CHAPTER

3

SYMPOSIUM

Orthobiologics in 2025 and Beyond

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ABSTRACT

Orthobiologics are biologic substances intended to enhance healing and treat a range of musculoskeletal pathologies. Commonly well-studied orthobiologics such as platelet-rich plasma, bone marrow aspirate concentrate, and micro-fragmented adipose tissue have more than 2 decades of scientific research and clinical use, although with variable outcomes. It is important to discuss both current utilization and future applications of the aforementioned orthobiologics while elucidating some novel orthobiologics with recent regulatory approval, and finally, those orthobiologics on the horizon and beyond. Orthopaedic applications of mesenchymal stem or stromal cells, cell-based cartilage implants, and perinatal cell–derived therapies all hold promise to treat a broad range of musculoskeletal ailments. The Biologic Association and American Academy of Orthopaedic Surgeons are at the forefront of these emerging technologies, cooperating together on behalf of their membership to provide resources for the purpose of scientific discovery, clinical validation, and translation of novel orthobiologic therapies.

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Introduction

The pathogenesis of osteoarthritis is influenced by altered joint biomechanics and is also biochemically mediated through an imbalance of anabolic-catabolic molecules, leading to inflammation and a series of changes in the environment that result in articular cartilage degradation. Preclinical evidence has demonstrated the capabilities of orthobiologics to affect many of these intra-articular environment changes. Standard-of-care management options for osteoarthritis include weight loss, nonimpact activity modifications, physical therapy, and brace treatment. Such measures target the biomechanical effects that give rise to arthritis by trying to normalize the forces across the joint. In addition, pharmacologic agents (eg, acetaminophen, NSAIDs, intra-articular injections of corticosteroids, and hyaluronic acid) are also commonly used in the initial stages of osteoarthritis. The goal of these strategies is to relieve pain and improve function; however, the disease will often progress despite these nonsurgical interventions. In recent years, there has been an increased interest in biologic therapies with regenerative potential that could potentially delay disease progression. Treatments have been focused on the molecular level by acting on biochemical pathways that can lead to or block the symptoms of osteoarthritis, especially in the knee. Additional efforts have included the use of these agents for tendon repair intraoperatively and in certain painful tendinopathies.

The latest information available is summarized for the most common biologic therapies in clinical use and in research development. This information builds on the foundational knowledge of the current use of orthobiologics with consideration toward the next generation of products and procedures in the orthobiologic arena.

Background

Orthobiologics encompass a wide range of autologous and allogeneic biologic therapies used to enhance healing and treat a range of musculoskeletal pathologies. Some biologics such as platelet-rich plasma (PRP) are widely available in clinical practice, whereas others are making their way through translational clinical trials[1] (**Figure 1**).

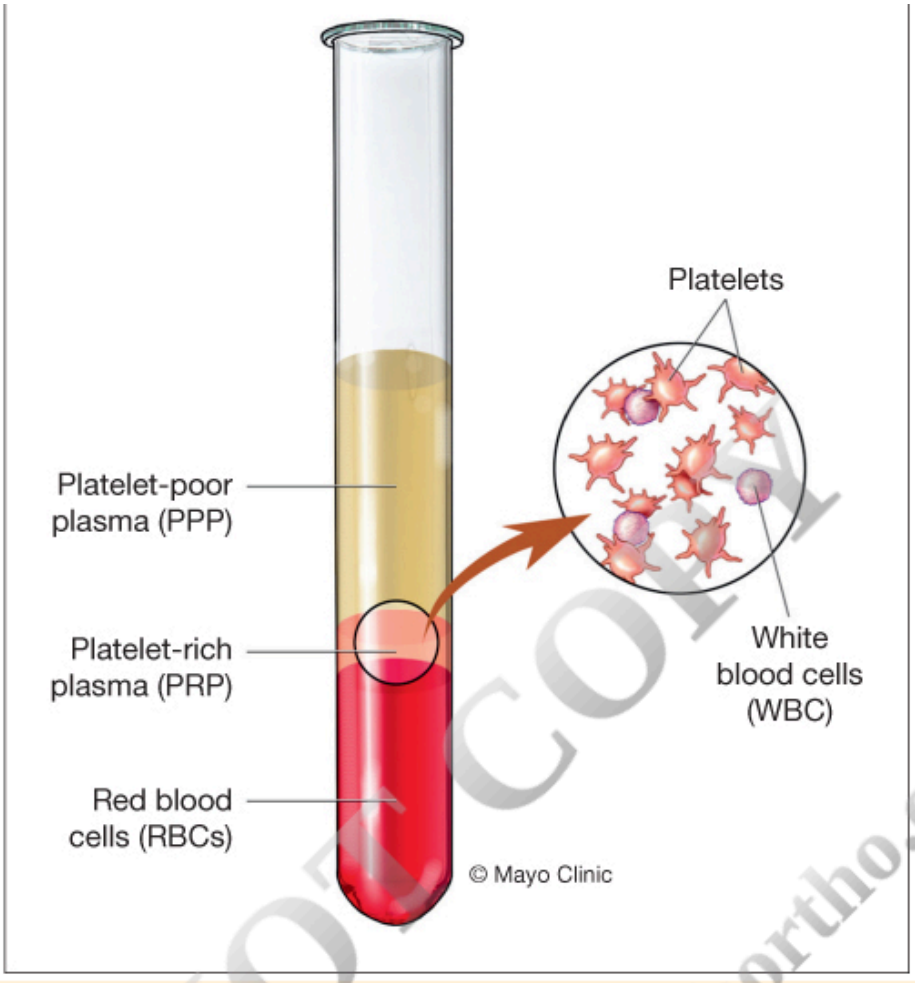


FIGURE 1 Illustration of the dual-spin technique for platelet-rich plasma manufacturing via density gradient centrifugation; this technique produces three distinct layers including a platelet-rich buffy coat layer. (Copyright Mayo Clinic.)

Orthopaedic conditions such as osteoarthritis and tendinopathy have been the most common targets of novel orthobiologic treatments. Osteoarthritis, specifically knee osteoarthritis, is a leading cause of severe long-term pain and disability affecting approximately 10% of the global population. It is particularly common in the elderly population, with symptomatic knee osteoarthritis occurring in 10% of men and 13% of women older than 60 years. However, younger individuals may also be affected by posttraumatic osteoarthritis. This number is expected to rise because of the increasing life expectancy, the obesity epidemic, and a recent increase in knee injuries and subsequent surgeries from youth sports participation.[2]

Modern Treatment of Common Conditions Using Orthobiologics

PRP has shown success in improving the symptoms of certain tendinopathies. The treatment philosophy aims to get back to a healthy homeostatic tendon. PRP is an attractive biologic strategy because it is directly and easily obtained from the patient's own blood. After the blood is drawn, it is centrifuged, resulting in separation of red blood cells, plasma volume, and a buffy coat layer, which contains platelets with increased concentrations of growth factors, cytokines, and chemokines, which all can play a role in cartilage and tendon healing (Figure 1). PRP has been heavily researched since the 1970s and has been used for the treatment of multiple orthopaedic injuries, making it an innovative therapeutic alternative that has gained the interest of the orthopaedic community.

When it comes to tendon healing, the cytokines and growth factors released from platelets play a role in this healing process through angiogenesis and chemoattraction. Recent meta-analyses have shown that PRP may serve as a reliable choice for the treatment of symptomatic tendinopathy. Current evidence supports the use of PRP for the treatment of lateral epicondylar tendinopathy, plantar fasciitis, and gluteal tendinopathy because it is related to favorable short-term and long-term clinical results. In contrast, randomized controlled trials and meta-analyses have shown mixed results with the use of PRP in isolation for other conditions such as patellar tendinopathy, rotator cuff disease, and Achilles tendinopathy.[3]

Built on the success of PRP in treating lateral epicondylitis, intra-articular PRP was then trialed for treatment of symptomatic knee osteoarthritis. Although initial small patient numbers and study heterogeneity led to equivocal findings, more than 40 randomized controlled trials have

been conducted, investigating the efficacy of treatments for knee osteoarthritis. Systematic reviews and meta-analyses support the clinical efficacy of PRP over comparators, but the variety of PRP preparations available and study heterogeneity make optimal care using PRP difficult.[4,5]

In a recent meta-analysis by Oeding et al,[6] PRP demonstrated a significant advantage over hyaluronic acid. This included better symptom relief, lower reintervention rate, and more frequent pain improvement compared with alternatives. Bansal et al attempted to define optimal dosing for PRP. Two groups of 75 patients each were randomized to receive a 10 billion platelet dose of PRP for knee osteoarthritis or hyaluronic acid injection and followed up for 1 year. There were significant improvements in the Western Ontario and McMaster Universities Osteoarthritis Index and International Knee Documentation Committee (IKDC) scores in the PRP group compared with the hyaluronic acid group at 1 year. Significant decline in interleukin (IL) 6 and tumor necrosis factor alpha levels was also noted in the PRP group compared with the hyaluronic acid group at 1 month.

PRP application has been complicated by wide variability in manufacturing systems and individual patient hematologic differences. This has led to PRP product heterogeneity and difficulty standardizing clinical trials. As a result, optimal PRP platelet dosing has received considerable attention recently.[7] Evidence is mounting via systematic reviews evaluating the optimal number of doses of PRP, as well as the effects of multiple injections over a specific period. It has been found, however, that repeating injections of PRP result in higher visual analog scale scores than single injections of PRP. In a study by Bansal et al,[8] it was found that high-platelet PRP had no statistically significant results at 1 month but did have statistically and clinically significant improvement at 3 months compared with placebo. In contrast, low platelet concentrations were not significantly different compared with placebo in showing improvement. Thus, higher doses of platelets provided superior pain relief and more durable functional improvement compared with lower concentrations, specifically when four times higher. It has been postulated that 10 billion platelets is an optimal amount to create an appropriate response and show clinically significant improvement. The authors theorized that an absolute count of 10 billion platelets in PRP preparations may lead to sustained effects up to 1 year in moderate knee osteoarthritis, and many clinicians have adopted the 10 billion platelet count as a marker of robust PRP formulation. Further study is required to validate such a proposal, but given the evidence to date, it appears that higher platelet counts will provide greater clinical efficacy when compared with lower platelet counts.

One of the more debated variables in PRP preparation is the presence of leukocytes in the injectate. Some techniques, in an effort to capture as many platelets as possible, allow for more leukocytes at the same time, and this is referred to as leukocyte-rich PRP. This is especially common in tendinopathies.[9-11] Other formulations seek to exclude leukocytes, especially in use for osteoarthritis, out of concern for a more inflammatory response because of the placement of leukocytes in the joint. Although some investigations would support leukocyte-poor PRP for intra-articular use when treating knee osteoarthritis, the most recent trials suggest no significant differences between leukocyte-rich and leukocyte-poor PRP preparations with respect to patient-reported outcomes in knee arthritis.[8]

PRP is increasingly being combined with hyaluronic acid to take advantage of each product's distinct therapeutic effect and to modify the intra-articular environment via more than one therapeutic mechanism. Several studies to date point to the possibility of a synergistic effect between PRP and hyaluronic acid preparations for knee arthritis.[12,13] Such strategies are now being investigated for the hip as well. In a meta-analysis of 16 randomized controlled trials with a total of 1,735 participants with hip arthritis, steroid injection was found to be significantly more effective than placebo injection on reported pain at 3 months, but no significant difference was observed at 6 months. Furthermore, steroid injection was considerably more effective than placebo injection for functional outcomes at 3 months, whereas the combination of hyaluronic acid and PRP injection was substantially more effective at 6 months.[14]

Bone Marrow Therapies

Bone marrow aspirate concentrate (BMAC) has been trialed and used as a therapeutic option for knee osteoarthritis. It is produced via density gradient centrifugation of autologous bone marrow aspirate concentrates and proposed as a source of progenitor cell therapy with initial use for bony nonunions followed by successful application in osteonecrosis.[15] Intra-articular injections of BMAC have been used to treat knee pain from osteoarthritis, but clinical trial outcomes have not been as robust as those from PRP clinical trials.[5,16-18] Additional utilization of BMAC as a surgical adjunct for rotator cuff repairs shows promise in early applications as well.[19,20] Despite early clinical trial heterogeneity, BMAC does appear to be a biologically active therapeutic option with the potential to modify orthopaedic disease through cytokine and paracrine mechanisms even if true tissue regeneration remains elusive.[21] As a result, the therapeutic mechanisms of action are being continually investigated, and debate exists regarding optimal formulations and dosing, as is similar in PRP product development. In addition, the procedure appears safe with very few reports of adverse events.[22,23] Some product developers have advocated for techniques to optimize bone marrow harvest and progenitor yield with the potential to forgo

concentration altogether. Despite claims, however, no robust clinical trial comparisons between BMAC and bone marrow aspirate for orthopaedic conditions exist.[24]

Bone marrow edema (BME) syndrome is a common source of knee joint pain in degenerative joint disease. Often termed bone marrow lesions, these MRI findings are not true lesions but represent subchondral insufficiency and are associated with meniscus tears, articular cartilage loss, and subchondral disruption.[25] Subchondral bone cysts and sclerosis will often pair with BME on MRI (**Figure 2**). Although off-the-shelf options for the treatment of BME syndrome exist in the form of subchondroplasty, given high levels of pain and high likelihood of rapid knee osteoarthritis progression in BME syndrome, efforts to restore the integrity of the subchondral bone have shifted to biologic solutions. BMAC can be used in treatment in these efforts.[26] A published case series of 20 patients treated with BMAC and demineralized bone matrix injection for BME syndrome found a dramatic reduction in visual analog scale scores and functional improvement in IKDC scores at 14.5 months of follow-up. BME improved on MRI as well.

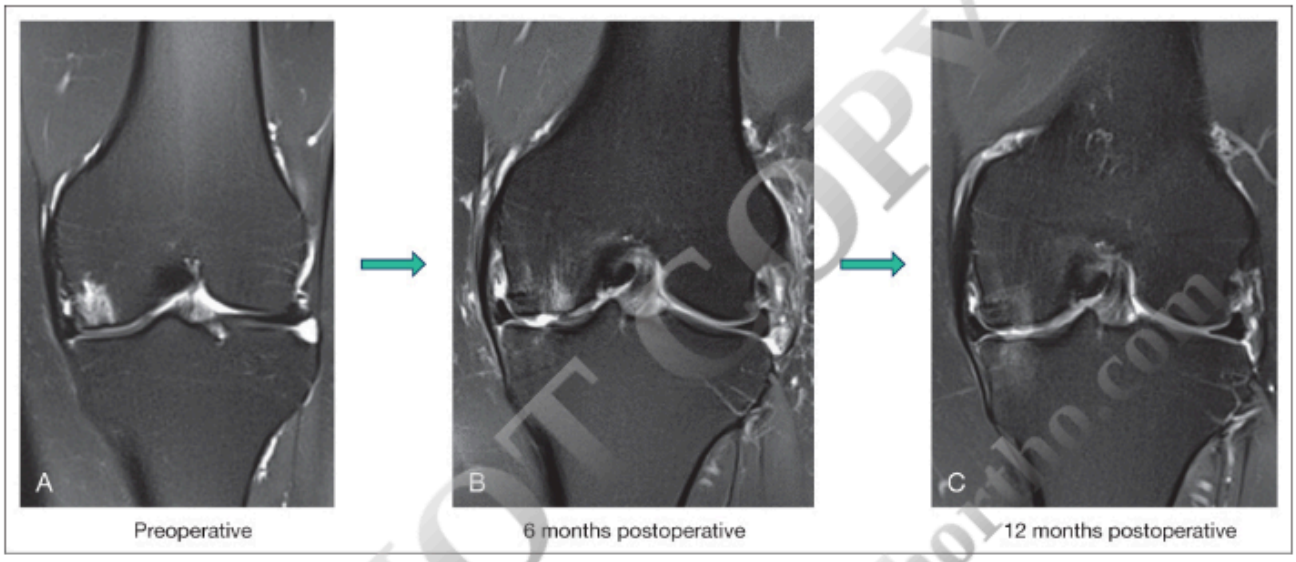
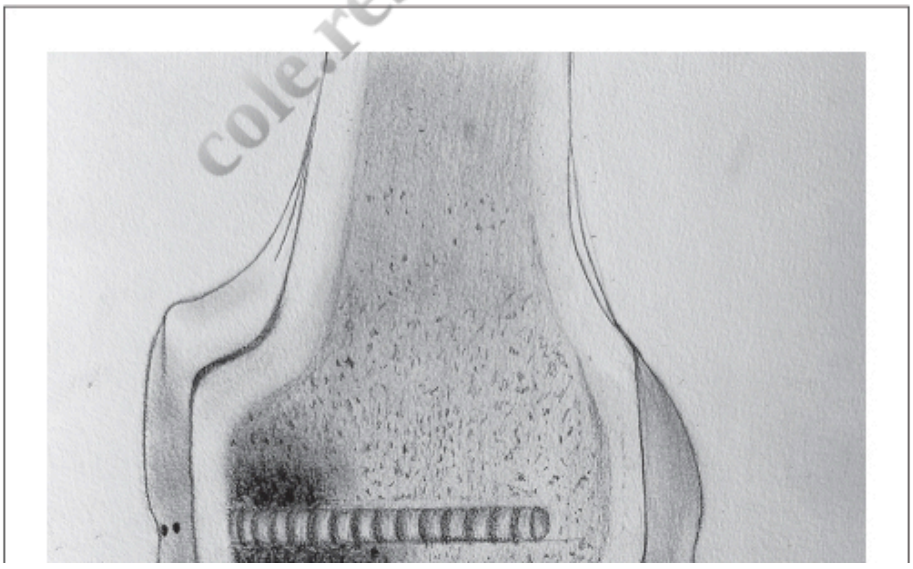


FIGURE 2 **A** through **C**, Magnetic resonance images showing 1-year progression after biointegrative nail raftering procedure.

Another emergent option is the utilization of a biointegrative fixation screw to repair bone stress, in which a rafter screw is leveraged using a 4-mm resorbable rigid nail to provide stability and promote a biologic healing response as the fixation undergoes biointegration and replacement by bone. The rafter screw is specifically designed with a pH that is balanced for optimal bone healing and made with continuous reinforcing fibers of osteoconductive minerals and poly(L-lactide-co-D-lactide) along with channels of interconnected pores that allow for flow of healing factors and clearance of degradation by-products (**Figure 3**).



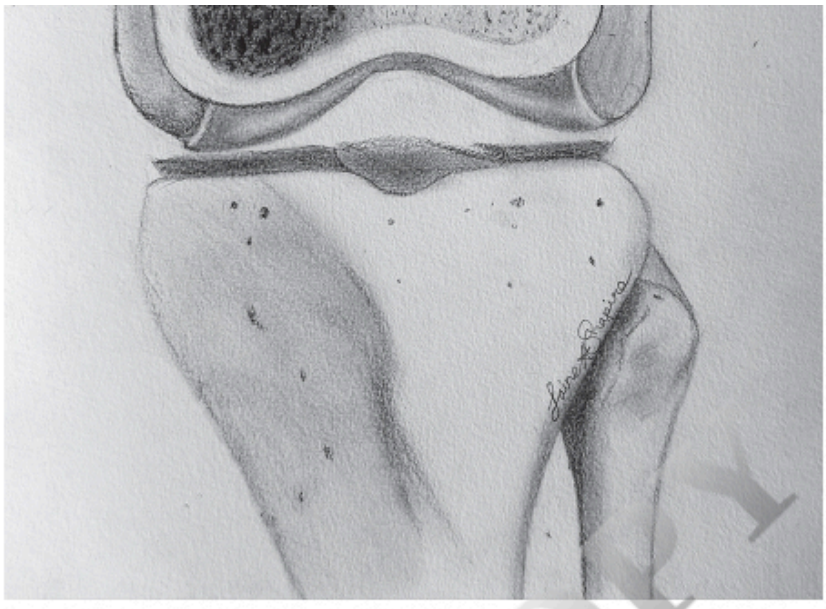


FIGURE 3 Representative illustration of a trimmable biointegrative fixation screw to repair bone stress in the medial femoral condyle to provide stability and promote a biologic healing response as the fixation undergoes biointegration and replacement by bone. (Courtesy of Laine Shapiro.)

In a case series using this surgical technique, nine patients with Kellgren-Lawrence grade 2 to 3 knee osteoarthritis and pain with BME lasting 6 months or longer on preoperative MRI underwent stabilization of the BME region, with improvements in pain and function as measured by IKDC score, Knee Injury and Osteoarthritis Outcome Score, Patient-Reported Outcomes Measurement Information System (PROMIS) Pain score, and PROMIS Physical Function score at 12 months and all patients meeting minimal clinically important difference for those patient-reported outcome measures[26] (Figure 2).

Adipose Therapies

Microfragmented adipose tissue (MFAT) prepared from autologous lipoaspirates and processed through commercially available 510(k) cleared kits serves as a biologically rich and viscous product that has been applied to both joint and tendon pathologies. The biologic premise of MFAT is the harvest of adipose tissue rich in progenitor cells and growth factors. The raw lipoaspirates are rinsed, washed, and sized in a regulatory-compliant manner. Numerous in vitro and preclinical trials support its biologic activity, and several clinical trials have been conducted to date. In knee osteoarthritis research, MFAT has been trialed in comparison with PRP injections.[27] In one such study, MFAT was clinically effective in the treatment of knee osteoarthritis, but no differences were found between the two injection groups in either clinical outcomes or radiographic and MRI

findings after the injection.[28] The authors did suggest a superiority of MFAT over PRP in IKDC outcomes in patients with the most severe arthritis. Baria et al[29] also found comparative efficacy between MFAT and PRP, suggesting a biologically active and efficacious intra-articular cell product, but with no ability to recommend one orthobiologic injection over the other. MFAT may have a role beyond osteoarthritis as well. In 2022, Randelli et al[30] demonstrated in a prospective randomized controlled trial that the augmentation of arthroscopic rotator cuff repair was safe and improved short-term functional results after single-row arthroscopic rotator cuff repair. Further study of how MFAT can be used in rotator cuff disease is warranted.

Stromal vascular fraction represents an additional option to harness the cellular capabilities of adipose tissue. Manufactured from lipoaspirates similar to MFAT, the adipose tissue undergoes additional processing with a collagenase enzyme allowing for the separation of the cellular fraction from the adipocytes. This digestion process yields an available mesenchymal stem and stromal cell percentage of 2% to 5% of total mononuclear cells while constituting an overall heterogeneous population of cells and growth factors in a more liquid form similar to BMAC. Manufacturers of stromal vascular fraction–producing devices are working their way through the regulatory approval process, with the promise of clinical and surgical availability of stromal vascular fraction on the horizon.[31]

Next-Generation Therapies

Hemoderivatives (PRP and alpha-2-macroglobulin [A2M]): Given the success of intra-articular PRP injections, the potential to harness other nonplatelet biologic capabilities of blood has been proposed. Other hemoderivatives include options such as platelet-rich fibrin matrix, autologous conditioned plasma, autologous conditioned serum, autologous protein solution, and A2M. Each of these options aims to harness circulating bioavailable factors within blood that can be activated or manipulated in a therapeutically advantageous manner. Based on the cartilage damage and increased inflammatory enzymes characteristics of osteoarthritis, A2M, a protease inhibitor that binds to and inhibits the inflammatory IL-1β, has been theorized to improve the symptoms of knee arthritis as a stand-alone injectable or used alongside PRP[32] (**Figure 4**).

FIGURE 4 Photograph showing that after platelet-rich plasma manufacturing, the platelet-poor plasma can be filtered to produce an additional biologically active therapeutic product rich in proteins such as alpha-2-macroglobulin. (Copyright Mayo Clinic.)

Devices to concentrate A2M from the platelet-poor plasma, typically considered a waste by-product from PRP centrifugation, are commercially available, but few prospective trials have been conducted. In trials to date, A2M has demonstrated efficacy but not necessarily superiority over other injectables for knee arthritis pain.[33] In addition, efforts are being made to reduce the pore size of the filters that have been used to capture A2M and possibly concentrate other valuable proteins such as IL1-RAP, which is a potent inhibitor of IL-1β prevalent in osteoarthritis synovial fluid. Such efforts seek to harness the therapeutic potential of blood beyond the effect of just PRP.

Hemocytometers have been advocated as a potential tool to deliver higher-quality PRP. Because of individual patient hematologic characteristics and the heterogeneity of PRP centrifuge devices, calls for standardization accompany the need

hematologic characteristics and the heterogeneity of PRP centrifuge devices, calls for standardization accompany the need to count platelet doses and concentration in the PRP products that are being delivered to patients. Several commercially available hemocytometers are already being used in clinical practice and longitudinal studies of PRP characteristics.[34]

Repurposing Current Biologic Drugs to Treat Tendinopathy

Another emerging biologic approach to tendinopathy aims to use immune checkpoint inhibitors commonly used in inflammatory arthropathies. The cytokine IL-17A mediates inflammatory and tissue remodeling events in early human tendinopathy. IL-17A is expressed in biopsies of human tendon with early tendinopathy and functions to remodel the extracellular matrix, also demonstrated to play a role in tenocyte apoptosis and type III collagen production. As a result, the IL-17 pathway may serve as a potential targetable intracellular signaling pathway that could have functional consequences.[35] Secukinumab is a human monoclonal antibody that acts via inhibition of IL-17 and has demonstrated efficacy in treating patients with psoriatic arthritis and other inflammatory arthritides. It has been demonstrated that secukinumab rapidly and significantly decreased synovitis in patients with psoriatic arthritis along with improved entheseal pain when compared head-to-head with other disease-modifying antirheumatic drugs, which has led to proposals for use in noninflammatory arthritis.[36]

Next Generation of Cartilage Regeneration Technology

A novel treatment of cartilage restoration includes Agili-C, which consists of a porous biphasic scaffold sourced from aragonite, which is an inorganic calcium carbonate purified from coral exoskeleton that has been approved for use in both Europe and the United States since 2022. This serves as a stable off-the-shelf option to implant for chondral and osteochondral lesions. The design allows for incorporation of bone marrow, progenitor cells, and chondrocytes. Additional advantages include its structural similarity to bone with osteoinductive and osteogenic properties. It is fully biocompatible and bioabsorbable. Early preclinical models using Agili-C in a cartilage explant model demonstrated the ability of chondrocytes to migrate outside cadaver cartilage and into the Agili-C scaffold with newly formed extracellular matrix enriched with type II collagen and aggrecan, while lacking type I collagen, indicative of hyaline cartilage. In clinical trials, the aragonite scaffolds demonstrated efficacy not only for osteochondral lesions but also in the context of mild to moderate knee osteoarthritis (Kellgren-Lawrence grades 0-3). In phased clinical trials, implantation of the scaffold led to both clinical and radiologic improvements over time over standard microfracture and débridement.[37]

Although Agili-C implantation is performed as an arthrotomy, progress in the utilization of juvenile cartilage allograft makes use of a commercially available tissue graft with characteristics that differ from those of adult cells and can be used as an arthroscopic graft. Juvenile chondrocytes, which are much more immature cells, have demonstrated the ability to modify adult chondrocytes in coculture experiments, suggesting that paracrine factors secreted from the young chondrocytes may have a therapeutic benefit. Juvenile chondrocytes have shown favorable attributes for cartilage repair with upregulation of genes that promote direct cartilage growth and expansion, as well as increased collagen and proteoglycan production, rates of proliferation, and cell density. With the juvenile cartilage graft applied arthroscopically to cartilage defects with fibrin glue, midterm follow-up studies show substantial cartilage improvements.[38]

REcycled CartiLage Auto/Allo IMplantation (RECLAIM) is hybrid technology that uses minced chondrons harvested from patient osteochondral defects and mixes them at the point of care with allogeneic culture-expanded mesenchymal stem and stromal cells. The cell mixture is then applied to the osteochondral defect with fibrin glue in a single-stage surgery (**Figure 5**). Midterm results to date have demonstrated the safety and efficacy of the RECLAIM procedure, and biopsies performed during second-look arthroscopies demonstrate hyaline-like cartilage, with isolated cells demonstrating higher strength than the analyzed original cartilage from the defect. An additional finding includes only patient DNA found in the regenerated cartilage, with absence of DNA from the allogeneic cell line used.[39] Given the promise and early results of the technology, RECLAIM has been awarded a Regenerative Medicine Advanced Therapy designation by the FDA with the benefit of streamlined pathways to clinical application and market, while clinical trials are underway for similar applications to treat lesions of the hip, making it the first human cell therapy applicable to the hip (**Figure 6**).

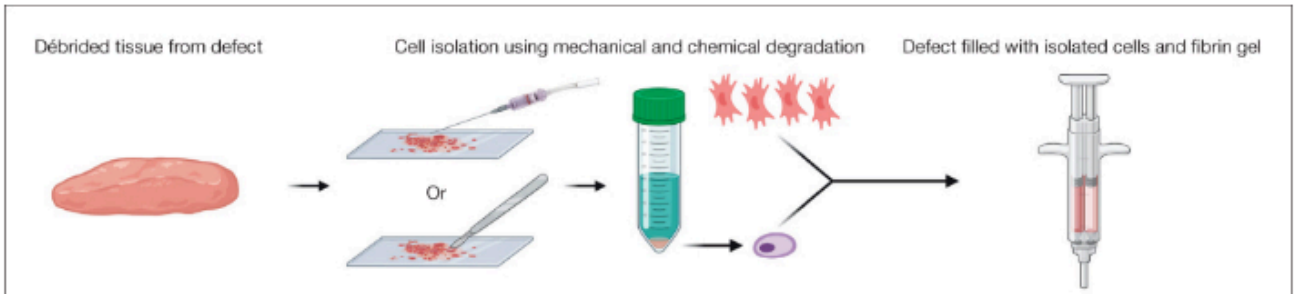


FIGURE 5 Illustration of the RECLAIM manufacturing and surgical procedure. (Copyright Mayo Clinic.)

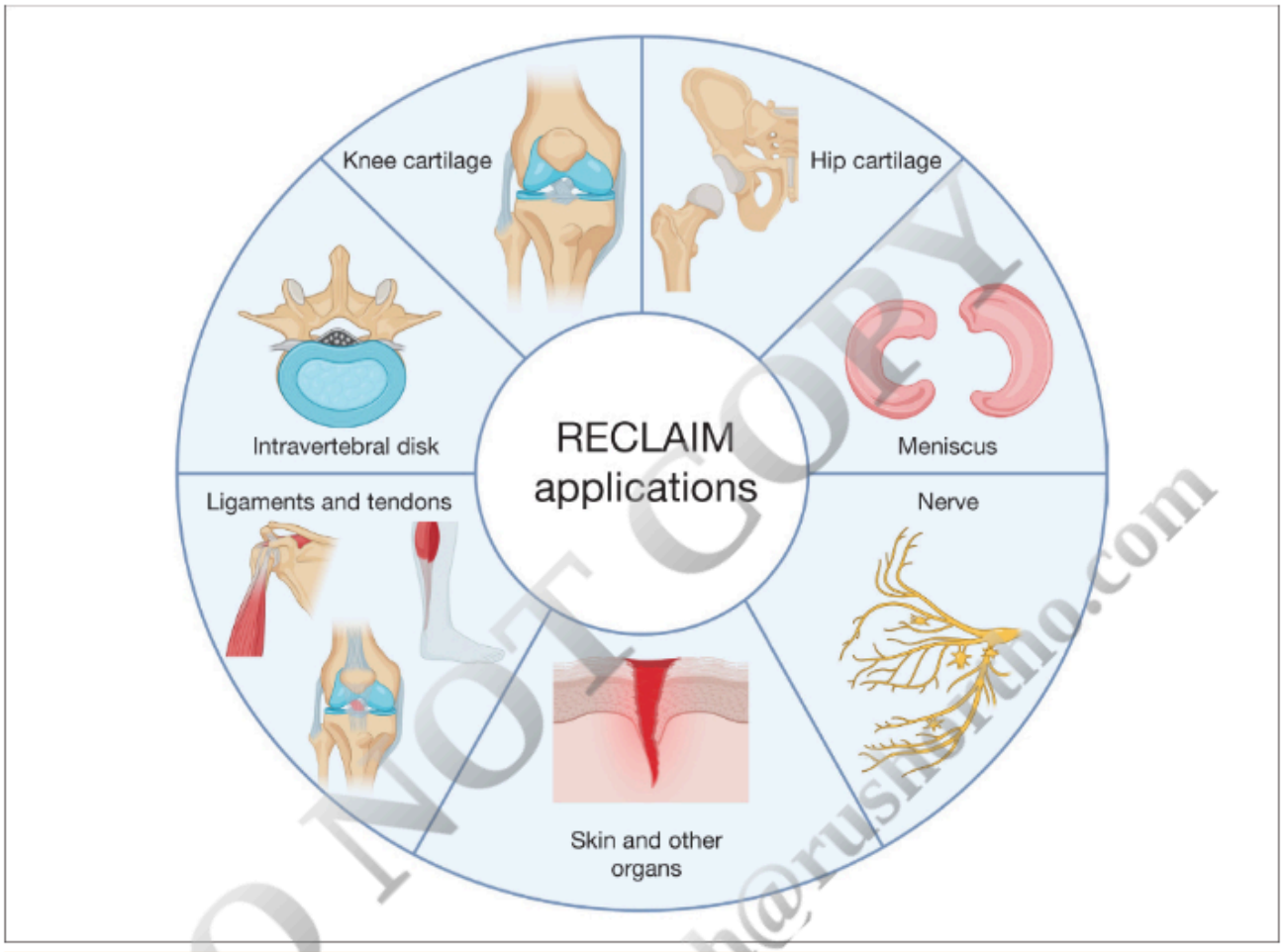


FIGURE 6 Illustration of additional use cases for the RECLAIM cartilage regeneration platform.

Cartistem is a pure mesenchymal stem cell therapy that uses allogeneic human umbilical cord blood–derived mesenchymal stem cells to regenerate cartilage in the knee. First approved in South Korea in 2012, caristem represents the first allogeneic stem cell product approved in the world. In a phase I/IIa clinical trial, investigators demonstrated evidence of durable cartilage regeneration along with clinical improvement, whereas no significant adverse events were observed over 7 years of followup. Several thousand patients have been treated in Asia, with plans for an ongoing phase III trial in the United States, which would allow for the pursuit of a Biologics License Application by the FDA to authorize its use in the United States.[40]

Perinatal Tissue Products

Perinatal orthobiologics are birth tissue–associated biologics that have been proposed for the treatment of orthopaedic pathologies. Broadly, these are allogeneic therapeutics sourced from tissues of healthy individuals during labor and delivery. Such perinatal products have been proposed as treatments of arthritis and tendinitis, with the advantage that they are easier to source and preserve than patients' own bone marrow or adipose tissue and therefore can be a source of growth factors and/or stem cells that are more readily available. Additional advantages include the capability for easier preservation and shelf stability. Multiple perinatal tissues such as umbilical cord blood, amniotic tissues, and Wharton jelly were in use in clinical practice before an FDA regulatory clarification in June 2021 stating that such products require FDA licensure or approval to be marketed to patients. Requisite clinical trials are currently ongoing for a number of perinatal products to treat orthopaedic conditions, with a few manufacturers of such products receiving Regenerative Medicine Advanced Therapy designation for hopeful accelerated review.[41]

Peripheral blood stem cells: Arthroscopic techniques augmented with peripheral blood stem cells with the goal of cartilage restoration show great promise in early clinical trials. Filgrastin causes stem cells from the bone marrow to be released into the peripheral circulation, where they are then collected via apheresis similar to bone marrow transplantation. Cells are then collected and stored in a Current Good Manufacturing Practices facility, where the advantage is they can be dosed on multiple occasions rather than within the same surgical procedure alone. The novel KART technique includes an arthroscopic technique that starts with drilling of the cartilage lesion followed by five serial peripheral blood stem cell injections at weekly intervals after arthroscopy during the cartilage maturation phase followed by booster injections at 6, 12, and 18 months. The theory behind the use of peripheral blood stem cells is to mimic the body's natural response to injury, which involves the recruitment of stem cells into the circulation and chemokines, which attract them to sites of injury. The procedure is now in phase III trial.[42]

Extracellular Vesicles and Exosomes

Exosomes represent a potent biologic therapeutic potential. True exosomes represent just one classification of extracellular vesicles as defined by the International Society for Extraceullar Vesicles, ISEV size 50 to 150 nm. Extracellular vesicles are signaling molecules (acellular) and nonimmunogenic, and thus represent opportunities to target different pathways within the musculoskeletal system to promote orthopaedic healing. Extracellular vesicles have classically been collected from multiple tissues via ultracentrifugation, but recent advancements in tangential flow filtration technology have improved extracellular vesicle capture in a more efficient manner.[43] Such purified extracellular vesicles have been tested in multiple subspecialty disease models, proving beneficial as anti-inflammatory agents, promoting increased chondrocyte migration, proliferation differentiation, and matrix synthesis, and reducing chondrocyte senescence, and may even have the potential to carry small molecule drugs to their target. Extracellular vesicles can be stored for shelf-stable use (sucrose), and several clinical trials are ongoing for orthopaedic indications.

AAOS and Biologic Association Collaborations

AAOS Biologics Platform: Orthobiologics currently used in clinical practice including PRP and other hemoderivatives BMAC, and MFAT all are procedures typically performed with devices that have FDA 510(k) approval, and these procedures are regulated as part of the practice of medicine.[44,45] Fat transfers, as performed in the MFAT procedure, adhere to the FDA's same surgical procedure exception.[46] Next-generation orthobiologics on the horizon will likely require greater oversight with premarket authorization in the form of a biologics license application from the FDA.

The AAOS recognizes the challenges of staying up to date in the rapidly changing landscape of orthobiologics and has created a searchable Biologics Dashboard where clinicians can search by either the type of biologic or the product name to learn more about the product and procedure and determine what constitutes a particular product and whether it has been approved for use in the United States.[467]

Additional physician resources are offered by the Biologic Association. The Biologic Association was founded by members of multiple orthopaedic professional societies with a mission to foster and convene a collaboration for shared and coordinated efforts, speak with a unified voice in the

musculoskeletal biologics environment, advocate for the responsible use of biologics in clinical practice, lead standard development, and assess and report on the safety and efficacy of biologic interventions. In addition to the Biologic Association's patient advocacy and regulatory advocacy efforts, its website includes searchable academic presentation videos. The Biologic Association has hosted annual academic summits, authored consensus articles,[34,44,48,49] and worked with AAOS on symposia and academic meetings in 2022, 2023, 2024, and 2025. The Biologic Association Registry and Biorepository is a longitudinal multicenter study of biologics for knee arthritis that includes seven academic medical centers collecting and storing patient samples of orthobiologic products, with more than 600 samples collected to date.

Additional efforts to advance the science and efficacy of orthobiologics may include ongoing efforts in the AAOS Registry Program to add a biologics registry to the academy's suite of already successful registry programs to support membership in this emergent field.

Summary

Orthobiologic science continues to provide promising options for common musculoskeletal ailments. Well-studied orthobiologics commonly used in daily practice provide patients with an expanding array of options for common musculoskeletal ailments, whereas next-generation biologic therapies aim to extend the slate of clinical offerings in 2025 and beyond. The Biologic Association and AAOS work together to provide resources for the purpose of scientific discovery, clinical validation, and translation of novel orthobiologic therapies.

Key Takeaway Points

- PRP, the most frequently used orthobiologic, is commonly used in daily orthopaedic practice to treat joint pain from arthritis and certain tendinopathies.
- Modern improvements to PRP and other hemoderivative biologics aim to build on the clinical application and provide more orthobiologic options to treat orthopaedic disease.
- BMAC and MFAT add to the potential applications of patients' own cellular options from bone marrow and adipose tissue for the treatment of certain expanding musculoskeletal conditions.
- On the horizon are more sophisticated cellular and cellular-derived orthobiologic options that harness the power of mesenchymal stem cells and exosomes through appropriate regulatory pathways for approval.

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