vericel offers its autologous cultured chondrocytes on porcine collagen membrane for knee cartilage repair. Biorez is developing its BioBrace biocomposite scaffold to support ligament and tendon repair and regenerate tissue in rotator cuff and other sports medicine applications while Carmell Therapeutics offers a pipeline of bone and tissue healing accelerant using allogeneic pooled plasma.

Many competitors in the space do not compete directly with Ortho RTI and offer bone filler products (Allosource, Xtant Medical) or are in adjacent orthopedic areas such as implants, joint replacement and reconstruction (Zimmer, Smith & Nephew, Corin, Integra and Stryker). We summarize many of the companies that compete in the orthopedic joint market in the following exhibit.

Exhibit XIII – Peers and Competitors

Ticker	Company	Price	MktCap (MM)	EV (MM)	Therapeutic Area
ANIK	Anika Tx	$36.20	$515	$438	Orthobiologic, dermal, surgical hyaluronic acid based products
CNMD	Conmed	$101.23	$2,895	$3,640	Surgical devices & related for minimally invasive procedures
CSBTF	Kuros Biosciences	$2.30	$58	$42	Bone grafting & fusion products
GMED	Globus Medical	$57.83	$5,706	$5,180	Orthopedic products for musculoskeletal disorders/Implants
IART	Integra Lifesci	$54.53	$4,595	$5,830	Surgical implants/medical instruments-neuro extremity & ortho surgery
JNJ	DePuy Synthes	$146.36	$385,299	$392,280	Broad portfolio of orthopedic products
MDT	Medtronic	$110.16	$148,100	$163,780	Diversified devices, surgical, orthopedic, implants, pumps, etc.
NUVA	NuVasive	$46.10	$2,364	$2,900	Spine surgery products, instruments, hardware, biologics, software.
OFIX	Orthofix	$36.15	$699	$642	Spine, biologics, bone growth, limb reconstruction, foot & ankle
ORGO	Organogenesis	$5.08	$548	$626	Wound care, sports med, regen med, surgical medicine
SNN	Smith & Nephew	$39.16	$16,972	$19,260	Joint replacement, wound mgmt, sports med & orthopedics/trauma
SPNE	SeaSpine	$13.83	$382	$304	Design, develop & commercialize spinal surgery tech/Orthobiologics
SYK	K2M Group	$232.86	$87,507	$93,470	Medical products for spinal disorders; 3D printing
SYK	Stryker	$232.86	$87,507	$93,470	Orthopedics, MedSurg, Neurotechnology & Spine
VCEL	Vericel	$23.68	$1,076	$1,020	Cell therapies for sports medicine, severe burn care, knee surgery
WMGI	Wright Medical	$29.98	$3,895	$4,980	Biologics, foot & ankle, upper extremities, wound
XTNT	XTANT Medical	$1.29	$94	$172	Orthopedic bone products and fixation systems
ZBH	Zimmer Biomet	$145.94	$30,250	$37,570	Musculoskeletal products & solutions: Bone, joint, soft tissue
pvt	Allosource				Allografts: dermal, bone, tendon using AlloTrue purification
pvt	Arthrex				Broad portfolio of orthopedic products
pvt	Axlom Regen Tx				Autologous regen med/cell based therapies, orthopedic conditions
pvt	Biorez				Tendon & ligament repair-BioBrace Implant/sports medicine
pvt	Bioventus Surgical				Allograft, cell & marrow & synthetic orthobiologic products
pvt	Carmell Tx				Plasma based bioactive materials for regen healing
pvt	Corin Group				Arthroplasty, data driven clinical decisions, hip & knee
pvt	Embody				Hip resurfacing instruments
pvt	Green Bone Ortho				Synthetic, acellular, resorbable bone substitute for reconstruction
pvt	Isto Bio				Spine & orthopedic cell therapy & rapid bone healing
pvt	JRF Ortho				Osteochondral allografts, tendons & fresh-frozen meniscus
pvt	Lipogems				Autologous adipose tissue processing & transfer device-joints
pvt	RTI Surgical				Design,develop, manuf & distrib biologic, metal & synthetic implants
pvt	Silk Biomaterials				Silk for use in endogenous tissue repair & regeneration
ORTH	Ortho RTI	$0.78	$25.8	$24.1	Orthobiologic tissue repair technologies/Soft tissue injury

Intellectual Property

Ortho RTI's RESTORE platform is protected by three patent families. The families are designated '782, regarding polymer composition and PRP; Patent Cooperation Treaty (PCT) '129, for freeze dried chitosan and lyoprotectant for use with PRP, blood and combinations to form an injectable solution; and PCT '130, encompassing lyophilized scaffold comprising at least one polysaccharide to have a variety of beneficial effects for tissue repair.

In the US, Ortho RTI was granted patent 9,427,469 entitled "Soluble physiological chitosan formulations combined with platelet-rich plasma (PRP) for tissue repair" relating to activated polymer composition for tissue repair use composed of PRP, chitosan solution, a salt such as NaCl or glycerol phosphate and a clotting activator such as $CaCl_2$ or thrombin and $CaCl_2$. This patent was granted on August 30, 2016.

Application 20170056550 for Lyophilized Polymer Scaffold Compositions, Processes for Preparation and Use in Anabolic Wound Repair covers a malleable lyophilized scaffold composed of at least one polysaccharide. The polysaccharide has a protonation level conducive to controlled rehydration of the scaffold so that when the scaffold comes in contact with an aqueous solution, it forms a microparticle dispersion that stimulates tissue remodeling and anabolic wound repair. The applied for patent also covers the process for preparing the lyophilized scaffold composition and the use of the composition for wound repair in mammals. The application was filed in the US as well as through the PCT in February 2015.

Finally, application 20170049696, entitled Freeze-Dried Polymer Compositions for Mixing with Platelet Rich Plasma to form Implants for Tissue Repair and/or Compositions for Therapeutic intra-articular Injections, was filed (US and PCT) February 2015, with national applications in August 2016 and acceptance for review in February 2017. The applied-for patent relates to lyophilized polymer composition containing chitosan and at least one lyoprotectant and the process for preparing the freeze-dried composition and the use of the reconstituted composition to prepare implants for tissue repair.

Exhibit XIV – Ortho RTI Patent Table[49]

Matter	Matter.Country	Matter.FilingDate	Matter.ApplicationNum	Matter.PatentNum	Matter.Status	Matter.Title	Expiry Date	Additional Comments
080000-P0002-EP	European Patent Office	Friday, November 19, 2010	10831011.1	2501392	Issued	SOLUBLE PHYSIOLOGICAL CHITOSAN FORMULATIONS COMBINED WITH PLATELET-RICH PLASMA (PRP) FOR TISSUE REPAIR	Tuesday, November 19, 2030	
080000-P0002-US	United States	Tuesday, September 4, 2012	13/510,663	9427469	Issued	SOLUBLE PHYSIOLOGICAL CHITOSAN FORMULATIONS COMBINED WITH PLATELET-RICH PLASMA (PRP) FOR TISSUE REPAIR	Tuesday, November 19, 2030	
068512-P0002-JA	Japan	Tuesday, June 9, 2020	2016-553370	2009-520705	Issued	FREEZE-DRIED POLYMER COMPOSITIONS FOR MIXING WITH PLATELET RICH PLASMA TO FORM IMPLANTS FOR TISSUE REPAIR AND/OR COMPOSITIONS FOR THERAPEUTIC INTRA-ARTICULAR INJECTIONS	Tuesday, February 20, 2035	
068512-P0002-US	USA		15/119,397		Pending	FREEZE-DRIED POLYMER COMPOSITIONS FOR MIXING WITH PLATELET RICH PLASMA TO FORM IMPLANTS FOR TISSUE REPAIR AND/OR COMPOSITIONS FOR THERAPEUTIC INTRA-ARTICULAR INJECTIONS		
068512-P0002-EU	European Patent Office		15752804.3		Pending	FrEEZE-DRIED POLYMER COMPOSITIONS FOR MIXING WITH PLATELET RICH PLASMA TO FORM IMPLANTS FOR TISSUE REPAIR AND/OR COMPOSITIONS FOR THERAPEUTIC INTRA-ARTICULAR INJECTIONS		
068512-P0002-CA	Canada		2939974		Pending	FREEZE-DRIED POLYMER COMPOSITIONS FOR MIXING WITH PLATELET RICH PLASMA TO FORM IMPLANTS FOR TISSUE REPAIR AND/OR COMPOSITIONS FOR THERAPEUTIC INTRA-ARTICULAR INJECTIONS		
068512-P0003-AU	Australia	Friday, February 20, 2015	2015221390	2015221390	Issued	LYOPHILIZED POLYMER SCAFFOLD COMPOSITIONS, PROCESSES FOR PREPARATION AND USE IN ANABOLIC WOUND REPAIR	Tuesday, February 20, 2035	
068512-P0003-EP	European Patent Office		15752604.7		Pending	LYOPHILIZED POLYMER SCAFFOLD COMPOSITIONS, PROCESSES FOR PREPARATION AND USE IN ANABOLIC WOUND REPAIR		
068512-P0003-US	United States		15/119,748		Pending	LYOPHILIZED POLYMER SCAFFOLD COMPOSITIONS, PROCESSES FOR PREPARATION AND USE IN ANABOLIC WOUND REPAIR		
068512-P0003-CA	Canada		2940012		Pending	LYOPHILIZED POLYMER SCAFFOLD COMPOSITIONS, PROCESSES FOR PREPARATION AND USE IN ANABOLIC WOUND REPAIR		

[49] Source: Ortho RTI Documents

Financial and Operational Results

Corporate Milestones

- Luc Mainville appointed CFO – September 2018
- Initiation of pivotal preclinical study of Ortho-R – February 2019
- Claude LeDuc nominated as President and CEO – June 2019
- Collaborative agreement with leading global orthopaedic company – August 2019
- $1,6 million private placement closed – October 2019
- $0.5 million private placement closed – December 2019
- RCT MRI evaluation positive results from pivotal preclinical study – March 2020
- $1.1 million private placement closed – April 2020
- Licensing agreement with Ingenew Pharmaceuticals – May 2020
- Michael Atkin nominated Chairman of the Board – June 2020
- RCT histology evaluation positive results from pivotal preclinical study – July 2020
- FDA designation and jurisdictional assignment for Ortho-R – August 2020
- $2.5 million private placement closed – August 2020
- Trading under ticker ORTIF began on the OTCQB – October 2020
- Mukesh Ahuja M.D., appointed VP of Clinical and Medical Affairs - November 2020

Financial
Ortho RTI reported fiscal year 2Q:21 results on September 25, 2020 for the period ending July 31, 2020. No revenues were reported. Net research and development expense totaled $195,000, near the prior year's $194,000. General and administrative expenses totaled $186,000, about half of prior year levels. Share based compensation rose 11% to $49,000 from $44,000 in the second quarter and financial expenses rose significantly to $201,000 from $63,000. In the R&D category, development, patient and depreciation costs were all down over the prior period due to timing of non-recurrent expenses incurred related to the Ortho-R program and the termination in 2Q:20 of a senior R&D staff member. This was offset by a smaller tax credit in 2Q:21 versus the comparable period. G&A expenses decreased year over year primarily due to severance pay of $120,000 incurred in the prior period due to the CEO transition. Share-based compensation fluctuates with changes in staff and with the timing of expense recognition associated with vesting of options issued. Consulting fees were also down modestly. Financing expenses have risen in recent quarters in response to the convertible debenture unit (CDU) financing, which totaled $3.2 million over the past year. Financing expenses also include $158,000 in interest accrued on the CDUs issued between October 2019 and April 2020, amounts which were absent in 2Q:20. Other financial expenses reflect $46,000 for interest tax credit loans outstanding. Cash at the end of 2Q:21 was $23,000 versus $42,000 in 2Q:20. Following the end of the quarter, Ortho was able to place $2.6 million in equity shares providing sufficient funding to advance the company through the next several quarters.

Operational
Year to date, Ortho RTI announced positive results from a pivotal preclinical study in RCT repair. The March 12, 2020 announcement revealed that the safety profile of Ortho-R had been confirmed, that efficacy was superior to standard of care and that the Ortho-R program was advancing. The announcement stated that Ortho RTI had completed preclinical work for Ortho-R with two studies in large animals completed, one pilot and one pivotal study conducted in 48 sheep. Both pilot and pivotal studies for Ortho-R demonstrated a decrease in tendon gap and showed equivalent safety at three months compared to standard of care. The pivotal study showed superior MRI signal intensity ratio, indicative of less trabecula, more fluid or combination thereof, at six months compared to standard of care. Pilot study also showed improved histopathology scores for Ortho-R at three months. On April 22, Ortho RTI issued a press release announcing that it had closed a non-brokered $1.1 million private placement of two year convertible debenture units where 1,060 unsecured convertible debenture units were issued at a purchase price of $1,000 per unit, totaling $1,060,000 in gross proceeds. Units are convertible at $0.30 per class A share. 2,000 warrants were issued for each unit with a 24 month life and $0.50 exercise price.

At the end of May, Ortho RTI announced that it had entered into a licensing agreement to expand its platform with Ingenew Pharmaceuticals Inc. Under the agreement, Ortho RTI is entitled to royalties on sales of products and

royalties on licensing revenues generated from products built on the RESTORE platform. Ortho RTI will receive a fully paid grant back license from Ingenew to access all platform improvements for orthopedic applications. Michael Atkin succeeded Steve Saviuk as independent Chairman of the Board in June. On July 23. 2020, Ortho RTI released results from its pivotal preclinical rotator cuff tear study, MD-82 discussed in our Candidates section. The study compared standard of care alone (control) and augmented with Ortho-R 2 mL and 3 mL treatment groups.

In July, Ortho RTI also announced a private placement offering to support regulatory pursuit of clinical trials and that it would issue 245,000 stock options to the CEO. Ortho additionally issued two million one-year warrants with exercise of $0.50 as compensation to a firm providing social media and branding support.

The FDA designated Ortho-R as a drug/biologic combination product delivered through accessory devices on August 6, 2020. Under this designation, jurisdictional assignment will be the FDA's Center for Biologics Evaluation and Research (CBER). August ended with the closing of a $2.5 million private placement followed shortly after by the close of another private placement for $137,600. Shares issued from the placements totaled 8.16 million.

In October, Dr. Mukesh Ahuja was appointed as the VP of Clinical and Medical Affairs, effective November 1, 2020 and the company's stock began trading on the OTCQB market under the ticker ORTIF as of October 28, 2020.

Exhibit XV – Ortho RTI Corporate and Clinical Milestones[50]

Past and Projected Milestones 2019-2022	Calendar Year	Calendar Quarters/Years						
		2019	Q1-20	Q2-20	Q3-20	Q4-20	H1-21	H2-21	2022
Corporate / Strategic									
MTA collaboration	Initial Phase	➔							
	interim report	☑							
MTA collaboration - Step 2	On-Hold (Covid-19)			●					
Licensing Agreement - Ingenew Pharma				☑					
Finance									
US OTC-QB Listing					➔	■			
Debenture Financing		☑		☑					
Private Placement - Unit Offering					☑				
Ortho-R Clinical Trial - Rotator Cuff repair									
CMC Manufacturing	Scale-up	➔	☑						
	Stability 2yrs - shelf life	➔		☑					
	Stability 3yrs - shelf life	➔							■
	Clinical batch			➔		■			
6-month pivotal animal trial	in-life portion	☑							
	results			■					
Pre-IND Meeting - FDA		☑							
US-FDA IND	Filing Pre-RFD		☑						
	Drug/Biologic Designation			☑					
	IND filing				□	■			
	IND approval				□	■			
US Human Clinical	CRO Selection	☑							
	Protocole completion				■				
	Lead Investigator selection				■				
	Final sites selection				□	■			
	trial START				□	➔			
	Patients enrolment initiated						■		
	50% enrolment completed						■		
	enrolment completed							■	
	12-mth patient follow up completed								■
	Study results								■

➔ Initiation
□ previous target last quarter
■ Current Target
☑ Completed
● On-Hold

[50] ORTH 2Q:21 Financial Report

MANAGEMENT PROFILES

Claude LeDuc, Chief Executive Officer

Mr. Leduc brings over 30 years of senior executive experience with both private and Fortune 500 companies to Ortho RTI. He has held multiple leadership roles as CEO or COO in medical device and biopharma companies. In particular, Mr. LeDuc accumulated over two decades of experience in the musculoskeletal space serving in senior positions at Genzyme, Biomatrix, Serono and BioSyntech. As CEO, Mr. LeDuc took BioSyntech public on the TSX-V exchange in 2004, raising over $50 million from public and private sources. Also, while at BioSyntech, LeDuc worked closely with École Polytechnique, an active partner in the development of Ortho RTI's RESTORE and was involved in the clinical and regulatory development of BST-CarGel, a chitosan-based product which was later acquired by Smith & Nephew. Mr. LeDuc also serves as Executive Chairman of Inception Therapeutics, Inc., served as President and CEO of MRM Proteomics Inc., as President, COO and Board Director of Axcelon Biopolymers Corp. and as CEO of Skeltex Technologies, Inc. Mr. LeDuc attended University of Montreal.

Luc Mainville, MBA, Senior VP, Chief Financial Officer

Mr. Mainville brings over 20 years of financial and operational leadership experience in the life science industry to his role as CFO. He has led or has been integral in five IPOs, as well as completed more than 25 public financings and managed over 50 licensing, M&A, and sale transactions. He also serves as SVP and CFO of Valeo Pharma. Mr. Mainville has held many roles including interim CEO of Acerus Pharma, SVP of Cardiome Pharma, Owner of Luma Life, Chairman of Zucara Therapeutics, President of Luma Capital, President & CEO of Neopharm Labs Inc., Board Member of Enobia Pharma, Chairman of Powertech Corporation Inc., Chairman of Alethia Biotherapeutics, President and CEO of LAB Research and CFO of RTP Pharma Ltd, among others. Mr. Mainville received his MBA from McGill University with a concentration in international marketing and finance.

Michael Atkin, Chairman of the Board

Mr. Atkin has over 30 years of experience in life sciences as an entrepreneur, start-up executive, leader and manager in the pharmaceutical and biotechnology industries and in advancing early stage research towards commercialization. Mr. Atkin is President of Syzent Partners, a consulting firm in life sciences based in Montreal, Quebec. Prior to its founding in 2008, he was Executive Chair and subsequently CEO of Ulysses Pharmaceuticals. He was previously the founding CEO of Aegera Therapeutics, an apoptosis control company formed by the merger of McGill spinout Exogen Neurosciences with Apoptogen. At the helm of Aegera, Mr. Atkin advanced multiple technology and product partnerships with major pharmaceutical companies, generating several million dollars in revenues.

Mr. Atkin was elected Chairman of the Board of antibiotic chemistry firm Sopharmia Inc in St. Joseph, Missouri in 2012. In 2015, Sopharmia intellectual property was acquired by Gladius Pharmaceuticals, which announced a $4 million seed financing. Mr. Atkin served as CEO of Gladius from 2015 to 2019. He serves on the board of a Université de Montréal spin-out company, Affinité Instruments, focused on laboratory and diagnostic tests. Earlier in his career, Mr. Atkin held senior executive positions in product development and licensing at Bristol-Myers Squibb Company and Lederle International, now part of Pfizer. He holds an MBA from Columbia University's graduate school of business and a BA from the University of Kent at Canterbury.

Michael Buschmann, Ph.D. Director and Acting CSO

Dr. Buschmann is Chair of Bioengineering at George Mason University in Fairfax, Virginia. From 1994 to 2017 he was a Professor at Polytechnique Montréal. Dr. Buschmann holds a Ph.D. in Medical Engineering and Medical Physics from MIT and Harvard University, with postdoctoral training in cartilage repair and histology completed at the University of Bern in Switzerland. Since 1994 he conducted a multidisciplinary research program at Polytechnique Montréal that focuses on the use of biomaterials to repair meniscus, rotator cuff and cartilage and to deliver mRNA and small interfering RNA using nanovectors.

Mukesh Ahuja, MBBS, MSc, Vice-President Clinical and Medical Affairs

Dr. Mukesh Ahuja, is a highly qualified, medical executive with fourteen years' experience as a clinical expert in Orthopedics, managing dozens of orthopedic clinical studies and partnering with surgeons to advance novel research approaches. He has validated expertise in leading and supporting clinical and medical affairs teams within biotechnology companies, medical centers and clinical research organizations, and has partnered with leading orthopedics companies in exploring novel technologies. Dr. Ahuja has practical knowledge of experimental and clinical research needs to support the development, commercialization and marketing of medical products and technologies. He has a long history of collaboration with physicians, surgeons, scientists/researchers, engineers, sales and marketing executives and other key advisors to identify new markets, and areas of growth and sustainability. Prior to joining Ortho, Dr. Ahuja worked at Orthofix Medical, Inc. where he was appointed to develop the clinical strategy for the motion preservation program of spine business franchise. He is also responsible to initiate and lead an IDE trial for a two-level cervical disc replacement device. Prior to Orthofix, Dr. Ahuja was the Director of Medical and Clinical Affairs for Medacta USA, Inc. At Medacta, he defined and executed a clinical affairs strategy that aligned with the market and commercial needs of company's orthopedic medical devices. He established the clinical department and developed and managed dozens of clinical trials, supporting the needs of the joint reconstruction, spine and shoulder business units. He also served as Research Administrator for the world-renowned Department of Orthopedic Surgery at Rush University Medical Center/ Midwest Orthopedics at Rush. While at Rush, Dr. Ahuja led research programs for Sports Medicine and Spine, consisting of teams responsible for FDA, NIH, and industry trials, as well as investigator-initiated research. He has extensive clinical research experience in Sports Medicine injuries and treatment products ranging from biologics, stems cells, tissues graft, devices and drugs. Dr. Ahuja holds a Master of Science in Clinical Research from Rush University Medical Center, Chicago, completed a Health Care Management Executive Certificate Program from Loyola University, Chicago, achieved his Certified Principal Investigator (CPI) certification from ACRP and received a Bachelor of Medicine and Bachelor of Surgery (MBBS) medical degree from Liaquat University of Medical & Health Sciences, Pakistan and a Bachelor of Arts – Political Science and History, University of Sindh, Pakistan. Mukesh is a member of ACRP and AAHKS and recently joined the regulatory committee of Biologic Association. He also serves as a peer reviewer for OREF research grants committee. Mukesh has contributed to several manuscripts and abstracts published in reputable journals.

RISKS

All investments contain an element of risk which reflects business uncertainty and opportunity. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are developing an undefined, new technology have a much higher level of perceived risk.

The life sciences space includes companies at both ends of the spectrum, from mega-cap pharmaceutical and device powerhouses that have dozens of established products, to small operations with a handful of employees conducting pre-clinical studies. Many of the risks faced by the large and small firms are similar; however, there are some hazards that are particular to smaller companies that have not yet established themselves or their products. The typical risks faced by companies operating in the life sciences space include risks related to liquidity, financing & trading, clinical trials, regulatory, personnel, intellectual property, marketing, and geopolitics.

Pandemic Risk

The pandemic has disrupted economic and other activity in the United States and around the globe. It has also caused significant volatility in financial markets. Economic activity worldwide has contracted and may take many quarters to reverse. While the financial markets have not declined in tandem with economic growth, risk perception may increase and financial markets may begin to reflect a lower level of economic activity and decreased availability of capital. Early stage clinical firms lacking revenues rely on capital markets to sustain development efforts and may be sensitive to changes in risk perception and trading dynamics. Ortho RTI has successfully raised funds through private placements in recent periods signaling the continued ability to fund development activities.

Ortho RTI has been at a preclinical stage of development and has largely remained undisturbed by the pandemic. However, as clinical trials for Ortho-R begin, patient recruitment and the ability for patients and physicians to meet, could be affected by social distancing and quarantine measures.

Liquidity, Financing & Trading

Access to financing comes and goes in cycles. During periods of improving confidence and plentiful liquidity, capital may be easy to obtain; however, during a crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they depend on the financial markets to fund their work. Pre-revenue biotech firms rely primarily on equity issuance to fund their operations. The duration of drug development is considerable, and can last as long as 12 to 15 years before product revenues come in the door. Funds can be sourced through debt or grants and tax credits; however, these sources may reduce the flexibility of the company and can create difficulties if debt is unable to be repaid.

If capital is not readily available when needed, a company may be forced to suspend research and development, sell equity at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising therapies without a viable route forward or force a company to accept onerous terms.

Trading volumes are lower for smaller biotech firms, creating liquidity risk for the investor and large transactions may have a material impact on share price. In periods of crisis or heightened risk perception, share price may be volatile. Companies with smaller capitalizations are typically considered riskier and changes in sentiment may adversely affect their trading prices and volumes. Smaller firms may also have less visibility, compete for investor dollars in a shallow market and be excluded from market indices.

Ortho RTI has endured operational losses since inception and is expected to continue to do so for the foreseeable future. Ortho has completed all of its preclinical work and following the near term submission of an IND, the company will begin early stage clinical trials. Several years of investment are required before Ortho-R can be commercialized.

Clinical Trials

For smaller early-stage companies, investing in product development is a lengthy process. The timeframe for conducting pre-clinical research to eventually commercializing can span many years and depends on regulatory, market and company-specific conditions. Candidates must obtain clearance to begin clinical trials and submit to trial design guided by regulatory agencies if they wish to be considered for approval. Pilot and pivotal studies are undertaken to generate data demonstrating the safety and efficacy required for approval.

Ortho RTI's candidates have completed the preclinical stage with Ortho-R preparing to enter the clinic. Following clearance of an investigational new drug (IND) application, Ortho-R will begin conducting clinical trials. It will bear risk related to enrollment, site selection, drug manufacturing, CROs and subcontractors. Several of these activities have already begun.

Due to the cost, magnitude and complexity typical of clinical trials, partners are often sought to share risk. They may have competing demands which can adversely affect the work they are managing on behalf of the firm. Contract research organizations (CROs) and subcontractors must abide by strict execution and trial parameters that, if violated, can jeopardize trial success. Subcontractors supervise and execute research, biometric and pharmacovigilance, which are complex tasks. Patient recruitment may be difficult. Clinical investigational centers need sufficient capacity and the candidate drug needs to be manufactured according to current Good Manufacturing Practices (cGMP) and available to administer. Finally, clinical endpoints need to achieve statistical significance to justify regulatory approval.

We apply a 12% probability of success for Ortho-R prior to entry into the clinic. The candidate is anticipated to begin phased trials in March 2021. Following investigational new drug (IND) clearance and enrollment of the first patient, a higher probability is appropriate. We believe that the likelihood of success for an orthobiologic candidate is greater than that of a pharmaceutical or biologic based on our review of the industry. However, there have not been similar studies conducted on orthobiologic candidates' success rates as there have been for pharmaceuticals and biologics. Other factors also support a higher likelihood of success for Ortho-R include the use of autologous PRP which can be used by itself without approval, the use of Class I devices to administer the Ortho-R and the approval of a first-generation chitosan product (BST-CarGel), which has been approved in 40 countries.

Development and Commercialization

Some biotechnology firms' have maintained relatively easy access to financing and their share prices have performed well during the pandemic, despite the economic contraction; however, many clinical trials have also been delayed and disrupted due to restrictions and reallocation of trial site resources. Biotechnology firms frequently have global aspirations and must navigate clinical trial, regulatory approval and marketing regulations in multiple geographies. Companies that have a long history of research success and experience in orthobiologics development, with opinion leaders and experts advocating for the product in the field will hold a more favorable position compared to those that do not. Mr. Leduc and Dr. Ahuja have in-depth experience in the orthobiologics space, have advanced other chitosan-based products and have led other successful clinical trials.

Regulatory and Legislative

Regulatory risk centers on a sponsor's interactions with regulatory authorities, such as the FDA and EMA, related to clinical trial requirements, marketing approval of the candidate, expedited pathways and associated oversight. Previous success with the FDA or other regulatory agencies is another attractive attribute for a sponsor. Success is uncertain and may take years depending upon the needs and desires of the determining authority. Substantial expense is undertaken to bring a product through clinical trials and address all of the regulatory agencies' concerns. Some accelerated pathways to approval are available such as those outlined in the Orphan Drug Act and the Breakthrough Therapy designation; however, changes in sentiment or perceived safety of drugs approved through these routes could influence the regulatory environment to demand a more rigorous process and the duration of the approval process may be extended or additional requirements may be put in place.

Companies with exposure to the United States' healthcare system have experienced legislative disruption with the Patient Protection and Affordable Care Act (PPACA) of 2010 and the Health Care and Education Reconciliation Act. These legislative actions impose non-deductible excise taxes on pharmaceutical manufacturers or importers that sell branded prescription drugs to government programs, which can increase drug prices as levies are passed through to consumers. Under the PPACA, some firms are required to provide a discount on branded prescription drugs equal to 50% of the government-negotiated price, for drugs provided to certain patients who fall in the Medicare coverage gap. PPACA increases the level of Medicaid rebates payable by manufacturers of brand-name drugs from 15.1% to 23.1% and requires collection of rebates for drugs paid by Medicaid managed care organizations. The PPACA also introduced changes to the 340B drug discount program that expanded the patient population with access to the drugs, though at a discounted price. Prior to the PPACA, Congress had adopted the Medicare Prescription Drug, Improvement and Modernization Act of 2003. The Act modified Medicare reimbursement and coverage policies for prescription drugs.

Personnel

Biotechnology companies rely on the expertise and leadership of their executives to make both technical and strategic decisions and investments. Due to the highly competitive nature of the industry, talented personnel are sought after and firms with the best resources are in the strongest position to attract the most effective leaders. Change in management is disruptive and can dramatically alter the course of a firm. Personnel turnover can place a small company at a disadvantage when compared to larger firms with more specialized employees and executives. Furthermore, there can be risks and challenges associated with adding talent as the firm grows in size, especially with capital constraints. The size of the firm, volatility of stock price and a large component of compensation comprised of equity-based compensation can deter certain talent from joining the firm or make it difficult to retain.

As a small firm, Ortho RTI has a limited number of personnel, all of whom play an important role. The loss of either Claude LeDuc, CEO, Luc Mainville, CFO, or Mukesh Ahuja VP Clinical and Medical Affairs would severely impact the firm.

Intellectual Property

Intellectual property is the core of biotechnology development. Even with government regulation, patent protection is not guaranteed. The patent application process requires time, capital and the disclosure of substantial detail on the company's technology which is eventually made public. Despite submission of an application, patents may not be granted. Patent protection requires legal resources that a startup biotech firm may not possess. Furthermore, jurisdictions differ in the degree and type of intellectual property protection. Some firms may in- or out-license intellectual property, which exposes parties holding the rights to risk of adherence and litigation regarding the parameters of the licensing. Finally, patent protection is temporary and there is no guarantee that the firm will benefit from the patent protection before it expires.

Market Risk

Successful marketing of approved drug candidates relies on adoption by patients and providers. The approved drug must have convincing clinical trial data and maintain a favorable reputation among prescribers. Marketing is expensive and requires an experienced sales force and a presence in the marketing area. Marketed products remain under surveillance and any unexpected adverse effects damage the product's reputation. Furthermore, the risk of a competing or superior therapy is a continuous threat. Insurance coverage is also important. Rapidly obtaining a preferred position on health plan and payor formularies is critical to achieving target penetration rates. If health plans and payors cannot agree on appropriate pricing for the drug and the compound fails to offer a significant benefit above standard of care, the product may not be available on formularies.

Geopolitical

Recent trade tensions between the US and China threaten the world economy and have been exacerbated during the ongoing pandemic. There has been a cross-pollination of capital and drug development between China and North America in recent years which may slow as a result of the trade and political dispute between the countries. This conflict may reduce the availability of capital, partnerships and future development deals between companies in the two nations. The UK seceded from the European Union in 2020, potentially creating additional difficulties for companies seeking to obtain approval and marketing rights throughout Europe. Previously, a drug approved under the centralized procedure in the European Union would be approved in all member states. However, with the withdrawal of the UK, additional efforts and expense may be required to obtain marketing approval in this large European market.

Valuation

Ortho RTI has created a combination product that may dramatically improve the success rate of orthopedic joint surgeries, including rotator cuff, meniscus and cartilage procedures. Ortho's proprietary combination of chitosan and platelet rich plasma (PRP) form a biopolymer matrix to augment and guide the regeneration of injured tissue. The product provides the characteristics necessary to adhere to soft tissues, coagulate, and increase PRP residence time, potentially improving surgical success rates and tissue repair. Ortho has development programs in place for its rotator cuff and meniscus tear repair programs and anticipates the first of these will begin enrolling clinical subjects by early 2021. We see RESTORE as a relatively low-cost mechanism to improve the success rate of joint repair surgeries with little downside due to its favorable safety profile. Penetration into the addressable market may exceed rotator cuff, meniscus and cartilage surgery failure rates as the product's use demonstrates the added potential to improve healing time and increase the likelihood of a successful operation.

We forecast unit sales of Ortho-R based on number of surgeries and an assumed penetration rate. Based on our review of available resources, we estimate approximately 460,000 rotator cuff surgeries annually in the United States,[51] 720,000 in the EU[52] and 46,000 in Canada. We assume a similar proportion of surgeries in the EU based on its population and we estimate Canadian volumes at 10% of US levels. Penetration of Ortho-R into the addressable market is estimated to be high due to the low relative cost of the treatment, the high level of failures with standard of care surgery procedures and the accelerated healing properties of Ortho-R.

For rotator cuff repair, we anticipate pivotal trial completion by 2023, submit a BLA in the US, MAA in the EU[53] and a new drug submission in Canada in 2024. Assuming approval, first sales will begin in the US in 2025. In the EU and Canada, we forecast a year long process to negotiate with government payors to determine pricing for first sales in 2026. In our model, pricing is set at USD$2,000 for Ortho-R per procedure in the United States, increasing at a rate of 3% per year. Pricing for Ortho-R in the EU and Canada is set at USD$1,000 per procedure.

Work on the meniscus tear program is forecast to trail one year behind the rotator cuff program. We see pivotal trials beginning in 2023 for a meniscus indication. A BLA, MAA and new drug submission are targeted for 2025 in the US, EU and Canada respectively. Sales for use in meniscus surgeries are expected to begin in 2026 in the US and in 2027 in the EU and Canada after a year-long period of negotiation with government payors. Pricing in all regions will match what is used in the rotator cuff indication.

Our valuation approach employs a discounted cash flow (DCF) model. Assumptions include a discount rate of 15% and a terminal growth rate of -10%. We assume that Ortho RTI will work with a partner that has an existing sales force and relationships in the orthopedic market for commercialization. In return for granting rights to the approved product, Ortho will receive upfront payments, milestones and royalties from these entities. We model a 33% royalty from product sales which includes all value from upfronts and milestones.

Penetration into addressable markets is forecast to start at 20% for rotator cuff surgeries in the first year of sales for all regions (2025 for US & 2026 for EU and Canada), followed by increases to 30% in year two, 40% in year three, 55% in year four and peak penetration of 58% in year five. After the 10th year, penetration is anticipated to decline. For Ortho-R sales in the meniscus indication, we assume first year penetration of 15% (2026 for US and 2027 for EU and Canada), rising to a peak of 53% penetration by year five, and declining after year 10. The lower peak is justified by the lower average failure rate for meniscus repair surgeries.

Operating expenses from FY:21 to FY:27 are summarized below. After FY:27[54] we apply a 3% rate of inflation in G&A costs and a decline in R&D expenditure to $1.5 million. After all current in-development products are commercialized, research and development spending falls to zero. A Canadian tax rate of 25% is appropriate after net operating loss (NOL) carryforwards are exhausted.

[51] We examined multiple sources to identify the number of rotator cuff surgeries in the US. Pearl Diver HealthCare Research (400,000 surgeries), iData Research (460,000 surgeries), Ortho RTI estimate (600,000 surgeries). Our estimate is equivalent to a prevalence of 0.14%.
[52] We include the United Kingdom in our definition of the EU which is equivalent to a total population of 514 million.
[53] We include the United Kingdom in our definition of the EU.
[54] FY:27 ends January 31, 2027

Exhibit XVI – Income Statement Forecasts FY:20 to FY:27

Ortho Regen Tech Inc.	2020 A	2021 E	2022 E	2023 E	2024 E	2025 E	2026 E	2027 E
Total Revenues ($CAD)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$47,292**	**$127,087**
Research & Development	$950	$1,160	$2,611	$4,500	$5,500	$5,200	$4,200	$1,500
General & Administrative	$995	$1,293	$1,719	$1,755	$1,854	$1,910	$1,967	$2,026
Share Based Compensation	$165	$164	$190	$200	$210	$222	$231	$240
Income from operations	($2,110)	($2,617)	($4,520)	($6,455)	($7,564)	($7,332)	$40,894	$123,321
Financing Expense	$306	$659	$360	$0	$0	$0	$0	$0
		$0	$0	$0	$0	$0	$0	$0
Pre-Tax Income	($2,416)	($3,276)	($4,880)	($6,455)	($7,564)	($7,332)	$40,894	$123,321
Provision for Income Tax	$0	$0	$0	$0	$0			
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	**($2,416)**	**($3,276)**	**($4,880)**	**($6,455)**	**($7,564)**	**($7,332)**	**$40,894**	**$123,321**
Reported EPS	**($0.10)**	**($0.12)**	**($0.13)**	**($0.11)**	**($0.12)**	**($0.10)**	**$0.51**	**$1.54**
Basic Shares Outstanding	24,752	28,245	38,841	56,675	65,200	72,400	80,000	80,000

Source: Company Filing // Zacks Investment Research, Inc. Estim

As more clarity is available regarding the development process and as candidates advance through the clinic, we will update our forecasts accordingly. Strong results from clinical trials and willingness of orthopedic surgeons to expand the use of the biopolymer into other soft tissue musculoskeletal conditions outside of rotator cuff and meniscus will have a positive impact on units sold. Based on the assumptions identified in our DCF model and after adjusting for anticipated share issuance, restricted stock and options outstanding, we generate a current valuation of CAD$1.80 per share.

CONCLUSION

Ortho Regenerative Technologies Inc. has developed a lyophilized biopolymer formulation that when combined with PRP, promises to improve the outcomes and success rates for RCT and MT repair surgery. The company's RESTORE platform features Ortho-R, a mucoadhesive, chitosan-based polymer matrix combined with PRP that aims to rebuild damaged tissue and improve surgery outcomes in multiple indications.

Ortho-R, which has been designated a device, drug and biologic, has shown the ability to help blood clot, reduce composite shrinkage and allow growth factors and cytokines to remain in contact with repaired tissue to stimulate healing. In animal models the product has demonstrated the ability to improve tendon attachment, provide a scaffold that allows nutrients to enter into the remodeled space and aid in tissue regeneration.

We expect a quick turnaround to the pilot study and completion of a Phase III trial in less than two years. Assuming success after a BLA filing, first sales can be achieved in 2025. An IND is expected to be filed before year end 2020 with clinical trials starting in early 2021.

The product is inexpensive to manufacture and easily reconstituted with autologous PRP for application *in situ*. With a high failure rate for many joint reconstructive surgeries, there is a strong incentive for orthopedic surgeons to incorporate Ortho-R in their procedures if it is able to show a material benefit in clinical trials. We estimate over one million surgeries for RCT and over 500,000 MT surgeries in Ortho's target markets of the US, EU and Canada. With penetration rates that are forecast to exceed 50% of the addressable market, Ortho-R is an attractive asset that we expect will do well in upcoming Phase I/II studies. While initial indications are focused on RCT and MT, the product may be used more broadly in other areas including cartilage, arthritis, ligaments and the nucleus pulposus among other opportunities.

Key reasons to own Ortho Regenerative Technologies shares:

- **Safe biopolymer combination product with favorable properties**
  - **Rapid coagulation**
  - **Avoids shrinkage**
  - **Adheres to soft tissues**
  - **Increase biologics residency time to augment and guide the regeneration of new tissue**
- **Demonstrated decreased tendon gap and improved bone structure in large animal RCT model**
- **No treatment-specific safety issues**
- **Sufficient capital raised to start phase I/II study in rotator cuff indication**
- **Unmet need in large markets with poor surgery success rates**
  - **About half of RCT surgeries fail**
  - **20% - 40% MT surgeries fail**
- **Chitin source material is abundant and inexpensive to procure**
- **Chitosan end product (Ortho-R) is inexpensive to manufacture**
- **Biologic product uses autologous PRP which can be sourced quickly and easily**
- **Lyophilized chitosan provides long shelf life**
- **Strong intellectual property protection in three patent families**
- **Clinical trials will include pharmacoeconomic benefit analysis**
- **Experienced management team and clinical advisory board**
- **Reputable CRO (MCRA) with orthopedics and biologics regulatory and clinical research expertise**

Ortho RTI has developed a promising product that is months away from entering the clinic. The unmet need in RCT and MT repair is clear and sizable, which should provide substantial demand following approval. We anticipate a relatively rapid development process as Ortho advances from pilot to pivotal trials, regulatory authority approval and first sales by 2025 in the United States. Our valuation work assumes addressable markets in RCT and MT in the US, EU and Canada with an anticipated 12% probability of success due to Ortho-R's preclinical status. Based upon our work, we initiate on Ortho Regenerative Technologies, Inc. with a valuation of CAD$1.80 per share.

PROJECTED FINANCIALS

Ortho Regenerative Technologies Inc. - Income Statement

Ortho Regen Tech Inc.	2020 A	Q1 A	Q2 A	Q3 E	Q4 E	2021 E	2022 E	2023 E
Total Revenues ($CAD)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
Research & Development	$950	$365	$195	$200	$400	$1,160	$2,611	$4,500
General & Administrative	$995	$507	$186	$350	$250	$1,293	$1,719	$1,755
Share Based Compensation	$165	$20	$49	$50	$45	$164	$190	$200
Income from operations	($2,110)	($892)	($430)	($600)	($695)	($2,617)	($4,520)	($6,455)
Financing Expense	$306	$168	$201	$200	$90	$659	$360	$0
						$0	$0	$0
Pre-Tax Income	($2,416)	($1,060)	($631)	($800)	($785)	($3,276)	($4,880)	($6,455)
Provision for Income Tax	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net Income	**($2,416)**	**($1,060)**	**($631)**	**($800)**	**($785)**	**($3,276)**	**($4,880)**	**($6,455)**
Reported EPS	**($0.10)**	**($0.04)**	**($0.03)**	**($0.03)**	**($0.02)**	**($0.12)**	**($0.13)**	**($0.11)**
Basic Shares Outstanding	24,752	24,752	24,779	30,250	33,200	28,245	38,841	56,675

Source: Company Filing // Zacks Investment Research, Inc. Estimates

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HISTORICAL STOCK PRICE

Ortho Regenerative Technologies Inc. (ORTH.CN) – Share Price Chart[55]



[55] Source: barchart.com

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