

ISTO Technologies Aims to Rescue Damaged Joints

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Every unmet medical need has its own version of the “holy grail.” For cartilage biologists, that search leads to cartilage repair. By the time people see orthopedic surgeons for tender knees, achy backs, or painful hands, joint damage is well underway. Once damage to cartilage and bone shows up on an X-ray, joints have already suffered irreversible harm.

On the good side, cartilage allows joints to glide and bounce. On the worrisome side, cartilage has a limited blood supply and thus a limited ability to heal. Like un-repaired chips along the surface of an ice rink, the tiny defects in cartilage from injury or wear and tear worsen over time. Chips turn into chunks, joint motion changes, and damage progresses to osteoarthritis, cartilage damage that extends to bone. Orthopedic surgeons consider this end-stage joint disease, leaving few options other than joint replacement.

According to an article in *START-UP*, a magazine covering the business of healthcare, as of 2009 there were 40 commercial efforts aimed at cartilage repair (Stuart, 2009). St. Louis-based ISTO Technologies is part of those efforts. ISTO licensed the technology from BJC Health Care in St. Louis to form the company. Mid-America Transplant Services in St. Louis was the major investor for the initial million dollars of capitalization and also provided space at their facility to initiate the research and to help the company get started in 1997.

Today ISTO Technologies has four programs: two are biologics, Denovo ET engineered cartilage tissue for knees and Denovo NT, natural tissue for cartilage repair in any joint. Both are distributed by Zimmer, the company’s marketing partner for these biologics since 2002. The other two are NuQu (also a biological platform), an injectable percutaneous delivery of chondrocytes to damaged spinal discs, and InQu, a bone graft substitute.

Annually, there are approximately 500,000 cartilage repair surgeries in the US on knees alone. People with damaged

knees have few options. Surgeons can shave damaged cartilage or drill holes down to the bone or make microfractures to stimulate healing, but cartilage formed from those procedures is fibrocartilage and not the sturdy hyaline cartilage found in joints. Thus far, the only FDA-approved articular cartilage repair product is Genzyme’s Carticel or ACI (autologous cartilage implantation). In this procedure, the patient’s own chondrocytes are harvested, sent to a lab for expansion, and then reintroduced into the damaged joint approximately four weeks later, after enough cells have grown. ACI is not ideal, say industry experts, because the technique requires two surgeries and can cost up to \$26,000.

Mitchell Seyedin, Ph.D., president and CEO of ISTO Technologies, says the company has come up with a way to replace damaged cartilage in one procedure with laboratory-grown cartilage. ISTO uses juvenile human chondrocytes from donors procured through Mid-America Transplant services and other organ procurement organizations. To make the laboratory cartilage, company scientists tease out cartilage cells from the dense extracellular matrix, expand them, and then put them in special cultures without the need for a scaffold. After a month or so, the chondrocytes form cartilage discs about the size of a quarter and nearly identical in toughness and composition to hyaline cartilage. Because chondrocytes can be expanded in one of ISTO’s many patented techniques, chondrocytes from a single donor can be expanded and frozen for future use and also cultured into Denovo ET, meaning that a single donor can treat thousands of patients.

Zimmer has dubbed this cell-based therapy Denovo ET (for engineered tissue). These cartilage discs can be delivered to surgeons who cut them to the size of the defect, dab on some fibrin glue, and then patch the hole in the cartilage. Eventually, the engineered cartilage blends in with the surrounding cartilage. Phase I and II clinical trials have already

been completed. The primary outcome measure was KOOS (knee injury and outcome score), in which patients assess their pain levels. Those data have not been published.

For Denovo NT (natural tissue), the donated cartilage is minced and sent to orthopedic surgeons, who then implant the tissue directly into chondral defects. Fibrin made from the patient’s blood holds the tissue in place. So far about 2000 patients have been treated over the past 2 years, mostly in knee and ankle joints, says Cheryl Blanchard, Ph.D., senior vice president and CSO at Zimmer and a member of ISTO’s board of directors. Because Denovo NT is a tissue transplant, no premarket clinical trials were needed. Zimmer is, however, conducting postmarket studies and preparing them for publication.

Actually, Blanchard says Zimmer is getting barraged with anecdotal results, including those from professional athletes and extremely active people like downhill skiers who have returned to their sports pain free. “That’s a big deal because you don’t hear those stories very often,” says Blanchard. “It’s really a significant innovation in the development of meaningful cartilage repair technology.” Blanchard says she chooses to say “meaningful” because Denovo NT requires one treatment, unlike ACI. While Zimmer doesn’t publish the cost, Blanchard says Denovo NT is “significantly less than ACI.”

Blanchard mentioned a few caveats, though. She says that Denovo NT is “very promising” but is still new and needs a few more years of treatment to measure the outcomes of the therapy. The larger issue with Denovo NT is that of the donated nature of the tissue. Although one donor can treat more than one person, there will always be some degree of supply constraint. “This tissue is a gift that families give when a child has passed away and that’s a very difficult decision to make. A whole bunch of people can get their lives back because

this gift has been made available to them. While it is a gift, it is a difficult thing to manage the supply and demand logistic just like with any transplant," says Blanchard.

Unlocking Cartilage Biology

The laboratory techniques that turned ISTO's cell-based therapies into a commercial platform were years in the making. Chief scientist H. Davis Adkisson, Ph.D., began studying cartilage biology as a graduate student in the early 1990s, work that continues today. Adkisson began by looking for characteristics that made cartilage different from tissues that have a blood supply. Adkisson reasoned that because cartilage doesn't have a blood supply, chondrocytes found a way to flourish in the dense extracellular matrix without certain nutrients, such as dietary essential fatty acids. Indeed, when Adkisson enriched chondrocytes cultures in fatty acids (EFA) normally found in the Western diet, the cartilage cells produced less matrix and generated a phenotype similar to tissue typical of osteoarthritis. Once Adkisson placed the cells into the EFA-free environment, they produced a 3D cartilage matrix in the absence of a scaffold.

This observation led Adkisson to formulate a special growth medium that remains a trade secret and involves pathways other than fatty acid metabolism. He also showed that with aging there is a flip of the fatty acid profile and proposed that this change (the oxidation of polyunsaturated fatty acids not normally present in young growing cartilage) might be associated with cellular senescence and dysfunction.

In 2000, Adkisson left academia to see whether he could use these observations to produce laboratory-grown cartilage with harvested juvenile chondrocytes, which produce cartilage much better than adult cells. He and colleagues also needed to expand chondrocytes from

juvenile donors for this technique to be scaled commercially.

The team needed to trick chondrocytes into thinking they were in the microenvironment of articular tissue so they would retain their phenotype in laboratory cultures. Otherwise, chondrocytes stretch and flatten, producing type I collagen rather than type II needed for hyaline cartilage.

By 2007, Adkisson and colleagues developed a now-patented way to expand chondrocytes through ten population doublings and still retain ability to produce cartilage matrix. "We went from one donor being able to treat 25 recipients to thousands of recipients. That's what really got this company going; the ability to expand the cells and retain the phenotype and find multiple applications," says Seyedin.

Cartilage has another feature that makes transplanted tissue less complicated. Adkisson and colleagues proved that chondrocytes truly are immune privileged and identified the mechanism (Adkisson et al., 2010). "This was purely speculation or anecdotal before our publication," says Adkisson. So patients who receive donor cartilage do not need immunosuppressants.

Today, a Broad Focus

With billions of human chondrocytes at their disposal, ISTO broadened into the spine market with NuQu, an injectible percutaneous delivery of juvenile chondrocytes intended for patients with back pain who do not respond to conservative therapy after three months. The cells are isolated, expanded, and put in a syringe with fibrin and injected into spinal discs in a minimally invasive procedure. This cell-based therapy is intended to become an improved therapeutic option for resolving back pain associated with degeneration of the intervertebral disc nucleus, which is filled with hyaline cartilage. The intervertebral disc is a large

cartilaginous structure that lies between the vertebral bodies of the spine, cushioning and anchoring them together.

Thus far, fifteen patients have been treated with NuQu in a phase I clinical trial. "There is almost no rehabilitation. Three hours after injection, patients can get up and walk," comments Seyedin. By April 2011, ISTO will complete analysis of the 6 month follow up and then submit safety data to FDA.

In 2008, ISTO began generating revenue through FDA 510 (k) approval with InQu, the company's bone graft extender and substitute and their first product to market. InQu combines PLGA, a biodegradable polymer, with hyaluronic acid, a molecule critical for tissue repair and regeneration. In procedures where a bone graft is needed, as for vertebral damage or as a bone extender for scoliosis deformities, the surgeon takes a chip of bone from the pelvic bone, mixes it with ceramics to induce bone growth, and transfers the slurry to the injured area.

InQu eliminates the need for iliac crest transfer and for ceramics. This platform technology comes in strips, granules, and paste that can be mixed with blood, bone marrow, or morcelized with bone. Company scientists are testing whether InQu can be used to regenerate other soft tissues that may be lost to injury or disease, says Seyedin.

According to Seyedin, 2010 closed with \$10 million in revenue for ISTO. "We are excited," he says. "We are very excited."

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