REVIEW ARTICLE

A Road Map to Commercialization of Cartilage Therapy in the United States of America

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Despite numerous efforts in cartilage regeneration, few products see the light of clinical translation as the commercialization process is opaque, financially demanding, and requires collaboration with people of varied skill sets. The aim of this review is to introduce, to an academic audience, the different paradigms involved in the commercialization of cartilage regeneration technology, elucidate the different hurdles associated with the use of cells and materials in developing new technologies, discuss potential commercialization strategies, and inform the reader about the current trends observed in both the clinical and laboratory setting for establishing clinical trials. Although there are review articles on articular cartilage tissue engineering, independent reports provided by the Food and Drug Administration, and separate review articles on animal models, this is the first review that encompasses all of these facets and is presented in a format favorable to the academic investigator interested in clinical translation from bench to bedside.

Introduction

CARTILAGE DEFECTS OF the knee range from cartilage lesions and osteochondritis dissecans to debilitating grade III or IV osteoarthritis (OA; see Table 1 for listing of abbreviations) and result in more than 200,000 surgical procedures annually.^{1–3} Current surgical treatment paradigms range from microfracture (MF) for initial impact injuries to total knee replacement in advanced cases; however, there are no universally agreed upon solutions that have unequivocally been shown to regenerate fully structural and functional cartilage.^{4–8} Specialized surgical treatments, such as autologous chondrocyte implantation (ACI), have emerged over the past few decades and have often been used among younger patients. However, ACI has not been as successful for long-term treatment of older patients.^{9,10} MF is the established standard of care for focal cartilage defect repair and is commonly used as a comparator group in clinical trials with devices and autologous grafts.^{11,12}

Academic tissue engineering solutions endeavoring to restore and repair cartilage have traditionally used the triad approach (cells, biomaterials, and bioactive factors) with common materials such as polycaprolactone, poly(ethylene glycol)-based materials, poly(lactic-co-glycolic acid), agarose, chitosan, collagen, and hyaluronic acid, which have all been employed in other products that have been Food and Drug Administration (FDA) approved.^{13–15} Different sources of cells, such as chondrocytes, bone marrow

mesenchymal stem cells (MSCs), adipose-derived stem cells (ASCs), and cells derived from the umbilical cord, have been employed in efforts to differentiate these cells toward a chondrocyte-like phenotype using polymeric substrate adherence, novel cell culture media, growth factors, and/or gene therapy.^{16–19}

Over the years, biomaterial strategies have evolved from a single polymeric substrate to superior hierarchical matrices that mimic the native tissue and attempt to enable directed differentiation.²⁰ Recently, raw materials²¹ such as cartilage matrix^{22–24} (including decellularized cartilage [DCC]^{25,26}) and demineralized bone matrix have been used directly or combined with other biomaterials to create hybrid materials that provide biochemical and mechanical cues for the cells to differentiate.^{22,26–28}

Some of the current products that employ this technology are DeNovo NT from Zimmer^{29,30} and DeNovo[®] ET (Engineered Tissue Graft) from ISTO technologies, which obtained special rights and permission from Zimmer.^{31,32} Both products employ juvenile DCC with a combination of cells and materials to treat cartilage lesions. BioCartilage from Arthrex³³ employs micronized allogeneic cartilage to treat osteochondral lesions.

Despite so many new innovative approaches and technologies that address articular cartilage regeneration, there are very few FDA-approved products and only a handful of products currently in clinical trials³⁴ (Tables 2–4). Unfortunately, academic training does not typically provide a clear

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TABLE 1. LIST OF ABBREVIATIONS

AC	Articular cartilage
ACI	Autologous chondrocyte implantation
ACL	Anterior cruciate ligament
ADS	Adipose derived stem cells
ASC	Adipose-derived stem cells
BMI	Body mass index
DMEM	Dulbecco's modified eagle medium
ECM	Extracellular matrix
GMP	Good Manufacturing Practice
HA	Hyaluronic acid
IGF	Insulin-like growth factor
IKDC	International knee documentation committee
IND	Investigational new drug
KOOS	Knee injury and osteoarthritis information store
MRI	Magnetic resonance imaging
MSC	Mesenchymal stem cells
NDA	New drug application
OA	Osteoarthritis
OATS	Osteochondral autograft transplantation procedure
OCD	Osteochondritis dissecans
PCL	Polycaprolactone
PDS	polydioxanone
PEG	Polyethyleneglycol
PEO	Polyethyleneoxide
PGA	Poly(glycolic acid)
PRP	Platelet-rich plasma
PLG	Poly(lactic-co-glycolic acid)
PLGA	Poly(L-lactic-co-glycolic-acid)
WOMAC	Western Ontario and McMaster universities osteoarthritis index

picture of the various steps involved in therapeutic product design, development, registration, and launch.³⁵ A thorough understanding of the challenges in translation, restrictions due to government regulations, funding opportunities, and overall study design is of paramount importance to help academics think about product development while designing hypothesis-driven research, proposing innovative and novel strategies, designing animal studies with the final clinical study in mind, and understanding the cost-benefit ratio in every step of the process to enable a smoother transition from preclinical animal studies to human clinical studies.

Review articles have done an excellent job in covering various facets of cartilage regeneration in depth, such as animal models,^{36–38} FDA regulations,^{39,40} osteochondral scaffolds for cartilage tissue engineering,^{35,41–44} challenges of stem cell technology,^{10,17,45,46} product legislation in other countries,⁴⁷ and hurdles and general trends in biomaterial commercialization.^{48–53}

However, the current review endeavors to classify the different categories of tissue-engineered products and their relative benefits and challenges associated with specific product examples. Second, we also discuss different animal models, inclusion and exclusion criteria for clinical studies, primary and secondary endpoint analyses, and a standard set of FDA recommendations. Third, we aim to give the reader a brief introduction into other commercialization considerations to keep in mind before launching into translation.

Finally, the current review aims to introduce a product development-based perspective to the academic investigator

in anticipation of future healthcare commercialization. Therefore, building on other outstanding reviews, the current review fills a gap in the literature to provide a road map to commercialization for academic investigators to translate their cartilage regeneration technologies.

Methods

A review of all of the tissue-engineered and industrial products, inclusion and exclusion criteria, and FDA approval statuses was performed using clinicaltrials.gov with the search terms “articular cartilage” and “osteoarthritis” in March 2015 to determine the current status of active clinical trials for cartilage repair treatments. Additionally, the corresponding company's website was also reviewed for additional product information. FDA guidance documents, clinical trial recommendations by the International Cartilage Repair Society (ICRS), and large animal study articles for cartilage repair were reviewed and cited accordingly.

Surgical Techniques

Three common surgical procedures are utilized to address OA or cartilage degeneration. The first procedure, MF, is a marrow stimulation technique, whereby a full-thickness chondral defect is created, including removal of calcified cartilage, followed by puncturing the underlying subchondral bone with a drill or awl to create small holes for bone marrow constituents, including MSCs, to fill the defect.^{54,55} The resulting tissue is less durable, less organized, and has a higher quantity of collagen type I than normal articular cartilage.⁵⁶ Poor clinical outcomes from MF have been associated with inadequate filling of defect with repair tissue and osseous overgrowth.^{57,58} Good outcomes are typically limited to young patients (<40 years with small lesions [$<2\text{ cm}^2$]), low body-mass indexes, and acute onset of symptoms.⁵⁹ Otherwise, clinical results are highly variable.

Approaches to improve the repair process initiated by MF are being actively explored. BioCartilage from Arthrex (Naples, FL), employed frequently with platelet-rich plasma (PRP),³³ and another approach by Milano *et al.* from Catholic University (Rome)⁶⁰ have both employed MF in combination with their scaffold and are comparing that with a scaffold-only approach (i.e., without MF) to evaluate the complementary effect of MF. The final data from the BioCartilage study are expected to be available in June 2016. The importance of MF as an emerging comparator group in clinical studies will be discussed in the next section.

The second procedure is mosaicplasty, or osteochondral autograft transfer, which involves surgical transfer of mature autologous or cadaveric tissue from a nonload-bearing region to a cartilage defect.^{61,62} While this relatively inexpensive reparative technique has helped to serve the growing need for cartilage repair, grafting is a suitable option only for small ($<2\text{ cm}^2$) to medium-sized ($3\text{--}5\text{ cm}^2$) defects^{63,64}; with time, patients seem to develop symptoms attributable to the donor area, thus reducing the overall effectiveness of this technique.⁶⁴ In addition to donor site morbidity, the technically challenging autologous procedure adds complexity for the surgeon and requires longer operating times.

The third and most widely used procedure is ACI. ACI is a two-step procedure wherein chondrocytes are harvested arthroscopically from healthy cartilage and expanded *in vitro*

before reimplantation through a second more invasive surgery that requires a periosteal flap to be harvested from the patient that must be sutured to the cartilage surface to keep the cells in place. ACI is technically challenging, costly, requires two surgeries, must receive health insurance approval, and has been associated with high reoperation rates.^{65,66} Several modifications to ACI have been introduced. The most popular is the matrix-induced ACI (MACI), which involves implantation of *in vitro* expanded chondrocytes in a suitable matrix, which is then fixed in the defect area using fibrin glue and/or sutures.⁶⁷ This does not refer to the Sanofi biosurgery registered MACI[®] product. Several articles have evaluated side-by-side performance of ACI, MF, and mosaicplasty over long periods^{5,68,69} and have produced recommendations factoring in the age and nature of cartilage injury (stage of OA and size of the lesion). In one study, both MF and osteochondral autograft transplantation procedure (OATS) showed encouraging clinical results for athletes under the age of 40 with the OATS group producing slightly increased results over MF, assessed over a period of 37.1 months.⁷⁰ Gudas *et al.*⁵ compared the effect of MF, OATS, ACI, and debridement in articular cartilage lesions associated with ACL injuries and a 3-year follow-up. Pain scores revealed that intact articular cartilage during ACL reconstruction yields more favorable International Knee Documentation Committee (IKDC) subjective scores compared with any other articular cartilage surgery type.⁵ However, if an articular defect is present, the subjective IKDC scores are significantly better for OATS versus MF or debridement after a mean period of 3 years.⁵

The choice of the comparator group is largely dictated by the regulatory requirement for the specific type of product. For cell-based products, ACI is the most commonly employed comparator group. The use of ACI as a comparator group is challenging as it is expensive and logistically demanding and, consequently, has not been widely adopted. On the other hand, MF is a more straightforward procedure and is the most commonly used first-line procedure for cartilage regeneration; it has therefore been a popular choice as a comparator group in clinical trials. However, the defect type and disease state of the joint must be considered to be within the clinical indication for MF.

Choice of comparator group in clinical trials

Comparator groups for cartilage therapy change according to the treatment modality and include placebo and standard of care groups. FDA guidelines require that experimental groups demonstrate statistically superior primary endpoints of treatment over a current comparator group such as MF, debridement, mosaicplasty, and ACI.^{40,71} MF is the most commonly used comparator group for late-phase clinical trials as it is inexpensive compared with ACI, easier to perform, and is widely performed throughout the world. However, FDA guidance also allows ACI as a control group for large defects (greater than 5–7 cm² lesions) where MF may not be indicated.^{71,72} In summary, choosing a comparator group depends on the nature of the defect, the standard treatment for the defect type and disease state of the joint, results of existing or previous clinical studies, and guidance from FDA/consultants. It is important to note that the recent literature suggests that for most focal defects of the knee cartilage and small-sized lesions due to impact injuries, MF is emerging to be a

superior comparator group in light of effective repair tissue formation and availability of uniform instruments with which to perform the surgery throughout the country.

Current Translational Technologies in Cartilage Repair

The following sections will highlight the FDA classification scheme and briefly cover the different approaches (i.e., devices, drugs, and biologics) with current examples in clinical trials and, finally, provide a summary of these translational technologies as well as their relative benefits and limitations.

FDA classification of cartilage repair therapies

Within the FDA, the Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER), and the Center for Drug Evaluation and Research (CDER) are responsible for devices, biologics, and drugs, respectively (Table 6).⁴⁰ The type of classification impacts the number of subjects enrolled, the nature of primary and secondary endpoints, and the implementation period in the market. The duration of a study is also impacted by the nature of control groups, recovery periods, long-term pain evaluation, device performance tracking, and postmarket surveillance. Tables 2–4 list all of the products currently in the process of seeking FDA approval, which are classified as device, drug, biologic, or a combination of any of these three, along with a brief product description and their current status.

Most of the devices, biologics, and drugs are classified under section 351 or 361 of the Public Health Service Act.⁷³ Scaffolds, polymeric constructs, and injectable pastes are likely to fall under the device classification, while stem cell technologies, combinatorial products that employ cells and materials, and incorporation of protein molecules like amino acids and growth factors are most likely going to be treated as a drug or biologic. Given that some cartilage tissue engineering technologies may be considered combination products, any ambiguity in classification can be directed to the Office of Combination Products. A company must submit a Request for Designation (RFD) to the FDA, which enables the FDA to determine the primary mode of action and to thus decide (within 60 days of RFD filing) the lead agency (CDRH, CBER, or CDER) for premarket review and regulation.

Before using any product for clinical trials, the FDA must approve an investigational device exemption (IDE) for devices or an investigational new drug (IND) for drugs and biologics. It must be noted that CBER may also regulate some devices (e.g., cellular products), in which case the IDE route is followed. In addition to the FDA IDE or IND approval, institutional review board (IRB) approval must be obtained before clinical trials, and one should expect that their IRB(s) would require FDA involvement before merely allowing a pilot clinical study. The clinical safety and efficacy data collected with IDE approval for devices are then used for either a Premarket Notification [510(k)] or Premarket Approval (PMA) application, which, if approved, allows the company to sell its device in the United States. The PMA is a longer, more complex, and more costly process than the 510(k). A 510(k) pathway requires that the device to be marketed is substantially equivalent (i.e., at least as safe and effective) to a predicate device, which includes a device

TABLE 2. LIST OF DEVICES UNDER CLINICAL TRIALS FOR TREATING KNEE FOCAL DEFECTS OR OSTEOARTHRITIS

<i>Product</i>	<i>Clinical study center(s)</i>	<i>FDA phase</i>	<i>Technology overview</i>	<i>Material composition</i>	<i>Defect size</i>	<i>Treatment condition</i>	<i>Comparator group</i>
CAIS	Canada	2	Morselized autologous cartilage affixed on resorbable implant using fibrin sealant and implanted back into the knee	Resorbable implant: copolymer of PGA and PCL reinforced with PDS mesh	1–5 cm ²	Osteochondritis dissecans and ICRS grade 3 lesions	MF
MaioRegen Surgery	Italy	4	Bioceramic multilayer scaffold comprising deantigenated type I equine collagen and magnesium-enriched hydroxyapatite	Chondral layer: 100% Type I collagen, tide-mark layer: 60% collagen 40% HA, bone gradient: 30% collagen and 70% HA	2–9 cm ²	Knee osteochondral lesion	MF
HYTOP [®] graft	Germany	N/A	HYTOP [®] is typically grafted with debridement or MF	Upper layer of porcine splint skin and lower layer of collagen fleece containing hyaluronan	Width and length: 20 × 30 mm Thickness: 1.1–2 mm	Focal chondral defects	None (open-label, single-group safety study)
Matrix encapsulated chondrocytes	Mexico	3	Cells implanted in a collagen scaffold are arthroscopically implanted	Six million cells are implanted in a 10-mm collagen scaffold	1.5–4 cm ²	Focal chondral defects	MF
TruFit CB	EU—mc	4	TruFit CB plugs are implanted into defect regions	TruFit CB: resorbable material comprising PLG copolymer, calcium sulfate, PGA fibers, and surfactant	1–2 cm ²	Single cartilage lesion	MF
Agili C Biphasic implant	EU—mc	4	Graft implanted perpendicular to defect site	Cartilage phase: modified aragonite and HA, bone phase: aragonite	Area <2 cm ² after debridement, depth up to 3 mm	Osteochondritis dissecans	Agili C implant

(continued)

TABLE 2. (CONTINUED)

<i>Product</i>	<i>Clinical study center(s)</i>	<i>FDA phase</i>	<i>Technology overview</i>	<i>Material composition</i>	<i>Defect size</i>	<i>Treatment condition</i>	<i>Comparator group</i>
Denovo®	United States of America, Canada	Postmarket analysis	A miniarthrotomy is performed and after removal of defective cartilage, the cartilage pieces are implanted and held in place with fibrin sealant	Viable juvenile cartilage pieces held in place with fibrin sealant	Each package fills 2.5 cm ²	Femoral and patellar articular cartilage lesions	None (open-label, single-group safety study)
Bone Graft	Canada	Pilot; 0	Chondral lesions are filled with augment bone graft	Material: matrix of beta tricalcium phosphate and highly purified recombinant human platelet-derived growth factor	OCD >1 cm ²	Osteochondral defects	None (open-label, single-group safety study)
Chondron™	Republic of Korea	3	Patients implanted with chondron are analyzed to evaluate device performance	Cell–gel mixture: autologous chondrocytes are mixed with fibrin and cultured for 3 days	1–15 cm ²	Ankle cartilage defect	None (open-label, single-group safety study)
BST-CarGel	Canada	N/A	Chitosan-based matrix, which acts like a plug after the ACI procedure	Cytocompatible liquid chitosan solution at physiological pH	No specific size mentioned	Focal articular cartilage defects	MF

Source: clinicaltrials.gov
 FDA, Food and Drug Administration; PCL, polycaprolactone; PDS, polydioxanone; PGA, poly(glycolic acid); PLG, poly(lactic-co-glycolic acid); OCD, osteochondritis dissecans; ICRS, International Cartilage Repair Society; HA, hyaluronan; ACI, autologous chondrocyte implantation; mc, multicenter; MF, microfracture; CAIS, cartilage autograft implantation system; N/A, not applicable.

TABLE 3. LIST OF BIOLOGIC PRODUCTS UNDER CLINICAL TRIALS FOR TREATING KNEE FOCAL DEFECTS OR OSTEOARTHRITIS

<i>Company/Institute name</i>	<i>Product</i>	<i>Clinical study center(s)</i>	<i>FDA phase</i>	<i>Technology overview</i>	<i>Treatment condition</i>	<i>Comparator group</i>
Medipost Co. Ltd.	CARTISTEM®	United States of America	1, 2	Human umbilical cord mesenchymal stem cells are mixed with biopolymer solution	Full-thickness grade 3–4 articular cartilage defects of the knee	MF
Royan Institute	N/A	Islamic Republic of Iran	1	Single intra-articular injection of MSCs	Osteoarthritis	Placebo injection
TissueGene, Inc.	TG-C	United States of America	2	MSC injections of different cell concentrations	Osteoarthritis	Placebo injection
Taipei Medical University and Wanfang Hospital	PRF	Taipei, Taiwan	N/A	PRP injection, following success in pig model	Knee meniscal repair	None (open-label, single-group safety study)
The Catholic University of Korea	N/A	Korea	1, 2	PRP injection, second injection after 4 weeks	Degenerative chondropathy, early osteoarthritis	None (open-label, single-group safety study)
Stanford University	ASC	United States of America	1	Fibrin glue, dermal matrix, and ADSC cells	Degenerative lesion of articular cartilage	MF
University of Marseille	Arthroscopic marrow cells with protein injection	France	0	Autologous cells are isolated and mixed with patient's protein and injected	Defect of articular cartilage	None (open-label, single-group safety study)
Red de terapia celular	MSV	Spain	1, 2	ACI, followed by MSC injections	Osteoarthritis of grade II–IV	Intra-articular injection of 60 mg hyaluronan
University Hospital, Basel, Switzerland	N/A	Switzerland	1	Nasal cartilage is isolated, grown on collagen type I/III membrane, and implanted in knee	One or two full-thickness cartilage defects	None (open-label, single-group safety study)
Hospital Znojmo	PRP	Czech Republic	N/A	Nine PRP injections administered over a duration of 1 year	Grade II or III chondromalacia	None (open-label, single-group safety study)
Exactech, Inc.	BiCRI	Taiwan	3	One or two scaffolds were placed in condyles	Focal chondral and osteochondral lesions	MF
ISTO Inc.	Revaflex	United States of America	3	Decellularized neocartilage scaffolds are implanted in defect	Articular cartilage lesions in the femur	MF

(continued)

TABLE 3. (CONTINUED)

<i>Company/Institute name</i>	<i>Product</i>	<i>Clinical study center(s)</i>	<i>FDA phase</i>	<i>Technology overview</i>	<i>Treatment condition</i>	<i>Comparator group</i>
Tigenix	Chondroselect	Europe—mc	3	ACI performed along with Chondroselect that isolated cartilage-specific cells	Cartilage single lesion	ACI
Histogenics	Neocart	United States of America—mc	3	ACI performed and cells are seeded on scaffolds and reimplanted in knee	Articular cartilage defects	MF
University of Jordan	MSC and platelet lysate injection	Jordan	2	Intra-articular injection of MSC and/or platelet lysate	Moderate/severe articular injury	None (open-label, single-group safety study)
Istituto Ortopedico Rizzoli	PRP	Italy		PRP versus viscosupplementation with Hyalubrix	Early knee articular degenerative pathology	None (open-label, single-group safety study)
Fondren Orthopedic Group	N/A	United States of America	N/A	ASC isolated from fat pad and injected into defect site	Arthritis	MF
University of Columbia—Missouri, Arthrex	Biocartilage	United States of America	FDA-approved to augmentation to microfracture	Microfracture and biocartilage versus microfracture	Defect of articular cartilage	MF
Tetec AG	NOVOCART 3D	Germany	3	Autologous cells are mixed with novocart and implanted into patients	Articular cartilage lesion	MF
Stempeutics Research Private Ltd.	N/A	India	2	Ex vivo cultured adult allogeneic MSCs	Osteoarthritis	Plasma lysate
University Hospital, Montpellier	N/A	France, Germany	1	Autologous adipose-derived stem cells administered for intra-articular use	Moderate or severe osteoarthritis	None (open-label, single-group safety study)
Cytori Inc.	Celution® device	United States of America—mc	1	Idiopathic osteoarthritic patients are administered an intra-articular administration of Celution processed adipose-derived regenerative cells	Osteoarthritis	Placebo injection
StemGenex	SVF injection	United States of America—mc	N/A	Impact of stromal vascular fat on joint pain and functionality due to osteoarthritis	Osteoarthritis	N/A—observational study

Source: clinicaltrials.gov.

ADSC, adipose-derived stem cells; MSC, mesenchymal stem cell; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; SVF, stromal vascular fraction.

TABLE 4. LIST OF DRUG PRODUCTS UNDER CLINICAL TRIALS FOR TREATING KNEE FOCAL DEFECTS OR OSTEOARTHRITIS

<i>Company/Institute name</i>	<i>Product</i>	<i>Clinical study center(s)</i>	<i>FDA phase</i>	<i>Technology overview</i>	<i>Treatment condition</i>	<i>Comparator group</i>
Shetty-Kim research foundation	PRP	United Kingdom	NA	Effectiveness of PRP injection	Early cartilage defects	Hyaluronic acid injection
Orthotrophix	TPX-100	United States of America	2	Intra-articular injection of TPX-100 (chondrogenic peptide)	Bilateral osteoarthritis	None (open-label, single-group safety study)
Merck kGaA	AS902330	EU—mc	1	AS902330 injection into knee defect	Primary osteoarthritis of the knee and Kellgren—Lawrence Grade 2 or 3	Placebo
Universidad Nacional de Rosario	12.5% dextrose injection	Argentina	2, 3	Arthroscopic injection of one glucose injection at 1, 2, and 3 months	Stage IV knee osteoarthritis	None (open-label, single-group safety study)
Hospital Universitario Dr. Jose E. Gonzalez Bioiberica	PRP	Mexico	N/A	PRP injection given every 2 weeks for 6 weeks	Mild knee osteoarthritis	None (open-label, single-group safety study)
Nantes University Hospital	Condrosan Hydrogel with MSCs	Canada France	3 NA	Injection of chondroitin sulfate Blood, bone marrow, and Hoffa's fat pad samplings during surgical intervention	Osteoarthritis Osteoarthritis	Placebo None (open-label, single-group safety study)
Genzyme	Synvisc	United States of America	Approved	Hylan G-F 20 (Synvisc) is an FDA-approved hyaluronate derivative used to treat knee OA	Symptomatic knee osteoarthritis	Placebo
Novocart®3D Plus	Tetec AG	Germany	3	Combination of autologous cells in a biphasic 3D collagen-based matrix	Traumatic articular cartilage defects	MF
The First Affiliated Hospital of Anhui University of Traditional Chinese Medicine	Xinfeng capsule	China	China Health Authority	Traditional chinese herbal medicine Xinfeng capsule	Osteoarthritis	Glucosamine sulfate
Biomet	APDD-33-00	United States of America	2	Autologus protein solution delivered as an intra-articular injection for patients who have failed atleast one conservative OA therapy	Osteoarthritis	Placebo
Kyunghee University Medical Center	WIN-34B	Korea	Korean-FDA phase 2	Herbal drug used to treat inflammation	Osteoarthritis	Placebo

Source: clinicaltrials.gov.
OA, osteoarthritis.

that was legally marketed in the United States before May 28, 1976, a device that has cleared through the 510(k) process, or devices that have been downclassified from Class III to Class II or Class I. The necessary proof of safety and efficacy is determined predominantly through preclinical studies, although in some cases, a clinical study is required. Nearly all Class III medical devices, which include most cartilage repair technologies, require a PMA, which is the most stringent type of device marketing application required by FDA. Unlike a 510(k), a PMA requires clinical studies that will need to demonstrate either noninferiority or superiority against a control group, the determination of which depends on risk–benefit considerations posed by the product. In some rare cases, evaluation against an objective performance goal or criteria rather than an active control group may be appropriate. Clinical trials for PMAs typically consist of a small feasibility/pilot study to determine safety and a pivotal study to demonstrate efficacy in addition to safety.

There are no predicate devices (Class I and II) for most cartilage repair products; therefore, a PMA is required to legally market them. Some devices indirectly related to cartilage repair may be amenable to the 510(k) pathway. In contrast to devices, clinical safety and efficacy data collected with IND approval for biologics and drugs then lead to either a Biologics License Application (BLA) (via CBER) or a New Drug Application (via CBER or CDER), respectively, which if approved, allows the company to sell its product in the United States.

Devices

The CDRH is responsible for the approval of cartilage repair devices, including biodegradable scaffolds, osteochondral plugs, and injectable substances that can fill defects. Depending on an RFD, the CDRH may also serve as the lead agency for combination products if the FDA determines that the primary mode of action is as a device. The two primary routes to acquire FDA approval for medical devices are through a 510(k) or PMA; each of which has different requirements for approval.^{40,74,75}

It is important to note that most devices for cartilage application that are currently in clinical trials are from non-US-based companies and/or universities. Notable among them are HYTOP[®] from TRB Chemida (Germany), Agili C Biphasic Implant from CartiHeal (EU), and BST-CarGel from Piramal Healthcare (Canada).^{29,75–77}

According to information found at clinicaltrials.gov, DePuy's Cartilage Autograft Implantation System (CAIS) is a kit of devices that employs morselized autologous cartilage harvested arthroscopically from a nonweight-bearing region, affixed onto a synthetic resorbable implant using fibrin sealant, and implanted in a single surgical procedure. CAIS has just completed Phase 2 clinical trials with MF as the comparator group.³⁰

HYTOP is a two-layer bioresorbable matrix consisting of an upper layer of highly purified porcine splint skin and a lower layer of purified collagen fleece containing hyaluronan. The primary working hypothesis is that HYTOP is safe and suitable as a cell-free matrix to support hemostasis, as a cover for the cartilage lesion, and eventually to enhance cartilage regeneration in a one-step surgical procedure. TRB Chemida AG, a German company that is sponsoring the study, utilizes the

scaffold in conjunction with cartilage debridement and/or MF of the subchondral bone.

The Agili C Biphasic Implant[™] is an off-the-shelf cell-free biphasic plug and is CartiHeal's trademarked product used in the treatment of focal articular cartilage and osteochondral defects. The biphasic implant comprises calcium carbonate in the aragonite crystal form and comprises modified aragonite and hyaluronic acid in the cartilage phase. Holes are drilled into the bottom phase comprising coral material, through which the top phase material (hyaluronic acid) is gradually added to initially form a gradient, followed by a controlled deposition to form the desired height.⁷⁸ The product has currently secured approval for use in the European Union market and is running a multicenter, postmarketing clinical study (phase IV). As of 2015, the company secured four patents (three in the United States and one in Japan) for its proprietary cell-free, off-the-shelf cartilage regeneration technology for patients with injuries to the articular surface of joints.⁷⁶ The product is not currently commercially available in the United States.

BST-CarGel is a Canadian Piramal Healthcare product that is prepared by mixing chitosan and a buffer to form a liquid-like gel that has scientific evidence for biocompatibility and adherence to tissue. The BST-CarGel, which is fabricated under Canada's certified good manufacturing practice (GMP) protocol, is mixed with a patient's own blood and implanted into the surgically prepared defect lesion site. BST-CarGel was found to be safe and effective according to multicenter, randomized, controlled clinical trials.^{79,80} According to the company's website, the safety was assessed to be similar to that of MF, and results demonstrate greater quantity and quality of repair cartilage.

Injectable drugs

According to CDER at the FDA, current cartilage treatments that fall under the drugs category include any modality that delivers compounds that elicit a repair response by a patient's own joint tissue.⁴⁰ By definition, compounds that address cartilage repair and are metabolized and are classified as drugs and injectable forms are also therefore considered a drug.⁸¹ It should be noted that viscosupplements, such as hyaluronic acid, are considered devices rather than drugs since their primary mode of action is viscosupplementation and not cartilage repair or metabolic mechanisms.⁸²

Approval of a drug requires a phased approach with separate dosing (phase I), assessment of small-scale safety and effectiveness (phase II), and assessment of large-scale randomized safety and effectiveness (phase III); it therefore imposes more financial and clinical expenditure than the device route. Most of the cases that consult drug treatment are advanced OA and are usually not treatable by the device or biologic paradigm due to the condition of the joint or other reasons. Thus, in most cases, drugs represent a palliative treatment paradigm and are usually used to treat advanced OA.

Examples of approved drugs include injectable Synvisc by Genzyme, topical NSAID cream Pennsaid by Nuvo Research, and other steroid-based painkillers that address inflammation, such as Supartz by Smith and Nephew and Mobic by Boehringer Ingelheim. A few drugs in phase III clinical trials include Condrosan by Bioiberica and dextrose injection by Universidad Nacional de Rosario. Condrosan is

a prescription drug containing highly purified chondroitin 4- and 6-sulfate of bovine origin in a concentration of not <98%. It has an average molecular weight of about 15–16 kDa and an intrinsic viscosity of about 0.02–0.06 m³/kg, and it has been approved as a prescription treatment for OA in many European countries.⁸³ Some other notable drug treatments include TPX-100 from the United States of America, Condrosan from Spain and Canada, and AS902330 from Geneva.

TPX-100. According to the company's (OrthoTrophix) website, TPX-100 is a 23 amino acid peptide derived from matrix extracellular phosphoglycoprotein and has shown success in cartilage regeneration in large animal models through regulation of hard tissue and phosphate metabolism. TPX-100 is delivered through intra-articular injection and has shown success in phase I and II trials for dentin regeneration. It is currently under randomized, double-blind, placebo-controlled, multidose phase II trials for treating ICRS grade 3, 4 bilateral OA with focal defects no greater than 1 cm. There have been no adverse events from previous clinical and nonclinical studies.⁸⁴ Specific cartilage or bone tissue regeneration, lack of ectopic bone formation, promotion of chondroprogenitor cells, and a long-term pharmacodynamic effect make TRX-100 a viable drug option for treating OA.⁸⁵

Condrosan is a hard capsule of chondroitin sulfate marketed by Bioiberica in Canada and Spain. Publication and clinical studies revealed that Condrosan was found to perform better than Celecoxib, an anti-inflammatory, steroid-based painkiller drug,^{83,86} and reduced cartilage volume loss and marrow lesions in the knee as early as 6 months after administration.⁸⁶ Condrosan represents a symptomatic treatment, and future long-term analysis (phase IV) will help to determine efficiency of pain relief for arthritic patients.

AS902330 is a recombinant form of fibroblast growth factor 18 currently in phase II clinical trials sponsored by Merck KGaA from Geneva. The drug is delivered intra-articularly in the knees of patients with primary OA^{87,88} and measured for safety, efficacy, and residual AS902330 in blood compared against a placebo. Depicting superior performance over MF for clinically diagnosed stage I OA would be the next step in comparing drug treatment with standard of care.

In summary, drugs vary from steroid injection to anti-inflammatory drugs to hyaluronic acid injections. Since these treatments are mainly pain relieving either directly or indirectly, they often require multiple injections and life-long treatment and can be prohibitively expensive for the retired and elderly population. The drug route through the FDA is typically a longer process to demonstrate safety and efficacy in a large cohort, often with multiple comparator groups.

Biologics

Products that use growth factors and/or extracellular matrix in conjunction with cells to repair defects typically fall under the biologics or combination product category according to the CBER.⁴⁰ Similar to the drug criteria, biologic testing requires dosing, safety, and efficacy, and large-scale randomized safety and efficacy studies (phase I, II, and III), with each phase requiring an IND approval for

commencement in the United States. After phase III, a BLA is submitted to the CBER for review and approval.

Autologous cellular products. Utilizing a patient's own cells to repair osteochondral defects is achieved by an initial biopsy or cell isolation, in which cells are expanded *in vitro* and reimplanted into the defect area.⁸⁹ Genzyme's Carticel, one of the pioneers that paved the way for this technology, is also FDA approved and has been used to treat patients since 1995, according to the company's website.⁹⁰ Briefly, autologous chondrocytes are harvested from two full-thickness biopsies (5 × 8 mm) from the patient from a lesser weight-bearing nonarticulating surface and transported to Genzyme through a Genzyme Biopsy Cartilage Transport Kit. After about 6 weeks, the cells are transported back to the medical center and implantation is performed by a trained CARTICEL[®] surgeon. The defect region is prepared by damaged tissue debridement and procurement of a periosteal flap. After confirming homeostasis, the cells are resuspended to the defect region through a catheter and the defect is covered and sutured with fibrin glue and the aforementioned periosteal flap. In general, ACI has favorable reports of regeneration predominantly for a younger population (up to 40 years),^{91,92} whereas chondroplasty and MF are more common and routinely performed with the older age groups (<40 years).⁹³

Most cellular products under the biologic designation employ MSCs from bone marrow, adipose tissue, or umbilical cord with a combination of material and/or PRP and are delivered as a patch or injection.^{94,95} Notable among them are ASCs that are isolated from a patient's own fat pad, which can be processed by medium selection and seeded on a collagen dermal matrix with fibrin glue. Such a study is currently recruiting participants in a phase I clinical trial sponsored by Stanford University, with MF as the comparator group.^{96,97}

The University of Marseille in France conducted a pilot (phase 0) study to evaluate the efficacy and safety of scaffolds comprising fresh nonexpanded autologous bone marrow-derived mesenchymal mononuclear stem cells stimulated with a protein matrix and mixed in a collagen hydroxyapatite scaffold. This cellular paste was then transplanted in the prepared defect arthroscopically, with injection of PRP.⁹⁸

Investigators at the University Hospital of Basel in Switzerland, in collaboration with a nonprofit organization situated in Germany called Deutsche Arthrose-Hilfe, are currently in phase I clinical trials conducted in Switzerland for evaluating the safety and feasibility of implanting an engineered cartilage graft in the femoral condyle or trochlea of the knee after a traumatic injury with one or two symptomatic lesion(s) of grade III, IV, and a defect area between 2 and 8 cm². The graft is obtained by culturing expanded autologous nasal chondrocytes within a collagen type I/III membrane (Chondro-Gide[®]) into the cartilage defect on the femoral condyle and/or trochlea of the knee after a traumatic injury.⁹⁹ According to clinicaltrials.gov, it was found that the current study was a phase I, prospective, uncontrolled, investigator-initiated clinical trial involving 25 patients.

Allogeneic cellular products. Allogeneic products use human donor cells and tissues to repair damaged cartilage, thereby reducing the need for a primary biopsy, reducing

donor site morbidity, and allowing for a one-step procedure. Allogeneic products include morselized tissue and transgenic cells engineered to secrete growth factors,^{100,101} although some of the donor tissues, which are minimally manipulated, are regulated as an organ transplant and not as a biologic.

CARTISTEM[®], a product developed by Medipost Co. Ltd., has currently completed phase III clinical trials in the United States and was approved for clinical use by the Korean FDA. According to the company's website, CARTISTEM contains selectively grown MSCs from allogeneic umbilical cord blood, mixed with sodium hyaluronate, and delivered at the cartilage defect region, although it is unclear from available sources how the solution stays in the defect. The inclusion criteria for the study include patients with cartilage lesions between 2 and 9 cm² in area. The intervention by allogeneic treatment is being compared in clinical trials with MF. The Korean government approved the usage of CARTISTEM as an off-the-shelf stem cell drug manufactured according to GMP standards.^{102,103} The long-term efficacy of the drug treatment is the next question the company will be addressing through phase IV clinical trials.

TG-C, sponsored by TissueGene, Inc., is currently in phase II clinical trials in the United States and in phase IIb in Korea. Delivered through a local injection, TG-C offers a noninvasive therapy that treats the symptoms and causes of OA. Allogeneic human donor chondrocytes are transfected by viral vector to produce transforming growth factor- β 1 and are called the modified cells. The product comprises a 3:1 ratio of unmodified to modified chondrocytes delivered as an intra-articular injection to patients with grade 3 chronic degenerative joint disease of the knee and compared against placebo normal saline injection.¹⁰⁴ Before injecting the cells, synovial fluid is removed from the superolateral portal region of the joint and the knee is laid out straight in the supine position for 2 h during the course of slow injection to obtain a dependent position and avoid shear while injecting.¹⁰⁵

According to the company's website, TissueGene's allogeneic cells (i.e., donor cells) are mass cultured and mass packaged in Dulbecco's modified Eagle medium media and are delivered in a ready-to-inject off-the-shelf form to any patient.¹⁰⁵

Revaflex, used for the treatment of ICRS Grade III and IV articular cartilage lesions of the knee, is marketed by ISTO Technologies and has currently proceeded to conduct phase III clinical trials to evaluate safety and efficacy of the graft versus the MF technique.¹⁰⁶ The engineered tissue implant consists of living cartilage tissue grown in the laboratory, cultured using human cartilage cells. The scaffold is surgically inserted into the subchondral bone using fibrin glue for patients with cartilage defects.

Geographically independent companies like CARTISTEM from Korea, Chondrogen from Osiris, and RepliCart from Australia have marketed products in their respective countries and are currently in the regulatory space for product approval in the United States. Closely following the companies' clinical trials, outcome measures and learning along the way will reduce both cost and time for future applicants and introduce both the investigator and the FDA to a niche treatment modality.

Compared with cell-based products, allogeneic treatments such as MSCs offer the option of tissue storage, commercial opportunity through tissue banking, and also reduce a

patient's time in the hospital, thus reducing overall health-care costs.

Summary of the cartilage treatment technologies

For cartilage repair technologies, devices, drugs, and biologics are the three main pathways to secure US regulatory approval for licensing and marketing. On the one hand, devices currently have yet to show long-term successful cartilage regeneration, but they have adequately been shown to be safe and represent a faster approval route. Drug treatments, on the other hand, currently treat late-term OA symptoms, although many approaches are currently underway to treat early symptoms and results are yet to show long-term successful treatment of OA. Cell therapies present challenges for choosing animals for preclinical models. It is the responsibility of the investigators to ensure close mimicking of the human system; hence, choosing between allogeneic versus autologous cells becomes important. Moreover, choosing the right cellular phenotype, ensuring GMP standard of practice, evaluating the effect of immunosuppressants on overall health, and efficiency of the surgical procedure on older populations must be evaluated even at the preclinical step by using alternatives, such as older animal populations and carefully drafted assay procedures. Some of the major challenges of autologous cell-based techniques are the need for two or more surgeries in addition to production and facility expenses. Additionally, cost to the patient, healthcare expenses, and insurance reimbursement are major role players in determining the route of treatment and availability throughout the country. The principal investigator(s) may save a lot of time, money, and effort if preclinical data that are submitted to the FDA demonstrate durability, safety, and efficacy of the product/treatment/technique. Of special significance is the design of the large animal study and its clinical endpoints as it sets the stage for upcoming human clinical trials. Adequate physician and surgeon training for consistent device delivery into the defect region and employing uniform surgical practices for a given device/biologic dictate the overall power as well as aid in increasing the power of the experimental design.

Animal Studies for Clinical Trials

Small and large animal study

Several parameters to consider when choosing between small and large animals for cartilage repair are clearly outlined by Stannard and colleagues,³⁷ Chu *et al.*,¹⁰⁷ Ebihara *et al.*,¹⁰⁸ and Chang *et al.*¹⁰⁹ They provided extensive information and aid in understanding the balancing factors to leverage the translational potential of an animal model for cartilage repair and employed the information to outline repair strategies and to further refine control groups and outcome measures.

Outcome assessments of typical small animal models (e.g., rodent, rabbit) are mechanical testing, histology, immunohistochemistry, imaging, and gross morphological scoring. Outcome measures in induced defect live animal models such as sheep, dogs, and horses include arthroscopic scoring, computed tomography, radiograph, visual analog scale for pain assessment, range of motion, muscle mass around the defect area, kinematics, and India ink staining for

select biopsied tissue in addition to the ones described above.^{36,110} Immunohistochemistry is specifically relevant for large animal studies for elucidation of collagen II and aggrecan content and distribution.^{36,111} Specifically, please refer to Table 5 in Stannard and colleagues,³⁷ entitled “Comparison of commonly used animals models for carti-

TABLE 5. COMMON INCLUSION AND EXCLUSION CRITERIA TO DETERMINE ELIGIBILITY OF THE STUDY COHORT

Common inclusion parameters

1. Age: Commonly 18–50
2. Approved and signed IRB consent of the subject (includes ability to read, understand, and write)
3. Willingness to participate in postop rehabilitation and clinical assays
4. Normal BMI (≤ 35)
5. Willingness to use more than one contraceptive device for childbearing-aged women
6. Clinically normal hematology and serum values
7. Contralateral knee to be asymptomatic and functional
8. Intact meniscus on both the knees
9. Lesion region should be fillable by implant graft, if used
10. Defect grade: usually grade-III or grade-IV Kellergen–Lawrence
11. Defect dimension requirements (size, diameter, and depth) corresponding to a particular study
12. Sufficient adipose tissue for ASC-based procedures

Common exclusion parameters

1. Pregnant or nursing women
2. History of malignancy or exposure to radiation
3. Autoimmune diseases (including rheumatoid arthritis) and immunocompromised patients
4. Allergy to drugs such as penicillin, acetaminophen, aspirin, ibuprofen, gentamycin, streptomycin, and polymyxin B sulfate
5. Allergy to calcium phosphates, bovine serum, or animal protein as described in the product
6. BMI > 35
7. Currently enrolled in other clinical studies
8. Current or history of alcoholism and/or drug abuse
9. Previous hyaluronic acid, PRP injection, or microfracture technique.
10. Abnormal level of liver enzymes, thyroid level, hepatitis, and anticoagulant therapy
11. Hemoglobin level too low and a very low platelet count
12. Undergone ACL in the last one year or rehabilitation in the last 6 months
13. No history of knee fracture
14. Patellofemoral instability
15. Multiple or kissing lesions
16. For treating lesions: patients must not have previous OA conditions
17. Knee instability, bipolar articular cartilage defect, and axis alignment of tibial spines
18. Anything that restricts MRI (metallic implants or pacemakers in body and gadolinium allergy)
19. Very high-performance athletes who cannot ambulate for 20–30 min a day
20. No amotrophic lateral sclerosis or multiple sclerosis

The values are specific to osteoarthritis, focal lesions of the cartilage, osteoarthritis, and osteochondritis dissecans disease pathology (Source: clinicaltrials.gov).

IRB, institutional review board; BMI, body mass index; ASC, adipose-derived stem cells; MRI, magnetic resonance imaging.

lage regeneration,” which outlines the benefits and challenges of using different animal models for demonstrating cartilage repair. The specific columns entitled “cartilage thickness” and “primary use” clearly correlate with each other and outline the data one can obtain from using a specific animal model, thus enabling the investigators to have an informed decision and understand the capability of the outcome measures. Additionally, the testing paradigms and measurement criteria are similar in both induced defect and animals with natural ailments. The FDA guidance to industry¹¹² indicates that they consider goats, sheep, and horses as acceptable preclinical models. The articular cartilage thickness in the horse is closest to that in humans. However, goats and sheep are recommended given that horses have much larger joints and forces and are not necessarily a relevant model for the veterinary market as patients, nor are they an ethically preferable animal model for induced defects and sacrifice. For goats and sheep as preclinical models, establishment of an appropriate control comparator group is required, preferably MF. Additionally, while employing pluripotent stem cells, issues such as ethical concerns, long-term stability, tumorigenesis, and mutagenesis must also be considered.

However, the challenge with MF in sheep and goats is mimicking the continuous passive motion and restricted weight-bearing rehabilitation protocol used with human patients, which lasts several weeks. Although no model will be perfect for mimicking the restricted weight-bearing period, investigators may consider limited activity, for example, being kept in smaller pens for a period of several weeks before returning to normal activity.

Two important documents for preclinical cartilage repair studies are the *Standard Guide for in vivo Assessment of Implantable Devices Intended to Repair or Regenerate Articular Cartilage*¹¹⁰ by the American Society for Testing and Materials (ASTM) and the FDA Guidance for Industry.¹¹² These documents convey the requirements for the approval of drugs, biologics, devices, or combination products intended to repair or replace cartilage in the knee, and serve as a road map for gaining clinical approval. It is beyond the scope of the current review to delve into FDA and ASTM guidelines, but several reviews and letters have covered the topic extensively, which the reader is encouraged to read.^{71,113,114} Based on the requirements of a typical clinical study, it can be said that a team of a biostatistician, an FDA regulatory consultant, a veterinarian, a biomedical engineer, an experienced orthopedic surgeon, and experts in biomechanical testing, musculoskeletal histology, and diagnostic imaging is necessary to overcome the challenges associated with clinical trials.

Preclinical and simultaneous veterinary market approach

There is logical progression from lab-based research to clinical trials, where stage 2 of research and development branches out to two animal-based applications: preclinical data and veterinary medicine.⁴⁹ The numerous approaches to cartilage therapy have increased the veterinary market population. Preclinical studies conducted in domestic animals such as dogs have facilitated rapid translation into veterinary medicine,³⁷ closing a gap between the human and

TABLE 6. FOOD AND DRUG ADMINISTRATION APPROVAL PATHWAYS FOR CARTILAGE REPAIR PRODUCTS

<i>FDA classification</i>	<i>Responsible center</i>	<i>Submission route</i>	<i>Clinical trial category</i>
1. Drug	Center for Drug Evaluation and Research (CDER)	New Drug Application (NDA)	Investigational New Drug (IND)
2. Device	Center for Devices and Radiological Health (CDRH)	Premarket Application (PMA)*	Investigational Device Exemption (IDE)
3. Biologic	Center for Biologics Evaluation and Research (CBER)	Biologics Licensing Application (BLA)	IND
4. Combination product	Lead center determined after request for designation (RFD)	Determined by Lead Center	IND/or IDE

From McGowan *et al.*⁴⁰

veterinary markets. Transparent publication of methods and results by the scientists who conduct large animal studies will help to establish a unified protocol useful for future investigators. The existing use of cartilage therapy in veterinary medicine creates an exciting opportunity for collaboration between veterinarians and physicians to advance the treatment of injury and disease in both human and animal patients.

Federal Regulations and Clinical Study Considerations

The only cell-based FDA-approved products in the United States are Genzyme's Carticel, a 510(k)-approved mixing and delivery system by Arthrex, and a 361 HTC/P-approved product, DeNovo ET, by Zimmer.¹¹⁵ The FDA in the United States of America has issued specific IND/IDE guidelines on cartilage therapy, and, depending upon the nature of the product, they are classified into different categories and accordingly handled by the designated control centers.⁴⁰

Overall, careful design of the clinical study, selection of intervention and comparator group, patient population, factors affecting enrollment and clinical endpoints, choosing appropriate investigators and medical clinic(s), and allocation of proper funds are crucial for the success of any clinical trial. Special emphasis is laid on choosing the appropriate patient population that targets the appropriate indication as it is crucial to demonstrate efficacy of the drug/product in disease treatment. In addition to careful selection, clinical endpoint determination must be formulated in reference to previous successful and unsuccessful clinical trials, collaboration with research scientists, orthopedic surgeons, regulatory personnel, and technicians to ensure standardization of testing procedures in the event of a multicenter study. Additionally, the FDA considers postsurgery follow-up a significant concern; obtaining more than 85% short and long-term follow-up data on pain, functional testing, and quality of life questionnaires is of great importance.⁴⁰

Clinical endpoints

Cartilage repair therapies include primary and secondary outcome measures, which measure pain and/or function using well-defined scales⁷¹ determined by the FDA. Apart from including robust primary and secondary outcome

measures, including too many individual measurements in a primary endpoint can be limiting financially and prove detrimental to the overall success of both the treatment and control groups. Primary evaluation endpoints are based on pain and function and since it is qualitative, the results depend on the actual success of the repair procedures and the patient population¹¹⁶ and enrollment numbers for statistical considerations. The endpoints for the purpose of clarity are divided into pain scoring and function scoring and typically comprise the following:

Pain based:

- I. Knee Injury and Osteoarthritis Outcome Score (KOOS)
- II. IKDC Subjective Knee Evaluation Form
- III. Symptom Rating Form
- IV. Western Ontario and McMaster University Osteoarthritis Index (WOMAC)
- V. Knee Society Score (KSS)

Function based:

- I. Cincinnati Knee Rating System
- II. Structural changes (magnetic resonance imaging [MRI] and magnetic resonance observation of cartilage repair tissue [MOCART])

The recommended primary and secondary tests included criteria for advanced stage arthritis and for sports-related injuries¹¹⁷ with recommendations from the ICRS. Pain is an important measurement, crucial to the success of the product, and is usually examined as an addition to the primary endpoints (WOMAC/KOOS pain analysis) or as a questionnaire to assess the nature and quality of pain.¹¹⁸

For most devices, tissue remodeling of the cartilage repair is typically measured noninvasively using MRI and MOCART and information regarding device and defect location, cartilage thickness, volume loss, and repair tissue characteristics, all considered as crucial secondary endpoints that demonstrate product efficacy, which further require standardization and validation across several instruments.^{119,120} However, for specific drugs that delay the onset of cartilage degradation, they are FDA approved to employ IND studies with the use of X-rays or MRI.¹¹⁹

Once again, the emphasis lies on selecting important primary and secondary endpoints and ensuring the elimination of redundant data sets. Maintaining uniform measurements

throughout the study and throughout all of the campuses in cases of multicenter trials is of paramount importance as this uniformity affects the overall quality of the data. Standard protocols, uniform time points, and diligent reporting of any aberrant information ensure hassle-free and expedited review of the data. In addition, clinical measurements, including general health data, reimbursement outcomes, and overall quality of life, can be collected and positively used to obtain the product in the market.

The primary outcome measures in clinical studies, namely pain and function, are different from preclinical studies, where the emphasis is on an objective analysis of cartilage morphology/structure. This difference can pose challenges in designing the clinical study and selecting outcome measures that will demonstrate the advantages of the therapy in a practical/feasible manner for clinical investigators and patients. Clinical studies of ACI versus MF, in which repair tissue was biopsied and evaluated histologically, did not find an association between better structural repair and improved clinical outcomes (pain and function) at 1–2 years of follow-up.¹²¹ Studies of ACI using a characterized cell therapy (termed characterized chondrocyte implantation [CCI]), where patients were followed long term, did not demonstrate superior clinical outcomes over MF until 3 years postsurgery¹²²; the clinical outcomes were again comparable between the two groups at 5 years, except for a cohort of patients who were treated early (<3 years from onset of symptoms) and who did experience clinical benefits with CCI.¹²³ This finding suggests that the clinical benefits of producing more hyaline-like repair tissue may take many years to translate into improved clinical outcomes and may be restricted to certain patients/injuries. Consequently, clinical trials for cartilage repair technologies may require long-term follow-up and careful enrollment to reach endpoints, thereby increasing the financial burden of product development. Ongoing work in the development and validation of new biomarkers for cartilage repair and joint preservation will be valuable for the translation of cartilage repair technologies, especially if biomarker(s) can be used at early time points to predict long-term outcomes.

Other commercialization considerations

It is important to note that FDA approval of a cartilage repair therapeutic, regardless of the specific regulatory pathway, depends not only on completion of a successful clinical trial but also on establishment of design control, GMP manufacturing processes, and quality control systems to ensure safety and efficacy of drug/device products. FDA clearance of a device/drug and medical need do not guarantee coverage by insurance companies. Therefore, a reimbursement strategy is often critical to the commercial viability of a cartilage repair product. While the FDA focuses on safety and efficacy, insurance companies focus on superiority of the product relative to the gold standard and economic evaluation (e.g., cost per quality-adjusted life year).¹²⁴ To determine coverage, it is possible that insurance companies may require data beyond those provided to the FDA for clearance to determine drug/device value and impact on patient care, depending on if/how the clinical study was conducted. It may be advantageous to consider the requirements for FDA approval and reimbursement simultaneously in designing the clinical efficacy study.

Conclusions

Although there are several surgical and tissue engineering-based treatments that treat osteoarthritis and other cartilage disorders of the knee that have achieved differential success rates for both short and long terms, a successful product line recommended uniformly across all healthcare facilities does not exist. While many upcoming products are at different stages in their FDA trials, there is still an unmet need for a translational technology for cartilage tissue engineering.

Common tissue engineering approaches for cartilage regeneration can be broadly divided into cell-based and material-based strategies. Cell-based strategies include autologous or allogeneic chondrocytes, bone-marrow MSCs, and ASCs. Currently, under the FDA, the only cell-based therapy is Carticel from Genzyme. While cell-based therapies offer great potential for regeneration, they require two surgeries (if autologous) and can be costly. Allogeneic treatments offer greater convenience, but carry additional risks of infection, immune rejection, or graft-versus-host disease, which makes the cell-based therapy system financially demanding and a long path to FDA approval.

Material-based strategies such as osteochondral plugs and injectable paste-like materials offer a one-step solution, which is financially appealing, and may ensure uniform treatment across several institutions without worrying about device implantation and contamination. However, long-term efficacy in terms of cartilage repair and functional restoration of a device system has not yet been demonstrated. Currently, Zimmer Orthobiologics is in the final stages of obtaining FDA clearance and around five other products from different companies based in other countries are in phase 3 or 4 clinical trials on the brink of securing approval to use in respective countries.

Drugs, on the other hand, consist of predominantly intra-articular injection or oral capsules taken by the patient at regular time intervals, although demonstrating efficacy with these approaches for treating large defects or advanced stage osteoarthritis has proven to be difficult. Such injections are expensive and are mostly focused on relieving pain. While such approaches may in general not be considered regenerative medicine strategies, they reduce pain and restore daily function for a finite period of time.

The time period from commencing feasibility (i.e., phase 0) clinical trials to actual product sales in the market is dependent on several factors, such as success of the clinical trials, selection of primary and secondary endpoints for the clinical study, establishment of approved protocols, creation of a manufacturing process to meet GMP standards, and working with a fine team to address concerns. One important factor to consider is the selection of a proper comparator group (i.e., control, standard of care). The information from clinicaltrials.gov suggests that ACI, OATS, and MF are commonly used as comparators for most devices and biologics, with a trend toward using MF for late-phase clinical trials. Owing to being the most common surgical treatment for cartilage injury and having zero product cost, MF is the gold standard of comparison that orthopedic surgeons will need to see a product surpass if a company wants to convince the surgeons to adopt their product. MF has thus emerged as a preferred control group for clinical trials and

we recommended it as the comparator for preclinical and even small animal cartilage repair studies as well.

It is worth emphasizing that MF may also be a desirable first step for certain cartilage repair devices. For example, a porous chondral-only (as opposed to osteochondral) device approach could leverage the infiltrating cells from the marrow for cartilage regeneration as opposed to requiring exogenously seeded cells before the surgery.

In addition to selecting an appropriate comparator, other important factors that need to be emphasized for running successful clinical trials include knowledge of common inclusion and exclusion criteria, strategies to improve the power of the clinical trial, ensuring successful enrollment, choosing the right geographic location, and establishing uniform data collection in the case of multi-center trials. As already mentioned, adequate care must be taken to include pain measurement and important primary and secondary endpoints that can also be used for future funding agencies.

In general, the route taken to achieve federal regulatory approval may seem daunting, but with multidisciplinary expertise, an understanding of the dynamic regulations, and lessons learned from animal studies, we can expect to formulate better study design aimed toward translational goals.

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