Orthobiologics in the Foot and Ankle

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KEYWORDS

• Cartilage particulate • Micronized bone • Osteoprogenitor stem cells • Amnion

KEY POINTS

- Many allogeneic biologic materials, by themselves or in combination with cells or cell products, may be transformative in healing or regeneration of musculoskeletal bone and soft tissues.
- By reconfiguring the size, shape, and methods of tissue preparation to improve deliverability and storage, unique iterations of traditional tissue scaffolds have emerged.
- This improvement, combined with new cell technologies, has shaped an exciting platform of regenerative products that are effective and provide a bridge to newer and better methods of providing care for orthopedic foot and ankle patients.

INTRODUCTION

Biologic materials play an important and increasing role in musculoskeletal repair and regeneration in general; this is especially true in the foot and ankle. Advances in stem cell recovery, isolation, and processing combined with autogeneic, allogeneic, and synthetic scaffolds present new and exciting opportunities to address challenging clinical problems like full-thickness cartilage defects, segmental bone loss, pseudoarthroses, and delayed wound healing.

This review focuses on select cartilage, bone and soft tissue repair, and regeneration strategies. Many recent developments and commercial products, although encouraging, lack sufficient basic scientific foundation and adequate clinical outcome data. The strengths and limitations of the techniques and products are discussed, and representative commercial products are compared.

CARTILAGE

A significant number of techniques are coupled with biologic materials for full-thickness cartilage defects.[1] Successful outcomes are reported with microfracture

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alone, but many of the defects, on reinspection, are incompletely healed,[2] and the resulting fibrocartilage lacks the biomechanical properties to satisfy the demands of joint function.[3,4] Although some, using T2 mapping to assess repair cartilage after microfracture, report good results along with improved functional scores,[5] short and intermediate magnetic resonance studies by others observe the resulting cartilage to be inferior to the adjacent normal cartilage.[6] Other biologic techniques include autogeneic cartilage transfer (mosaicplasty), allogeneic cartilage transfer (fresh and cryopreserved), and autologous chondrocyte transplantation.

Cartilage Graft

Mosaicplasty is a consideration for small and intermediate-size defects but is limited and complicated by donor site availability. The reconstruction is hardly congruent but remodels over time resulting in good short-term and intermediate-term results.

Structural cartilage allografts for intermediate and large defects involve both fresh and cryopreserved tissues. Cryopreserved grafts heal well and in the short and intermediate term produce acceptable functional results. Ultimately, however, they fail because the chondrocytes do not survive. Chondrocyte damage is thought to occur during the slow rate freezing process. The theory behind slow rate freezing with a cryopreservative is to limit the amount of heat released from the cell that ultimately results in crystallization and cell damage. Although techniques exist to reduce the rate of cell freezing down to $-150^{\circ}C$ in an attempt to limit the rate of cellular heat release, they do not eliminate the phenomenon and subsequent crystallization. Most isolated cells treated in this fashion survive thawing and appear to grow normally in culture. These chondrocytes in tissue, however, do not sustain normal cell function over time, and arthrosis supervenes.[7] Other factors may contribute to cell demise, such as selection of cryopreservation alternatives, surgical technique, joint congruity, the relative health of the seemingly normal adjacent cartilage, and the underlying subchondral bone.

Alternatively, fresh grafts represent the gold standard of cartilage repair and can produce excellent long-term results in select individuals. The primary limitation of this technique is graft availability and variability in processing techniques, principally, the time interval between recovery and transplantation. Chondrocyte viability decreases significantly after 21 days in primary culture based on ex vivo and reimplantation studies.[8]

Recent investigations using particulate cartilage as a structural and potentially inductive matrix after microfracture show promising results in preclinical and early clinical studies.

Cellular Therapy for Cartilage Regeneration

Cellular therapies for cartilage regeneration are not new. Autologous cartilage cell therapy (Carticel) is a long-standing commercial product. This technique requires recovery of cells from the joint, ex vivo growth and expansion, and reintroduction into the cartilage defect. Some investigators advocate this technique for patients who do not respond to microfracture for osteochondral defects in the talus.[9] Early results were encouraging, but the fundamental lack of an associated matrix on which the cells grow in vivo may be a limitation to this strategy. Stem cell therapies with or without a matrix have not been adequately studied to comment on their efficacy.

Particulate Cartilage Allografts

In the foot and ankle, particulate cartilage allografts are attractive for small and intermediate-size osteochondral defects. These allografts can be introduced arthroscopically, produce hyalinelike cartilage matrix, appear to remodel over time, and

have shown good and excellent short-term outcomes.[10] Relative to fresh and cryopreserved allografts and autologous cellular strategies, they are also relatively inexpensive.[11]

The biological basis is substantiated in several studies. The observation of a hyalinelike material forming in large full-thickness osteochondral defects in nonhuman primates set the stage for further investigation of this material.[10] In an in vitro study by Cheng and colleagues,[11] incubation of adipose stem cells with a lyophilized cartilage particle resulted in substantial upregulation of type II collagen, and the resulting cellular morphology and matrix was reminiscent of that observed in hyalinelike articular cartilage. In the same study, defects were made in the medial femoral condyles of rabbits (full-thickness cartilage defects). In comparing the control full-thickness cartilage defect with defects filled with particulate cartilage, there were striking histologic differences. In the control, there was a thin layer of predominately fibrous tissue in the defect (fibrocartilage) versus robust chondrocytes in an abundant matrix that was similar to adjacent normal hyaline cartilage in the treatment group. In addition, there was persistent upregulation of cartilage phenotypic markers, collagen IIa, and aggrecan.[12]

In anecdotal, unpublished reports, particulate cartilage was used in treating damaged cartilage in the first metatarsal phalangeal joint after cheilectomy. A clinically important site of particulate transplantation is the talus, wherein select patients with contained and small osteochondral defects treated with cartilage particles can obtain early and sustained symptomatic relief of pain and exhibit hyalinelike cartilage matrix.

In one study, smaller pore sizes used in synthetic scaffolds seemed to influence stem cell differentiation toward chondrocytes.[13] This finding may be the basis of improved chondrogenesis after microfracture and the use of micronized particles of allogeneic cartilage in nonhuman primates. Similar to experimental and clinical observations in bone, the juxtaposition of small particles seems to create a microporous structure that may influence stem cell differentiation and migration. Magnetic resonance studies, specifically proton sequences, of patient's knees after particulate cartilage repair have found inhomogeneity and slightly lower signal than normal cartilage. Also observed was decreased inflammation in the surrounding subchondral bone and remodeling of the tidemark line (T Subawong, MR imaging of BioCartilage augmented microfracture surgery utilizing 2D MOCART and KOOS scores, unpublished data, 2015).

Experimental models using cells and growth factors (transforming growth factor–β) showed substantial upregulation of proteoglycan production when compared with use of the particulate matrix alone[10] (**Table 1**).

BONE

Historically, structural and particulate bone allografts were used for closed and open segment defects. Structural autograft and allograft bone have been the mainstay for segmental defects in bone. In the foot and ankle, they serve as structural support and inductive scaffolds for bone replacement in procedures such as metatarsal phalangeal fusion after failed hemijoint implants with significant shortening, osteotomy wedges for midfoot alignment corrections, hindfoot procedures to correct alignment and height, and for segmental metatarsal defects after tumor resection and trauma.

For closed-segment defects, there are several options, both biologic and synthetic. Biologic options include both autograft and allograft bone. In the foot and ankle, autograft bone is typically recovered from the distal tibia or iliac crest depending on the size of the defect and the surgeon's preference. Autograft bone is alleged to be the gold standard of grafting material but has significant limitations, which include donor

Table 1
Overview of commercial stem cell products

Name, Distributor	Description	Processor	Cell Origin	Cell Counts	Indications	Delivery	OC/OI/OG
Via Graft and Via Form, Vivex/ UMTB Biomedical, Inc	Combination product with vial of cryopreserved viable cells, bone gel, and particulate blend packaged separately to be combined at back table	UMTB	Bone marrow of vertebral bodies	At least 150,000 cells/ mL, supra physiologic levels of OPCs and MIAMI cells	Bone void filler	Cryopreserved; bone gel jar, particulate bone jar and cell vial, DMSO free	OC, OI potential, OG
Map3, RTI	Combination product with vial of cryopreserved viable cells and bone chips packaged separately to be combined at back table	RTI Biologics	?	?	?	Cryopreserved; bone chips in plastic vial, cells in vial	OC, OI potential, OG
Trinity Evolution Orthofix	Cancellous bone matrix, demineralized cortical bone, viable MSCs and OPCs.	MTF	Bone	Guaranteed a minimum of 250,000 cells/mL, of which at least 50,000 are MSCs and/or OPCs	Allograft intended for the treatment of musculoskeletal defects	Cryopreserved; bone chips delivered in a plastic vial with DMSO	Yes
Trinity Elite, Orthofix	Third-generation moldable allograft with viable cells	MTF	Bone	Guaranteed a minimum of 500,000 cells/mL, of which at least 100,000 are MSCs and/or OPCs	Allograft intended for the treatment of musculoskeletal defects	Cryopreserved; bone chips delivered in a plastic vial with DMSO	Yes

Osteocel Plus, Nuvasive	Cancellous bone matrix, demineralized cortical bone, viable MSCs and OPCs	AlloSource or LifeLink	Bone	Confirm a minimum of 250,000 cells/mL (including MSCs and OPCs) or 50,000/mL, conflicting literature	This product is restricted to homologous use for the repair, replacement or reconstruction of musculoskeletal defects	Cryopreserved; bone chips delivered in a plastic vial with DMSO	Yes
Biomet Cellentra, VCBM	Viable Cell Bone Matrix; Viable osteogenic cells, demineralized component, and a cancellous bone matrix	Tissue Bank International	Bone	250,000 cells/mL including MSCs, OPCs and preosteoblasts	Intended for homologous use in the repair, replacement, reconstruction, or supplementation of the recipient's tissue in musculoskeletal defects	Cryopreserved; bone chips delivered in a plastic vial with DMSO	Yes
Allostem, Allosource	Adipose (fat) derived MSCs seeded on partially demineralized 3-dimensional cancellous bone scaffold	AlloSource	Adipose (fat) tissue	Testing showed consistent, viable cell numbers between 66,255 cells/ mL $\pm$ 27,696 from 103 donors	Allograft intended for the treatment of musculoskeletal defects	Cryopreserved; chips, cubes, dowels, or strips delivered in a pouch or vial with DMSO	Yes
ViviGen, DePuy Synthes	Cryopreserved live viable cells within a cortical cancellous bone matrix with demineralized bone, delivering all properties required for bone formation	Lifenet	Bone	?	Allograft intended for the repair or reconstruction of musculoskeletal defects	Cryopreserved; delivered in DMSO and Human serum albumin; delivered in a ported pouch	Yes

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Table 1
(continued)

Name, Distributor	Description	Processor	Cell Origin	Cell Counts	Indications	Delivery	OC/OI/OG
BIO4, Stryker	BIO4 is a viable bone matrix containing endogenous bone-forming cells including MSCs, OPCs, osteoblasts, osteoinductive, and angiogenic growth factors. BIO4 possesses all 4 characteristics involved in bone repair and regeneration: osteoconductive, osteoinductive, osteogenic, and angiogenic.	Osiris Therapeutics	Bone	600,000 cells/mL (70% viability postthaw) including MSCs, OPCs, osteoblasts, and growth factors (claim angiogenesis)	?	Cryopreserved in DMSO, but claim no decanting is required?	Yes, plus angiogenesis

Abbreviations: MSC, mesenchymal stem cells; MTF, musculoskeletal tissue foundation; OC, osteoconductive; OI, osteoinductive; OG, osteogenic; OPC, osteoprogenitor cells; ?, not reported.

site morbidity and graft availability. Furthermore, allogenic bone particles in specific size dimensions are found to incorporate as well, and in some cases, better than autograft.[14] Knowing this, the use of autograft bone in general, and in the foot and ankle in particular, is rarely necessary.

Processing and Preparation

Scaffolds differ in many ways: processing, mineralized and demineralized, cryopreserved and freeze dried, secondary sterilization or aseptic processing, and size. Although there are inductive advantages in having small particle sizes, there is no general agreement on optimal scaffold preparation and function.

Allograft bone is available in many different preparations but in general includes fresh frozen, cryopreserved, and freeze-dried compositions; however, there are few instances or indications in which fresh frozen or cryopreserved bone is needed or used clinically. In fact, the presence of hematomyelopoietic cells in both frozen and cryopreserved bone may be detrimental to bone healing because of the possibility of evoking a host immune response in addition to the increased possibility of disease transmission. For this reason, in most, if not all circumstances, freeze-dried bone preparations are preferred. Freeze-dried bone can be either cortical, cancellous, or corticocancellous and may be structural or nonstructural. Among the nonstructural types, there is great variability regarding size and the presence or absence of demineralization. Bone demineralization is thought to mobilize bone morphogenic protein and thus create a substrate that has greater inductive osteogenic potential than nondemineralized bone. It is important to remember, however, that in the process of acid denaturation of bone, other antigens may be exposed, thus, potentially increasing immunogenicity to the substrate. Demineralization may involve the surface of bone only (partial) or the entire bone (typically <5% calcium by most standards).

Effect of Particle Size

Particle size is an important factor in the rate and quality of bone incorporation. In one study of nonhuman primates, closed-segment defects were made in the distal femoral condyles, and various sized particles were used to fill the defects, which were then compared with a control animal in which no graft material was used. Animals were killed at 6 weeks, and radiographs and histologic preparations were made and stained with hematoxylin and eosin. This study found that particle sizes between 100 and 300 μm resulted in optimal osseous incorporation compared with smaller and larger particle sizes.[15] This study was followed by another prospective nonrandomized clinical trial in human subjects with similar defects, mostly in metaphyseal region bones throughout the appendicular skeleton. Again, rapid healing was observed, usually within 6 weeks and, as anticipated, progressed from the periphery at the host bone allograft interface to the center of the graft. Also important was the observation that these bone particles did not form heterotopic bone in the soft tissues. The rate of healing and quality of the resulting bone were equal to or, in some instances, better than those cases in which autogenous bone was used.[15] These observations supported those of the preclinical study,[16] suggesting that microparticle bone in the 100- to 300-μm range by itself is a powerful inductive scaffold for bone formation. Other investigators found that particle size is an important factor in osteogenic activity of freeze-dried allogeneic bone.[17,18]

Cellular Component of Allograft

Significant variation in the types of scaffolds and composition of cells exists among the several iterations of commercial stem cell products (see **Table 1**). All cell products

cited herein fall under the auspices of Tissue Rule 21 CFR 1271 and are considered "361 Human Cell and Tissue Products" meaning that they comply with 2 important conditions in addition to safety; these are minimal manipulation and homology. This definition means that the cell products are not substantially changed from their normal or natural constitution and that the cells are derived from a site (ie, bone or bone marrow) and are used in or applied to that specific site clinically.

Cell claims are different from one product to another. In some preparations, the numbers and types of cells are well understood, whereas in others, this is not the case. Moreover, it is unclear what number and types of cells alone or in combination are necessary for optimal bone healing. It is not even certain how many cells survive freezing and thawing, as most cell products rely on dimethyl sulfoxide (DMSO), which is toxic to cells and requires significant dilution before use to avoid toxicity to the recipient. Therefore, the end concentration of cells delivered to tissue for the purpose of repair is substantially less than the product specifications. For these reasons, it is difficult for the end user to have a perspective on the best product for a given patient or indication of use.

In the foot and ankle, cell matrix products may have a beneficial effect in achieving fusion in joints that are sometimes difficult to fuse, such as tibiotalar arthrodesis, talonavicular arthrodesis, or failed first metatarsophalangeal fusion with concomitant bone loss and scarred devascularized soft tissue. This finding may be especially true for stem cells that are relatively primitive insofar as they may have the capacity to repair other tissues in addition to bone such as blood vessels and nerves. Other indications for using allogeneic cell matrix products are segmental bone loss after trauma as an augment to structural grafting and for patients with significant comorbidities that adversely affect fusion, such as, rheumatoid arthritis, diabetes, vascular disease, and poorly vascularized surrounding soft tissue. The fundamental problem is precise characterization of the cells thought to be participating in the repair and the lack of clinical trials that directly compare control subjects with subjects with scaffold only and others with both scaffold and matrix. Furthermore, altering a cell in such a way that genes or microRNAs are inserted by transduction or transfection to promote osseous bone formation falls well beyond minimal manipulation as does cell expansion.

Other Scaffold

Several other scaffolds are reported that include, but are not limited to, bioglasses and ceramics. By themselves, they are not inductive but osteoconductive only. These scaffolds can also be used in combination with allogeneic bone particles or molecules, such as bone morphogenic protein in which case they also become inductive. Other potential strategies exist that combine pedestrian allograft compositions with growth factors that, in some studies, show improved bone healing. One such example is a product that combines recombinant platelet-derived growth factor with β tricalcium phosphate. In a prospective study comparing 20 patients with autologous bone graft with augment for patients undergoing foot and ankle fusion, the investigators noted equivalency between the 2 groups regarding rate of radiographic union, time to full weight bearing, and outcomes scores.[19] The use of a single molecule in supraphysiologic doses to effectively heal bone as efficiently as autologous bone graft is interesting, as bone healing involves many different molecules that appear temporally throughout the healing process.

WOUND HEALING

Many products, both biologic and nonbiologic, are used for wound healing, mostly for chronic wounds of the foot and ankle associated with diabetes, vascular insufficiency,

or trauma. Discussion of all of available products, even product categories, is beyond the scope of this article. Instead, the focus is on an old remedy, placental membranes,[20,21] recently retooled and packaged in a heat stable form to treat both acute and chronic wounds, prevent adhesions, reduce inflammation, and decrease pain. These membranes are considered barriers and contain growth and anti-inflammatory factors, are immune privileged, may have antimicrobial properties, and produce local analgesic effects.[22] These membranes are not substitutes for the basic tenants of wound management, specifically, debridement, relief of pressure, restoring adequate vascular flow, and appropriate antibiotic intervention, but may play a role in improving the rate and quality of soft-tissue healing. They are powerful adjuncts to wound healing[23] (**Fig. 1**).

Placental Membrane

Placental membranes may include the chorion in addition to the amnion or the umbilical cord itself. The configuration of tissue (double folded amnion), addition of the chorion layer, or use of the umbilical cord can create tissues of greater thickness, which improve their handling characteristics and provide a mechanical contribution to a repair such as an Achilles tendon or rotator cuff. The increased tissue thickness

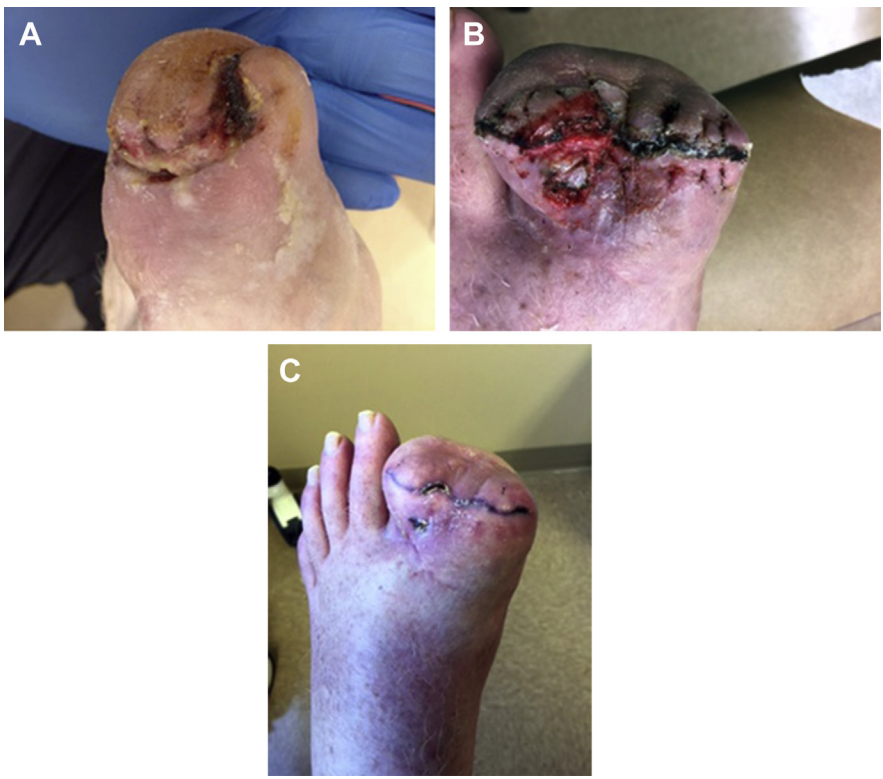

Fig. 1. (*A*) 42-year-old man with a history of a hamartoma of the great toe who underwent an amputation through the proximal interphalangeal joint that was complicated by a wound infection and osteomyelitis. (*B*) The patient underwent a revision of the distal residual digit that resulted in a wound dehiscence. (*C*) Appearance of the wound after 3 weeks of amnion therapy.

and improved handling characteristics allow for arthroscopic or laparoscopic introduction, placement, and anchoring of the tissue.

Amnion Membrane

Several companies distribute amnion tissues, most of which are freeze dried and stable at room temperature. The types of tissues and claims made by the respective companies are listed in **Table 2**.

In general, amniotic membranes are thin and contain an epithelial layer and basement membrane. These membranes are generally applied to the surface of the wound, on top of a tendon or nerve, or potentially interposed between joint surfaces. Thin membranes are applied dry, whereas the thicker membranes may be applied and manipulated in a wet form. In certain regions (ie, over the anterior distal leg and ankle where wound healing complications are not infrequent after trauma and surgical procedures or over the taloachilles tendon) the application of amnion in the subcutaneous tissue, over the tendon, and on the skin as a "biological bandage" may substantially improve wound healing. Although, to the authors' knowledge, there are no specific reports of the use of amnion after nerve sheath tumor excision the authors' observation is that amnion decreases postoperative pain, diminishes the intensity of neuritic pain, and seems to restore normal function more rapidly. To validate these preliminary observations, further controlled studies are needed. Similarly, the direct application of amnion to the posterior tibial nerve following decompression after tarsal tunnel release acts as a barrier to scar formation and may mitigate the use of veins, for example, as a protective barrier to scar formation and nerve dysfunction. Freeze-dried amniotic tissues have been used clinically to augment sites of nerve repair,[24] and Meng and colleagues[25] observed significant benefit in using amnion as a wrap in repairing sciatic nerve injuries in rats. The membrane adheres intimately to the nerve and does not require anchor sutures. The thicker membranes (double folded) or those containing both amnion and chorion layers can be used at the site of tendon repairs to reinforce the repair and augment wound healing. Amnion is an excellent soft tissue adjunct to wound healing for tumors in the foot, especially in select patients who undergo resection of plantar fibromatosis in which wound healing is challenging. Finally, after radiotherapy in the foot for malignant tumors, the authors observed improved healing and diminished radiation fibrosis when using amnion in the operative bed and as a bandage on the skin.

Amniotic Fluid

Amniotic fluid is also a rich source of growth and anti-inflammatory factors. Like the placental membranes and umbilical cords, amniotic fluid is recovered from normal 38-week pregnancies before cesarean sections. Typically, 200 to 300 mL of fluid is recovered and processed by a variety of techniques. Then, depending on whether viable cells are claimed to be part of the product, a cryopreservative may be added, typically DMSO. It is then stored in a frozen form and thawed immediately before use.

In our own laboratory, we identified a substantial amount of cell debris but have been unable to isolate anything reminiscent of amniotic stem cells and conclude that the presence of these cells in 38-week gestational amniotic fluid is rare, and claims otherwise should be carefully scrutinized.

The amniotic fluid is generally delivered as an injection into a tendon sheath, plantar fascia, around an inflamed nerve, or into a degenerative of inflamed joint. Zelen and colleagues,[25] in a prospective randomized trial, used micronized amnion in fluid suspension compared with lidocaine and saline and observed significant improvement in patients receiving the amnion composition compared with controls. Werber

Table 2
Types of amnion tissues

Company	Name(s)	Sizes	Storage	Storage Timeframe
AmnioGenix	AmnioDryFlex AmnioExCel	1.5 × 2 cm, 2 × 3 cm, 2 × 6 cm 15 × 20 mm, 20 × 30 mm	Room temp	2 y
Applied Biologics	XWRAP Hydro Plus XWRAP Dry XWRAP ECM	2 × 2 cm, 2 × 6 cm, 4 × 4 cm, 4 × 6 cm, 4 × 8 cm	Room temp	1 y
BioDlogics	Fence DryFlex Optix	2 × 3 cm, 2 × 6 cm, 4 × 4 cm, 4 × 8 cm, 10 × 10 cm 1.5 × 2 cm, 2 × 3 cm, 2 × 6 cm, 4 × 4 cm, 4 × 8 cm 1.5 × 2 cm, 2 × 3 cm – 9-, 12-, and 15-mm discs	Room temp (in saline) Room temp	2 y 5 y
BioTissue	Prokera AmnioGraft AmnioGuard	Small sizes for ophthalmic applications	−80°C	2 y
Bone Bank AlloGrafts	SteriShield II single-layer patch SteriShield II double-layer patch SteriShield II double-layer disc	1 × 1 cm, 2 × 2 cm, 4 × 4 cm, 4 × 6 cm 1 × 1 cm, 2 × 2 cm, 2 × 3 cm, 4 × 4 cm, 4 × 6 cm, 4 × 8 cm 10- and 16-mm discs	Room temp	3 y
Derma Sciences	Amnioexcel	1.5 × 1.5 cm, 2 × 3 cm, 4 × 4 cm, 4 × 8 cm	Room temp	2 y
MiMedx	AmnioFix Sheet AmnioFix Wrap EpiFix	2 × 3 cm, 3 × 3 cm, 4 × 4 cm, 4 × 6 cm, 16-mm disc 2 × 2 cm, 2 × 4 cm 4 × 6 cm 2 × 3 cm, 4 × 4 cm, 4 × 6 cm, 14-and 16-mm disc	Room temp	5 y
NuTech	NuShield	2 × 3 cm, 4 × 4 cm, 4 × 6 cm, 6 × 6 cm	Room temp	—
Regenerative Processing Plant	Cryo-Activ	2 × 2 cm, 4 × 4 cm, 4 × 6 cm, 8 × 8 cm	−80°C	1 y

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Table 2
(*continued*)

Company	Name(s)	Sizes	Storage	Storage Timeframe
Single Source Surgical	AlloShield AlloShield Dry	1 × 1 cm, 1 × 2 cm, 2 × 2 cm, 2 × 3 cm, 2 × 4 cm, 2 × 6 cm, 4 × 4 cm, 4 × 6 cm, 4 × 8 cm, 8 × 8 cm	Room temp	2 y
Skye Biologics	ActiveBarrier 45 ActiveBarrier 200 OculoMatrix VisiDisc	2 × 2 cm, 2 × 4 cm, 4 × 4 cm, 4 × 6 cm, 4 × 8 cm 1 × 1 cm, 2 × 2 cm, 2 × 4 cm, 4 × 4 cm 10 mm disc	Room temp	5 y
Vivex	Cygnus Solo Cygnus Matrix Cygnus Max	1 × 1 cm, 1 × 2 cm, 2 × 2 cm, 2 × 3 cm, 3 × 3 cm, 3 × 4 cm, 3 × 6 cm, 3 × 8 cm, 4 × 4 cm, 4 × 6 cm, 4 × 8 cm, 7 × 7 cm, 10 × 10 cm, 10 × 12 cm, 2 × 12 cm	Room temp	5 y
AmnioGenix	AmnioDryFlex AmnioExCel	1.5 × 2 cm, 2 × 3 cm, 2 × 6 cm 15 × 20 mm, 20 × 30 mm	Room temp	2 y
Applied Biologics	XWRAP Hydro Plus XWRAP Dry XWRAP ECM	2 × 2 cm, 2 × 6 cm, 4 × 4 cm, 4 × 6 cm, 4 × 8 cm	Room temp	1 y
BioDlogics	Fence DryFlex Optix	2 × 3 cm, 2 × 6 cm, 4 × 4 cm, 4 × 8 cm, 10 × 10 cm 1.5 × 2 cm, 2 × 3 cm, 2 × 6 cm, 4 × 4 cm, 4 × 8 cm 1.5 × 2 cm, 2 × 3 cm – 9-, 12-, and 15-mm discs	Room Temp (in saline) Room temp	2 y 5 y
BioTissue	Prokera AmnioGraft AmnioGuard	Small sizes for ophthalmic applications	−80°C	2 y

Table 3
Various amniotic fluid products

Company	Name(s)	Description	Dilute	Storage	Sizes	Processed by	Product Positioning
Amnio-Technology	PalinGen Flow	Liquid	Yes	Frozen	S, M, L, XL	Pinnacle Transplant Technologies	Revolutionizing the way we repair nerve, tendon, ligament and soft-tissue defects. Heal faster, live better.
Amniox	Clarix FLO, Neox FLO	Particulate AM and UC	Yes	Room temp	25, 50, 100, 150 mg	TissueTech	Provide higher volumes of the critical matrix proteins innate to the tissue
BioD	BioDRestore	Morselized flowable	Yes	Frozen	S, M, L	BioDlogics	Get back in action naturally A better approach to regenerative medicine
	BioDFactor	Liquid	No	Frozen	S, M, L, XL		
MiMedx	EpiFix Particulate	Particulate	Yes	Room temp	40, 100, 160 mg	MiMedx Tissue Services	Dehydrated amnion/chorion
	OrthoFlo	Liquid	No	Frozen	.25, .5, 1, 2 mL		Better healing, better repair
NuTech	NuCel, ReNu	Liquid		Frozen	S, M, L, XL	WuXi AppTec	Provides an enhanced environment for tissue growth, repair, and healing
Skye	ActiveMatrix, WoundEx, PX50, ScarEx Flow	Liquid	No	Room temp	M, L, XL	Human Regenerative Technologies	The right formulation for the right indication
	CryoMatrix and RX Flow	Liquid	Yes	Frozen	M, L, XL		
	Integra BioFix Flow	Liquid	No	Room temp	M, L, XL		
Applied Biologics	FloGraft, FloGraft Freedon (Sports)	Liquid	No	Frozen	M, L, XL		Discover the power of biological healing
Vivex	AlloGen, AlloGen-LI	Liquid	No	Frozen	S, M, L, XL	UMTB	All-natural liquid matrix

demonstrated dramatic and sustained pain reduction on injecting liquid amnion into the Achilles tendon and plantar fascia in symptomatic patients.[26] Finally, Hanselman[27] in another prospective randomized study comparing steroid injections to amniotic fluid found safety and comparable efficacy.[28] Amniotic fluid can also be aerosolized and sprayed into or onto tendons or nerves alone or to augment the membranes during an open procedure. The various products are listed in **Table 3**.

SUMMARY

Many allogeneic biologic materials, by themselves or in combination with cells or cell products, may be transformative in healing or regeneration of musculoskeletal bone and soft tissues. By reconfiguring the size, shape, and methods of tissue preparation to improve deliverability and storage, unique iterations of traditional tissue scaffolds have emerged. These new iterations, combined with new cell technologies, have shaped an exciting platform of regenerative products that are effective and provide a bridge to newer and better methods of providing care for orthopedic foot and ankle patients.

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