

Cartilage Repair: What's the Right Combination?

START-UP counts some 40 commercial development efforts in cartilage repair and regeneration, most of them within small start-ups. Almost 15 years after the introduction of *Carticel*, the first cell-based implant for cartilage repair, are we any closer to knowing which combination of technologies and business models will help companies penetrate this challenging market?

BY MARY STUART

- The repair of cartilage, especially in the knee, remains an unsatisfied market populated by large numbers of patients demanding better solutions.
- First-generation product *Carticel*, introduced by Genzyme in 1995, provided a good validation of cell-based therapies for the regeneration of articular cartilage, but also elucidated the challenges and difficulties of this market.
- There are at least 40 companies aiming to serve a waiting market, offering various combinations of scaffolds, cells, growth factors, and glues. Many products are commercially available following small clinical trials, and the absence of significant clinical data is creating a crowded and confusing category.
- The lesson many companies learned from *Carticel* was the desire for a one-step procedure for patients and surgeons, and that's the focus of several "second-generation" companies; but many would argue that's not the point...yet.
- One hurdle remains the demonstration of efficacy, both in the short term and beyond two years. Genzyme and others are finally doing this with statistically powered clinical trials, which hint that efficacious products will come to market in the foreseeable future.
- It's also not clear what kind of products the market is looking for—products with the potential for long-term durability, as the cell-based products promise? Or will the market prefer lower-cost, minimally invasive pain-relieving procedures to bridge patients to the next options? Start-ups are placing their bets on one side or the other.

The recipe for hyaline cartilage—the slippery cartilage in the knee joint—is simple: seven parts water, two parts collagen, and one part glycoproteins. That simplicity, however, belies the complexity of how cartilage functions in the knee to keep the joint smoothly gliding under compression and shear forces, and is in contrast to just how difficult it has been for industry to come up with products to replace worn and injured cartilage.

Today, patients of all ages with knee pain due to degenerated cartilage can do very little to stave off the ultimate descent of the injured knee into osteoarthritis and the eventual need for a total knee replacement. In failing to properly cushion the knee and keep it in alignment, damaged cartilage will contribute to the degenerative process of the joint until one day a prosthetic knee joint is necessary. Although the longevity of total knee implants is improving and the age of potential recipients falling, this is still not the ideal solution for most patients under the age of 60, given the fact that a total knee replacement may last for 20 years at best.

That leaves a large, unsatisfied group of active patients aged 20 to 60 that, despite their cartilage injuries, still want to run, ski, garden, play basketball, or simply move about without pain. In the US, there are approximately 500,000 cartilage-related treatments running the gamut from an arthroscopic clean-up of ragged cartilage tissue to the implantation of cultured autologous cartilage cells, but in many patients, pain relief is only transient, and a large proportion of them are back in the doctor's office within two years, again seeking relief from pain.

Current options for pain relief include debridement and lavage, a cleaning procedure to smooth rough cartilage edges and remove debris in the joint, and microfracture, the most common first-line treatment for cartilage damage. In this procedure, the surgeon punches holes in the subchondral bone to let in blood to promote the formation of a fibrin clot, as well as the migration of stem cells, growth factors, and

other helpful agents from the bone marrow to the site of injury. This procedure results in pain relief, and is in fact the gold standard against which all new cartilage repair therapies are measured in clinical trials.

However, many patients don't experience long-term relief. Microfracture results in the formation of fibrocartilage, which doesn't have the same mechanical properties as normal hyaline cartilage. A thousand or so patients each year undergo osteochondral grafting procedures—the implantation of plugs incorporating both bone and cartilage taken either from a non-weight-bearing portion of a patient's own knee, or allograft tissue. The weak link in these interventions is the interface between the graft and cartilage, where implants often fail to integrate.

Finally, there is autologous chondrocyte implantation—the *Carticel* procedure pioneered by **Genzyme Corp.** In that procedure, healthy cartilage cells are biopsied from a patient's knee, sent off to an expansion facility, and after four to six weeks, a sufficient number of cells are sent back to the hospital to be reimplanted into the knee. There have been approximately 12,000 *Carticel* implants since the product's introduction in 1995, at the rate of 1,000 to 1,500 procedures a year. It works well for many patients, with durable results, but has several drawbacks, including its expense—an average of \$26,000 per procedure (depending upon how large the defect is and how many vials of cells are required), the difficulty of the surgical implantation procedure, and the inconvenience of a two-stage procedure, in addition to its uncertain efficacy for a large number of patients. Still, *Carticel* is the standard by which new companies measure improvements in the field, and many believe they can, with improved economics and increased efficacy, capture larger percentages of patients, although it won't be easy.

UNUSUALLY CROWDED AND CONFUSING

Cartilage repair and regeneration present a long list of requirements, and no single product or technique has yet been able to meet them all. Articular cartilage is a highly specialized tissue that's only found on

long bones. It is avascular and very limited in its ability to repair itself. It's required to cushion compressive, tensile, and shearing force and transfer loads during motion, and is much more slippery than ice. The biomaterial or engineered tissue designed to meet those requirements must be able to stay where it's put in

Exhibit 1

Selected Cell-Based Cartilage Repair Products

COMPANY	APPROACH
Advanced Technologies and Regenerative Medicine LLC	<i>CAIS (Cartilage Autograft Implantation System)</i> is one-step system (no culturing/expansion step) that morselizes autologous cartilage harvested arthroscopically in the OR, and seeds scaffold with the harvested tissue. Phase III study ongoing. J&J's Depuy Mitek is development and marketing partner.
Arthro Kinetics	<i>CaReS</i> Cartilage Regeneration System for focal, large articular cartilage defects in the knee using ACI* is a collagen matrix embedded with cells. Products are commercialized in China, Taiwan, and Hong Kong. <i>CartiPlug</i> is a high-density, compressed, off-the-shelf acellular collagen matrix.
CellCoTec	Single-surgery <i>INSTRUCT</i> harvests two tissue types in the OR: cartilage and bone marrow. Automated cell processor extracts cells and seeds them into scaffold for implantation. Preclinical phase complete, about to begin clinical trial in Europe.
CellGenix	<i>CartiGro ACT</i> (Autologous Chondrocyte Transplantation) plus <i>Chondro-Glide</i> collagen membrane from Geistlich Biomaterials. Marketed by Stryker in Austria and Germany.
Genzyme Biosurgery	In addition to <i>Carticel ACI, MACI</i> , (Matrix-assisted autologous chondrocyte implantation) is on the market in Australia and Europe and in clinical trials in the US. New product is seeded onto a collagen membrane that can be implanted without suturing, the latter being a drawback of the <i>Carticel</i> procedure.
Histogenics	<i>NeoCart</i> is new cartilage grown <i>ex vivo</i> in hydrostatic device that simulates conditions in the knee; low oxygen, cyclic pressure. Two-stage procedure begins with biopsy, ends with new cartilage shipped back to the surgeon. Completed Phase II, beginning large pivotal trial.
Interface Biotech	<i>Cartilink-3</i> is third-generation ACI* technology. Based on <i>ASEED</i> biodegradable porous scaffold technology developed by Coloplast.
ISTO Technologies	<i>DeNovo ET</i> is implant grown from allogeneic juvenile chondrocytes. ISTO cultures tissue in its manufacturing facility, delivers new cartilage tissue to surgeons. Has co-development agreement with Zimmer.
ProChon Biotech	Autologous cartilage regeneration system <i>BioCart</i> is two-stage process that uses a variant of fibroblast growth factor to expand de-differentiated cartilage cells. Cuts down cell processing lead time to two weeks (vs. six weeks for first-generation ACI* approaches) and yields predictable number of cartilage cells, which are dispersed evenly throughout a 3D matrix.
RTI Biologics	Fresh-stored osteochondral allografts; <i>CR Plug</i> , cancellous and demineralized bone plug.

*ACI=Autologous Chondrocyte Implantation

SOURCE: Company interviews and web sites

a dynamic, load-bearing joint; integrate with native tissue; and function stably for years. In short, the goal is to fill in the cartilage defect with a product that is as much like natural hyaline cartilage as possible.

Orthopedics companies, biomaterial and tissue engineering firms, and venture capitalists know there is a large and waiting market for the right product, and that's undoubtedly why at least 40 companies are focused on cartilage repair. They group themselves into several camps, and *START-UP* spoke with select representatives of each (finding it difficult to comprehensively cover a market where the entrants are so numerous). There are those that believe cells will be necessary to create hyaline-like cartilage, and among those, there is a split between technologies focused on improving the commercial feasibility of a two-step procedure (biopsy, followed by a period of cell or tissue culture, then a second procedure for implantation of the final product), in the manner of *Carticel*, and those that insist a one-step procedure will ultimately be critical for surgeon and patient adoption. Our interview subjects **ProChon Biotech Ltd.** and **Histogenics Corp.** belong to the first group; **ISTO Technologies Inc.** and **CellCoTec BV** to the second. (See Exhibit 1.)

Many companies feel that specially engineered scaffolds will be enough to encourage native agents to form hyaline-like cartilage, perhaps preferring the well-understood regulatory pathway offered by devices under the aegis of CDRH rather than the biologics agency CBER. In this group, we spoke with **Kensey Nash Corp.**, **Regentis Biomaterials Ltd.**, and **Carticept Medical Inc.** And finally, one start-up, **NuOrtho Surgical Inc.**, developer of an electrosurgical instrument for cartilage contouring, hopes to eliminate pain and buy more time for patients' knee joints with a new alternative to debridement. (See sidebar, "Cartilage Contouring Preserves Tissue.")

It would seem, from the multiplicity of companies approaching cartilage repair and the diversity of their offerings, that the field is still wide open. That diversity reflects the extent to which the cartilage repair market still remains somewhat undefined. Companies operating here tend to estimate the size of the market for their products as approximately 500,000 patients, the number of knee cartilage procedures today. But that doesn't take into account the number of people that have cartilage damage, nor which patients should be treated to prevent joint degeneration.

It's also not clear what kind of product the market is looking for—products with the potential for long-term durability, as the cell-based products promise? Those expensive and complex biological products—as well as any other product that requires an invasive surgery—will require large, carefully controlled clinical trials demonstrating long-term efficacy, if they're ever going to be paid for in a cost-constrained global health care environment.

Or will the market prefer lower-cost, minimally invasive pain-relieving procedures to bridge patients to the next options? Indeed, some of the largest products for osteoarthritis—chondroitin sulfate and hyaluronic acid—bring in billions of dollars, even though they haven't been proven efficacious in clinical trials, simply because of their ease-of-use and lower cost. Injectable and arthroscopically delivered biomaterials may succeed if they provide temporary results, simply because of their cost and lower barrier to entry.

The large variety of products may also be a function of the diversity of patients in the cartilage repair market, each perhaps responding better to one approach than another. Younger patients may have a different healing status than older patients, or a different need for durability. A small defect might be more amenable to a low-cost biomaterial-based product than a large one, and osteoarthritis might require a different solution than a fresh sports injury. Full-thickness defects, which allow blood into the wound site, clearly respond differently to treatment than superficial defects. These variables complicate the process of finding the right combination of product attributes for the right set of patients, but they also give start-ups hope that there is a sweet spot for their particular technology.

WHAT WE KNOW NOW THAT WE DIDN'T KNOW THEN

There's still some distance to cover; the next products are several years away from market launch, but companies that have taken the time to study large numbers of patients in controlled clinical trials are advancing knowledge in the field, and time is lending some perspective to first-generation treatments.

Genzyme is now in a position to give orthopedic surgeons the 10-year data that they really long for. In March 2008, the company announced findings from a large, multicenter, observational study that investigated the long-term durability of *Carticel*. The study

Exhibit 2
TiGenix Pivotal Trial Highlights

Trial began in 2002; multicenter trial (13 surgeons at 13 orthopedic centers in Europe). Prospective randomized controlled trial, 118 patients randomized, aged 18-50 with grade III-IV symptomatic cartilage defects, 61 to microfracture, 57 to <i>ChondroCelect</i> .
Goal: to assess the efficacy of <i>ChondroCelect</i> as a first-line treatment for symptomatic cartilage defects of the knee compared with microfracture.
End points: structural superiority (better quality of regenerated tissue at 12 months as assessed by histologic examination); improved clinical outcome in the short term that is at least comparable in both groups.
Results: at 12 & 18 months the combined structural and clinical primary end points were met.
Three-year data demonstrated continued improvement in the <i>ChondroCelect</i> patients; 83% of patients treated with <i>ChondroCelect</i> improved vs. 61% of microfracture patients. <i>ChondroCelect</i> group also had lower failure rate at three years; two interventions required compared with seven in the microfracture group.
New findings: the sooner patients were treated with <i>ChondroCelect</i> following the onset of symptoms (within two to three years) the better the clinical outcome.

SOURCE: *American Journal of Sports Medicine*, Vol. 36, No. 2, pp. 235-246, February 2008.

found that the majority of patients who experienced improvement in knee function at early follow-up sustained their improvement at 10 years. Meanwhile, Genzyme is also moving forward, with a new autologous chondrocyte implantation (ACI) program in clinical trials, called *MACI*, for matrix-assisted chondrocyte implantation, for which it paid Verigen AG \$50 million, as well as a new product designed to halt osteoarthritis, acquired from **Osiris Therapeutics Inc.**

TiGenix NV was the first company with a cell-based cartilage repair product to complete a large, prospective, randomized study.

TiGenix set out to make improvements to ACI in two ways: by improving the quality of the cells chosen for implantation, and by simplifying the surgical implantation procedure. The company has discovered specific molecular markers that help it select and implant only those cells capable of forming stable hyaline-like cartilage, that is, cells that retain their pre-culture phenotype (since cartilage cells tend to de-differentiate in the expansion process).

The results of TiGenix's pivotal study, published in February 2008, yielded two new insights that will help advance the field. The ACI product *ChondroCelect* was superior to microfracture in

Cartilage Contouring Preserves Tissue

It is one of the major challenges of orthopedics that repairs for problems of the joints employ fixation techniques requiring the drilling of bone to place screws and plates. These techniques have the unwanted effect of damaging healthy tissue during the repair process, and when dealing with degenerative processes that might require more interventions in the future, tissue damage may compromise future repair efforts. **NuOrthoSurgical** came into being specifically to achieve the goal of tissue preservation in orthopedic repair procedures.

NuOrtho was founded last year by orthopedic surgeon Wayne Auge II, MD, who, in his ongoing quest to make existing procedures better, has developed many products that are currently on the market, and Roy Morgan, an engineer with an expertise in radiofrequency energy. Morgan worked at Stryker Endoscopy (and at Nipro, Abbott Laboratories, and Artemis Medical). The two began creating a patent portfolio about 10 years ago—seven patents have issued and more have been filed—and in 2008 formed NuOrtho Surgical to commercialize tissue-preserving ways of accomplishing orthopedic repairs. The company raised \$1 million from private investors in March 2009 and is focused on getting its first product to market in the area of cartilage contouring for the knee.

NuOrtho has a patented technology platform with multiple applications in soft tissue treatment and bone fusion. Its core technology is an instrument that delivers low levels of radiofrequency (RF) energy and is not yet FDA approved. In addition to the low levels of RF, the architecture of the NuOrtho probe also helps it avoid tissue damage because it protects the electrodes from coming into direct contact with tissue. The device is not ablative, as are the plasma-based RF devices of other orthopedics firms; those higher-energy devices are used to clear unwanted tissue from a joint and are alternatives to mechanical shavers and cutters. Rather, NuOrtho is positioning its device for the treatment of cartilage, as an early-stage intervention that staves off osteoarthritis, one of the leading indicators of which is fraying articular cartilage. The NuOrtho treatment is designed to create a smooth cartilage surface without cutting, shaving, or heating tissue to a high degree, all of which create collateral tissue damage. CEO Jeffrey Morrill, who once headed the RF business at Johnson & Johnson's Depuy Mitek division, says of the technology, "The ability to contour soft tissue without killing it is a breakthrough."

Morrill says that today, approximately 20% of cartilage lesions are treated, leaving some 2.6 million lesions unattended because of a lack of viable products. (In other estimates, focal chondral defects are found in 63% of patients undergoing arthroscopy of the knee). The goal in knee care is to alleviate patients' pain and keep the knee joint functional until the day a patient needs and is eligible for a total knee replacement. Indeed, Morrill imagines a future in which patients might have their articular cartilage contoured periodically to delay a knee replacement. Meanwhile, Morrill also notes that while there is a lot of development going on in the area of cartilage implants, there is still a need to prepare the defects to receive the implant, a market Morrill hasn't factored into his forecast for the company's controlled commercial launch next year.

NuOrtho is about to begin its 510(k) process and will build out manufacturing capabilities for its probes for an anticipated market launch in 2010. NuOrtho will avoid the capital equipment model by sourcing power generators for its RF device from existing suppliers already serving hospitals with RF generators, like **Valleylab Inc.** (a division of **Covidien Ltd.**) and **Erbe Elektromedizin GMBH**.

After gaining experience with knee surgeons in the chondroplasty indication, NuOrtho will be prepared for an even larger market in bone fusion, where it will begin in ACL (anterior cruciate ligament) repair. To repair a torn ACL, a surgeon may drill two tunnels, put a bone plug in, and insert screws, Morrill explains. Those fixation procedures damage healthy tissue, and down the road, if the patient retears his ACL, the doctor must address the prior screw placement and find new real estate in which to put new screws. "What if you could displace screws in an ACL procedure by using energy to stimulate and fuse bone to bone?" Morrill asks. That's where the company is going, he says, and it has seen success in the lab.

Morrill points out that NuOrtho has not just a single product, but a platform. The company's technology allows for minor development adjustments to apply its solution to other parts of the anatomy, including the hip or shoulder, or in other applications where the ability to contour soft tissue without killing it is a benefit, such as the craniomaxillofacial market.

For now, however, the company is focused on finding a strategic partner to help it gain rapid penetration into the knee market.

both the structure of the cartilage formed and in terms of clinical outcomes, and that superiority was even more pronounced over time. (See Exhibit 2.) Says Jens Riesle, chief scientific officer of CellCoTec BV, “Surgeons have always said, ‘Show us high-quality clinical data that demonstrate that cell-based technologies are really better than other technologies.’ Now they have it, and more importantly, there is a correlation of the clinical outcome with the repair tissue.”

The trial yielded a second insight: patients who were treated soon after the onset of their symptoms fared better than those who were treated later. Both findings support the elevation of ACI up to a first-line therapy.

Indeed, Mitchell Seyedin, PhD, president and CEO of ISTO Technologies sees a great value proposition in the early treatment of damaged cartilage, he says, because “it will prevent costly surgical procedures and disability and improve the quality of life for patients. We believe that the ability to regenerate cartilage and restore function will reduce lifetime costs for patients and for the overall health care system”

CARTILAGE THAT’S BETTER THAN YOUR OWN

In viewing *Carticel* as a clinical success, but not a commercial one, many saw as disadvantages the expense of Genzyme’s custom-manufacturing infrastructure, and the awkwardness of a two-stage procedure, broken up by an interval of four to six weeks during the cell expansion process. ISTO Technologies Inc. took on both of those challenges—the scalability of the product and the ease of delivery. ISTO uses allogeneic cells derived from juvenile cartilage tissue, because, according to Seyedin, they are much more potent at generating new tissue than adult cartilage cells. Compared with other tissues, cartilage is also a good candidate for allografting, because it’s immune privileged and can be implanted without fear of rejection. As for ease of delivery, ISTO grows hyaline-like cartilage in its manufacturing center and delivers to surgeons a pure, shiny, cartilage matrix, called *DeNovo ET*, which can be cut and affixed to the defect with biological glue. The company has no need for scaffolds; the cartilage cells make their own.

ISTO’s key patent revolves around the company’s method of expanding juvenile cartilage cells, a process that is not easy, says Seyedin, because cartilage cells are very susceptible to change. “They change morphologically, and become something else. We managed to find the right conditions, the right biological growth factors, and the right medium to grow these cells without changing them. We still have potent cartilage cells after expanding from a few million to several billion cells, and that gives us an off-the-shelf, scalable technology.” It takes a month or longer for the company to manufacture cartilage tissue, but the company can also take advantage of the product’s extended shelf life.

Seyedin believes ISTO is in a good position vis-à-vis the com-

petition. “Many companies are working on developing autologous cell-based technologies, but we believe these approaches will not be as effective due to scale limitations and the inherent superiority of ISTO’s cells.” Seyedin also points out that there are companies developing scaffolds alone, which are capable of providing off-the-shelf products, “but these may be useful only to treat small defects.”

Seyedin pegs his company’s initial market at 500,000 procedures per year in the knee (in the US), with a future similar-sized market in discogenic back pain where ISTO is developing *NuQu*, an injectable formulation of juvenile chondrocytes for early intervention in disc degeneration. ISTO has received FDA approval to begin a Phase I clinical trial for *NuQu*, which is scheduled to start in late 2009, and is seeking a marketing partner for the disc degeneration product. Altogether, Seyedin believes ISTO is addressing markets worth well over \$1 billion.

For now, ISTO is conducting clinical studies on *DeNovo ET*, in partnership with **Zimmer Holdings Inc.**, which became the company’s development and marketing partner under an agreement signed in 2002. The companies are working together on a second cartilage repair product, *DeNovo NT*, for which a post-market study is ongoing, to look at the use of particulated juvenile cartilage in the knee joint.

To date ISTO has raised just under \$40 million from a group of investors that includes Alafi Capital Partners, Ascension Health, Life Sciences Partners, Mid-American Transplant Services (its partner on tissue procurement), and Zimmer.

ELIMINATING THE TWO-STEP HASSLE

At a recent meeting of the International Cartilage Repair Society, Jens Riesle, PhD, chief scientific officer and a co-founder of CellCoTec, heard one surgeon refer to autologous chondrocyte implantation as “a two-step hassle.” The grumbling affirmed his own company’s mission. Founded in 2004 by a group of scientists formerly with biomaterials firm IsoTis (since acquired by **Integra Life-Sciences Holdings Corp.**), CellCoTec set out to develop a one-step autologous cell implantation procedure.

CellCoTec is still using autologous cells, but it has obviated the weeks-long expansion step required by *Carticel* and other ACI therapies to deliver a sufficient volume of cells to the defect. CellCoTec accesses its cells in the operating room during the implantation operation.

CellCoTec’s therapy uses two cell types—bone marrow and primary chondrocytes—in a product called *INSTRUCT*, “because one cell type tells the other what to do,” says Riesle. The two cells work synergistically to increase the yield of new cartilage. A third ingredient is a biomaterial scaffold tailored with the key mechanical properties of natural cartilage, so that at the time of implantation, mechanical functionality is restored. The scaffold is biodegradable, and as it degrades, the cells in the cartilage defect begin to make cartilage tissue.

The *INSTRUCT* procedure begins like the first step in ACI; the surgeon obtains cartilage cells by taking about 200 to 300 milligrams of cartilage from the edge of the joint, along with approximately 5 milliliters of bone marrow. The two tissues are put into a

**“Surgeons have always said, ‘Show us high-quality clinical data that demonstrate that cell-based technologies are really better than other technologies.’ Now they have it.”
—Jens Riesle**

small cell processor box containing some disposable components, which will automatically extract the cartilage cells out of the cartilage tissue, remove the red blood cells from the bone marrow, combine those two cell types after washing them, and finally, insert them into the interior of a scaffold, a porous composite of fibers that promotes cell uptake. The scaffold is now ready for implantation. The surgeon removes it, affixes it in the defect, and sutures the knee closed. That's the ultimate vision of the product, at any rate, in which the surgeon will put harvested tissue into the cell processor box and the device will do the rest. While CellCoTec validates the therapy in its first clinical trial, which will begin this year, surgeons will perform these steps manually.

CellCoTec plans to perform histological and surgical assessment to determine the type of tissue formed, to ascertain if it is in fact hyaline cartilage. If CellCoTec is successful, its product will not only be more convenient than ACI, but less costly. "We don't have the costs connected with expensive clean rooms and people to expand cells. We are providing a cell processor that process cells and combines them with a scaffold, and that's it," says Riesle. That also puts the company on a completely different regulatory road, he says, on the medical device path, at least in Europe, rather than the biologics route.

There don't appear to be any competitors offering one-step autologous cell therapies apart from **Johnson & Johnson's Depuy Mitek Inc.** division, with its *Cartilage Autograft Implantation System (CAIS)*, licensed from **Advanced Technologies & Regenerative Medicine LLC** and in Phase III clinical trials. *CAIS* consists of one device for morselizing cartilage, and a second one for placing it onto a scaffold in the OR. For the sake of argument, says Riesle, "Let's assume *CAIS* works. Most of the orthopedics companies won't have a product that competes with it. The market is certainly big enough for more than one company."

THE DEVICE ROUTE TO CELL SUPPORT

A large number of companies is focused on acellular implants, scaffolds specially designed to encourage cell ingrowth and cartilage regeneration. (See Exhibit 3.) Many feel that since the tissues within the knee need to be stabilized from a biomechanical standpoint anyway, a scaffold is the right place to start. Once that

Exhibit 3

Selected Acellular Cartilage Repair Products

COMPANY	APPROACH
BioSyntech	<i>BST-CarGel</i> is thermosensitive gel that is liquid at room temperature, solidifies at body temperature. Material is mixed with patient's blood at the time of the surgery and injected into the defect. Chitosan component promotes adherence. Results from ongoing multicenter pivotal trial (for the repair of cartilage lesions when applied to a microfractured lesion) on 80 patients expected in the first half of 2010.
Carticept	Permanent implant designed to replace, not repair, damaged cartilage is composed of PVA that has been crosslinked for additional strength. IP also includes surface patterning technology that fosters strong attachment of a polymer to bone. On the market in Europe, Carticept will conduct clinical trials in the US in MTP (small joint) indication, then knee repair.
Cartilix	<i>ChonDux</i> cartilage repair system. Photopolymerized hydrogel made of PEG and hyaluronic acid reinforces clot, discourages fibrous tissue growth following microfracture. Functionalized chondroitin sulfate adhesive supports cartilage attachment at interface.
Kensey Nash	Biphasic cartilage repair device creates optimal environment for cartilage growth; implant has a collagen zone for cartilage growth and a ceramic zone for bone growth. Company has submitted its IDE application.
LaGeT Musculoskeletal	Laser start-up stimulates growth of articular cartilage using ultraviolet laser light to stimulate expression of a therapeutic gene.
NuOrtho Surgical	Low-level RF energy probe is tissue preserving alternative to debridement in the knee joint.
Orthomimetics	Resorbable dual-layer porous implant containing collagen, glycosaminoglycan, and calcium phosphate encourages both the simultaneous repair of both the cartilage and the bone to which it is attached. In clinical trials.
Regentis Biomaterials	Implant to foster healthy cartilage formation after microfracture. Company crosslinks denatured fibrinogen with PEG. The device can take the form of a gummy substance that can be press fit in an open surgery, or the biomaterial can be injected in a liquid form that a UV light source solidifies <i>in situ</i> .
Smith & Nephew	<i>Trufit</i> is porous, resorbable scaffold composed of PLG and calcium sulfate. Comes in the form of a plug that can be press fit into osteochondral defects to support cartilage and bone repair.

SOURCE: Company interviews and web sites

is proven, many believe cells or growth factors can be added at the time of the surgery, or encouraged to enter the implanted matrix.

Russell Kronengold, PhD, VP of biomaterials research at Kensey

Nash, describes his company's device as a biphasic construct designed to repair both the articular cartilage and the underlying bone, and not necessarily because the bone has also been damaged, but rather because the company is trying to set up the conditions that promote cartilage formation.

One approach to tissue engineering is to rekindle or restart the developmental process that gives rise to a certain tissue, Kronengold says. "During fetal development, cartilage growth is linked directly to bone maturation, a synergy thought to be guided by biomechanical and biochemical signaling. We believe that the key to regenerating damaged articular cartilage is to also regenerate the underlying bone, by providing a dual-phase matrix with biomechanical and biochemical properties suited to both of these tissues."

Kensey Nash's construct for cartilage repair thus has two zones: a collagen region tailored to cartilage repair and a ceramic polymer component in the bone region. The scaffold is designed to restore the biomechanics of the knee so the patient can begin loading the joint and walking, but over time, it will resorb as cartilage and bone cells lay down their own matrix. The implantation procedure involves coring out the lesion in a circular fashion, and inserting the plug hydrated with bone marrow aspirate. The plug will swell slightly, anchoring it within the defect site. The company has completed preclinical testing on the implant and has submitted its IDE application to the FDA, and it hopes to

Exhibit 4

Cartilage Repair Products Currently in US Trials

PRODUCT	COMPANY	STUDY (TARGETED ENROLLMENT)	STATUS
<i>CAIS</i>	Depuy Mitek	Multicenter, randomized pivotal study to evaluate the safety and efficacy of the <i>Cartilage Autograft Implantation System</i> (300)	Phase III
<i>MACI</i>	Genzyme	Prospective randomized open-label parallel-group multicenter study to demonstrate the superiority of <i>Matrix-Assisted Autologous Chondrocyte Implantation</i> vs. arthroscopic microfracture (144)	Phase III
<i>NeoCart</i>	Histogenics	Randomized comparison of <i>NeoCart</i> with microfracture (30)	Phase II completed (but still blinded)
<i>BioCart II</i>	ProChon Biotech	Investigate the efficacy and safety of <i>BioCart II</i> in comparison with microfracture (40)	Phase II
Mesenchymal stem cells	Royan Institute Tehran University of Medical Sciences	Treatment of full-thickness articular cartilage defects in the knee with autologous bone-marrow mesenchymal stem cells and scaffold	Phase I
<i>CR Plug</i>	RTI Biologics	Evaluation of the composite of cancellous and demineralized bone plug for repair of defects created at the harvest site during the OATS procedure (20)	Phase III
<i>ChondroCelect</i>	TiGenix	Prospective multicenter randomized controlled trial of <i>ChondroCelect</i> vs. microfracture (112)	Phase III
Mesenchymal stem cells	Ullevaal University Hospital	Mesenchymal stem cells to heal articular cartilage defects (50)	Phase I
Human Allogeneic chondrocytes	University Hospital, Ghent	Non-randomized, open label, uncontrolled, single group assignment, efficacy study on reparation of cartilage injuries in the knee (10)	
<i>DeNovo NT</i>	Zimmer/ISTO	Post-market study of articular cartilage defects of the knee treated with <i>DeNovo NT</i> (natural tissue graft)	Post-market study
Low-intensity pulsed ultrasound	McMaster University	The effects of low-intensity ultrasound on medial tibial cartilage in patients with mild to moderate osteoarthritis (26)	Phase II
Autologous, culture-expanded bone marrow mesenchymal cells	Cairo University	The use of autologous bone marrow mesenchymal stem cells in the treatment of articular cartilage defects (25)	Phase II

SOURCE: Clinicaltrials.gov

start clinical trials by the end of the year. Kronengold believes the product will fill a need in the treatment of focal defects as large as 15 mm² in diameter.

In August 2009, Kensey Nash re-acquired rights to its *OsseoFit* bone void filler product line, which it had licensed to Biomet Inc., as an important component of its new cartilage repair technology.

Regentis Biomaterials Ltd. believes that an *in situ*, polymerized hydrogel called *GelrinC* will offer surgeons a solution for cartilage repair that's minimally invasive and easy to use.

GelrinC is a photopolymerizable, biodegradable implant made from polyethylene glycol diacrylate (PEG-DA) covalently conjugated to a structural backbone of separated denatured disulfide reduced fibrinogen chains. It's designed for filling traumatic chondral and osteochondral voids, and aims to eliminate discontinuities across a defect resulting from focal injury. The degradation of the implant is controlled and mediated by protease activity on the fibrinogen moieties and hydrolysis of the PEG which allows the implant to erode. The scaffold completely degrades within six to 12 months. The major products of degradation are PEGylated peptides, amino acids, and PEG, and have been shown to be nontoxic to chondrocytes, bone, and the body, according to Regentis CEO and co-founder Yehiel Tal (the former VP of business development at another Israeli cartilage repair company discussed below, ProChon Biotech).

During a surgical procedure, the defect site is resurfaced. The *GelrinC* solution is injected into the resurfaced defect site just below the upper boundaries of the native articular cartilage and solidifies *in situ* forming a stable matrix. The hydrogel is designed to slowly degrade and gradually be replaced by healthy functional tissue that fills in the space occupied previously by the implant.

Tal explains that following a standard microfracture procedure, a blood clot fills in the defect site to serve as a scaffold for regeneration of new tissue. This clot may degrade after a few weeks and it takes six to 12 months to grow new cartilage tissue. That leaves the developing cartilage without a scaffold and as a result a fibrotic tissue will develop. *GelrinC* fills the cavity of the cartilage defect, displaces the blood clot, and degrades within six to 12 months as healthy cartilage tissue takes its place. The implant adheres nicely, Tal says, because it relies on the attachment of protein to protein. The company is just beginning a 20- to 25-patient clinical trial in Europe to support a CE mark. Founded in 2004, Regentis has raised more than \$7.5 million from SCP Vitalife and Medica Venture Partners.

AN EARLY INTERVENTION FOR OSTEOARTHRITIS

Carticept Medical is unique among cartilage implant developers; it is not attempting to regrow cartilage, but to replace it, with a permanent synthetic polymer implant that behaves like cartilage. The company was founded by the management team that once led Proxima Therapeutics, before its acquisition by Cytex Corp. in 2005. Looking for a new opportunity, and with \$23

million in funding from two of Proxima's old investors, Domain Associates and New Enterprise Associates, the company acquired biomaterials start-up Orthonics, based out of Georgia Tech. Barbara Boyan, PhD, one of the founders of Osteobiologics (acquired by Smith & Nephew PLC) had co-founded Orthonics to develop polymers with the ability to induce bony fixation. Specifically,

Boyan developed a patterning technology for creating tiny snowflake-like patterns on the surface of a curved polymer and Orthonics had demonstrated that the patterns could attach the polymer onto a bony surface.

With a patterning technology, but no polymer, Carticept followed up with the asset purchase agreement with **SaluMedica LLC** in 2008, the developer of a PVA (polyvinyl alcohol) device already used in 2,500 cartilage repair procedures in Europe and Brazil. PVA is a biocompatible material used in contact lenses, nerve cuffs, anti-adhesion barriers, and embolic particles, among other medical applications. Although PVA has many properties that are ideal for a cartilage replacement product—it's lubricious, compressible, and can take up loads, it isn't durable enough to implant in a patient for five years or more says Carticept CEO Tim Patrick. SaluMedica thus developed a method for crosslinking PVA in such a way that no crosslinkers or other products remained in the PVA implant, yet it became much stronger.

Carticept is ultimately looking to replace articular cartilage in the knee, but its proof-of-concept market is cartilage replacement of the metatarsophalangeal (MTP) joint where the first toe connects to the foot. Cartilage damage in the MTP causes patients chronic pain and functional impairment when they walk, and the solution to the problem is usually fusion.

Carticept is supplying surgeons with a tool set to accomplish a quick 20- to 30-minute repair, whereby the clinician will drill a 10-mm hole at the end of the joint, then press fit the material into the space where the cartilage used to be. Once the surgical site is closed, the patient will regain mobility.

The company is poised to begin a 240-patient randomized study in the MTP joint in Canada, the UK, and the US, with the goal of gaining a US approval in cartilage repair. There are two to three million patients with osteoarthritis of the MTP, many of which go untreated today. That's a good-sized proof-of-concept market for the company, and perhaps a more achievable application in which to shoot for the first FDA approval of a synthetic cartilage repair product.

TWO STEPS FORWARD

Next-generation ACI companies need not offer one-step procedures to advance the state of the art. ProChon Biotech, for example, has a product combination with several advantages. First, the company has a process for expanding a patient's cells in 10 to 14 days as opposed to six weeks and in a way that

“During fetal development, cartilage growth is linked directly to bone maturation.... We believe that the key to regenerating damaged articular cartilage is to also regenerate the underlying bone.”

—Russell Kronengold

yields a predictable number of cells. Its scaffold is made of the natural materials fibrin and hyaluronic acid and facilitates cell growth through the scaffold, not just on its surface. CEO Patrick O'Donnell says, "We have evolved what it means to be a two-stage procedure; we enjoy the benefits of expanding the patient's own cells and the clinical outcomes of real hyaline cartilage for longer-term results."

ProChon's *BioCart* expands a patient's chondrocytes rapidly in the presence of a rationally designed variant of fibroblast growth factor and seeds them into a biodegradable three-dimensional scaffold with a porous, open channel structure that allows cells to penetrate it, resulting in a space-filling, sponge-like construct that has treated lesions from 1 to 8 cm². *BioCart* is on the market in Israel and Greece and the company has established a cell processing facility in Italy. ProChon is currently enrolling patients in a 40-patient Phase II clinical trial in the US.

ProChon was founded in Israel in 1997 but O'Donnell joined in January 2009 to put in place a management team to drive US Phase II clinical studies, transfer production to the US, and get the company acquisition-ready for a larger organization with a global reach. Meanwhile, ProChon has a source of potential early revenues under a license agreement with the tissue procurement agency the Musculoskeletal Transplant Foundation (MTF), also an equity investor in the company. MTF has exclusive rights to use the ProChon FGF technology in allograft tissue for orthopedic applications. Based on MTF's sales projections, the agreement could yield very significant royalties to ProChon, says O'Donnell, who adds that there remain numerous other licensing opportunities for the FGF technology.

EFFICACY FIRST

At this stage in the evolution of autologous chondrocyte implantation, there are no validated cartilage repair products with predictable and consistent long-term efficacy over microfracture, the standard of care. So the debate about one-step versus two-step procedures is a bit like putting the cart before the horse. Ken Andrews, president and CEO of Histogenics, says, "I think a lot of the market decided that *Carticel* didn't work because it required two steps when we needed a one-step procedure, which was a superficial analysis of the problem. I come from the biotech world [Andrews is the former chief commercial officer of Alkermes], so I think the focus should be on efficacy. There seem to be a lot of approaches with less than satisfactory patient outcomes. Bring me something that works first, and then we can optimize the number of steps that it takes."

The two-step business model of Histogenics may seem to be just as awkward as that of **Genzyme Biosurgery**. The surgeon takes a biopsy, sends it off to a Histogenics processing facility, and four to six weeks later, *NeoCart* is shipped back to the surgeon for implantation. But there the resemblance ends. *NeoCart* has several components: autologous chondrocytes, a hydrostatic cell processing device for processing the cells under cyclical pressure and low oxygen, which attempts to replicate the environment in the knee, and a proprietary collagen-based glue for fixing the implant in the defect. What Histogenics delivers to the surgeon is a piece of hyaline-like cartilage tissue that can be cut to size and glued into the defect in an approximately 45-minute procedure, a

mini arthrotomy done on an outpatient basis. "The patient comes in on Friday morning and leaves Friday afternoon on crutches," says Andrews. Andrews anticipates that the patient's rehab may be somewhat shorter than it is with microfracture, because there is no violation of the bone.

In effect, in the same amount of time it takes Genzyme to deliver a vial full of cells to a surgeon, or its next-generation MACI product, a scaffold seeded with chondrocytes, Histogenics delivers a piece of cartilage that is already stiff, cushiony, and slippery, according to Andrews. "People are getting a pretty mature piece of tissue and that's why we're seeing good early results," he says. Andrews can't discuss clinical outcomes in detail because the 30-patient Phase II trial is still blinded. However, he says Histogenics has Phase I patients out to three and a half years and "I can only say that all eight of our Phase I patients are doing great." (The company is also developing a one-step procedure called *Vericart* that does not require the harvesting of a patient's tissue.)

Histogenics is in the midst of raising a Series C round to fund its Phase III clinical trials. **Stryker Corp.** is an investor from an earlier round (as a financial investor, no special rights are attached to the investment), as are Boston Millennia Partners, Foundation Medical Partners, Altima Partners, Inflection Point Partners, and a private investor.

Histogenics' next challenge is to carry out a 200-patient Phase III study that will follow patients for three years. The company is focusing on the usual, but difficult, clinical end points of pain and function. "In this field, the secondary ways of measuring whether you have hyaline cartilage have not proven to be predictive of patient outcomes," Andrews says. "Long-term, you do want to make hyaline cartilage, but people go to the doctor because their knee hurts and they can't go down the stairs. Real clinical improvement is what patients want and what insurance companies pay for." Large and long clinical trials with subjective end points are what make this field so challenging; but from here on out, companies that conduct statistically powered trials that demonstrate measurable clinical benefits will command the market, Andrews believes.

So then, is the cartilage repair industry still all about waiting several years for efficacy data? Says Andrews, "Yes....but we are talking about a significant and meaningful dataset and a commercializable product at the end of 2013 or early 2014. That's not that far away."

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E-MAIL THE AUTHOR AT: M.Stuart@Elsevier.com



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