Beyond The Graft: Synthetic Scaffolds For Soft-Tissue Reconstruction

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Executive Summary

A field littered with failures sees few companies brave enough to try again. A big market awaits medtech start-ups that find a successful way to end the need for autografts and allografts for soft-tissue repair.

- Current methods for repair and reconstruction of damaged soft-tissue ligaments and tendons, while generally successful, have many problems. Along with the cost of surgery, healing time, rehabilitation, and pain, sometimes they fail, induce biomechanical degradation, and lead to comorbidities; allografts in particular raise disease transmission and tissue rejection concerns.
- Multiple prior attempts have been made to improve suturing of tears and develop biological or synthetic alternatives to tissue grafts to alleviate some or all of these problems, but nearly all have proved inadequate substitutes for human tissue.
- Rather than engineer artificial soft-tissue prostheses, a few small emerging ventures have developed alternative synthetic modalities engineered to serve as scaffolds enabling damaged and ruptured tissues to regenerate on their own.
- As a result of previous failures to end the need for grafts, skepticism remains in the orthopedic and investor community about possible alternatives to current methods. If successful, though, synthetic scaffolds could end the need for harvesting and implanting tissue and overturn an entire orthopedic industry segment.

Silver wire and carbon fiber; polyethylene, Dacron, and Gor-Tex: these are just some among the synthetic materials device makers have fashioned into ropes, cuffs, and straps to replace torn and ruptured ligaments and tendons. These prosthetic anterior cruciate ligaments, Achilles and elbow tendons, rotator cuffs, and more have often failed or sometimes set off such serious biomechanical, health, or immunogenic complications that surgeons needed to remove them. After a century of efforts to fashion synthetic implants, every attempt so far has fallen short of human tissue’s particular combination of biology, strength, flexibility, stability, and endurance. Surgeons must still rely either on transplanting human tissue harvested from a patient’s own body – autografts – or a cadaver – allografts – to rebuild seriously damaged soft connective tissue.

Surgeons fix ankle, knee, shoulder, and other soft-tissue tears and ruptures more than a million times a year, yet autografts and allografts, too, have important drawbacks. Autografts require cutting as much as a third of a patient’s tendon, weakening it, causing site pain and potential morbidity, biomechanical insufficiency, extended surgery time, and long recovery; allografts obviate the need to cut and damage the patient’s own tissue, but raise red flags from concerns about possible disease transmission – along with the potential for failure due to structural weakness in the allograft caused by sterilization processes. Despite the string of past failures, synthetic materials hold the promise of repairs and reconstructions that can be quick,
safe, and effective alternatives to natural tissue transplants with minimal trauma for the patient. After a century of trying, the goal of obviating or even ending the need for autografts and allografts may now be within sight. But device investors and entrepreneurs have largely abandoned the pursuit of an implantable prosthetic device as a solution to the challenge.

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Instead of replacing damaged soft tissue with an artificial rope, they are developing the biological equivalent of the tomato stake. These firms have engineered braided textile scaffolds that lend stability and strength to an injured joint while the body’s own regenerative powers work their magic. The hope is that the scaffold will end the need for either autografts or allografts, speeding surgery, reducing recovery time, and decreasing associated morbidity and safety concerns. In addition, bioresorbable meshes can serve as sutured onlays to strengthen repairs of damaged soft tissue, such as torn tendons and rotator cuffs, to prevent the stitches from tearing when stretched. If successful, soft-tissue scaffolds could radically reshape an industry segment that presently drives many billions of dollars in health care costs. But past failures to displace long-standing methods leave many investors wary of jumping into the soft-tissue repair and reconstruction field.

Joints take a beating, whether from playing sports or simply normal wear and tear. That results in aches, tears, and ruptures requiring medical intervention with astounding frequency. In 2010, patients visited physicians more than 11 million times for help with shoulder problems and closer to 19 million times for knee issues according to the American Academy of Orthopaedic Surgeons. Add millions more medical visits for ankles, hips, wrists, hands, and so on. For the vast majority, pain relievers and physical therapy alone were relief enough, but according to medtech data aggregator service BioMedGPS estimates, last year there were more than 500,000 repair procedures — virtually all of them reconstructive — for knee ligaments alone. ACL reconstructions accounted for some 440,000 of those surgeries. BioMedGPS also found that suture anchors were the primary means of fixation used in the more than 750,000 rotator cuff repairs and 175,000 labral repairs performed in the US in 2013. (See Exhibit 1.)

Age drives many of these injuries: reports show that some 13% of individuals ages 50 to 59 and 51% over age 80 tear their rotator cuff. With rising rates of injuries among young athletes, especially with the increased popularity of sports among women and risky extreme sports of all kinds, and continuing physical and recreational athletic activity among the swelling population of aging Baby Boomers, BioMedGPS forecasts steady growth across knee ligament procedures at around 5% annually. According to one orthopedics medical technology firm, expenditures last year for ACL reconstruction procedures alone were estimated to total over $3 billion worldwide, a figure that includes both the cost of allografts and the direct surgical costs of autograft harvesting and subsequent direct incremental rehabilitation and medication costs.

The Holy Grail?

Despite the high volume of procedures and increasing need for them, current modalities for soft-tissue repair and regeneration leave much to be desired. Left on their own, severely torn tendons and ruptured ligaments are unlikely to heal completely due to a lack of vascularization and their being encased in synovial fluid. Less active adults may opt to put up with the resulting instability and reduced biomechanics rather than go through surgery and recovery. However, for athletes, younger patients, active adults of all ages, and those experiencing significant pain or biomechanical deficits, only surgical replacement or repair procedures will enable full return to previous levels of movement and activity, particularly sports.

Ligaments are especially complex to rebuild. The bone-patella-bone graft remains the gold standard for ACL replacement owing to its strength and rapid incorporation within the bone tunnels. However, the need to harvest the mid-third of the patient’s patella tendon and the resultant pain and morbidity, which often
includes lag in knee extension and problems with kneeling, has resulted in a shift in ACL graft selection over the past five years to other tendon autograft sources for the majority of ACL reconstructions performed today. Whatever the autograft’s source, says Asheesh Bedi, MD, an orthopedic surgeon at the University of Michigan who specializes in ACL repairs, cutting away tendon tissue leads to lost power and strength – especially with hamstring grafts – and pain and discomfort from loss of patella tendon tissue.

By contrast, allografts preclude donor site morbidity and reduce surgery and recovery time. Moreover, some patients simply lack sufficient donor sites for harvesting their own tissue. That is why surgeons and patients will choose to rebuild an ACL one out of five times with donated and sterilized cadaveric human tissue. However, sterilization of the allograft tissue to prevent disease transmission and immunogenic responses may weaken the tissue, potentially resulting in failure of the reconstructed ACL. A widely cited 2012 study of cadets at the US Military Academy who had ACL reconstructions found that those with allografts were almost eight times more likely to experience failure requiring surgical revision than those with autografts.

Nonetheless, Lori Fulton, marketing director of Musculoskeletal Transplant Foundation, a nonprofit cadaver graft tissue bank that supplies much of the ACL allograft tissue in the US, says, “Allografts get unfairly a worse rap than they should in terms of performance characteristics. We have a number of studies showing the equivalence of MTF processed tissue to autograft.” As a result of surgeons’ confidence in ACL allografts, the market for foreign human transplant tissue remains substantial – with a typical cost in the range of $2,500 to $3,000 for the ready-to-implant allograft. BioMedGPS forecasts faster growth for the allograft market than the overall increase in the number of ACL procedures. (See Exhibit 2.)

Along with increased potential for failure, concerns linger about the possibility of allograft tissue transmitted disease, of which some frightening cases have been reported over the years. “In 2014,” says University of Michigan orthopedist Bedi, “there’s a healthy skepticism about [allograft] biology and safety.” In the end, says Bedi, both modalities “have advantages and disadvantages,” which remain challenges for the field.

Angela Smith, MD, an orthopedic surgeon at Nemours/A.I. Dupont Hospital for Children in Bryn Mawr, PA, and past president of the American College of Sports Medicine, describes a perfect way to repair ligaments as “the Holy Grail of orthopedics.” She says, “I’ve been around orthopedics a long time. All attempts to come up with alternatives to allografts and autografts have failed. That has put a bad taste in people’s mouths” about the possibility of developing alternatives to those tried-and-true techniques. Nonetheless, Bedi contends, “There’s a tremendous opportunity because harvested tissues are disadvantageous for patients.”
Exhibit 1
US Knee Ligament Repair Procedure Volumes

Exhibit 2
US Knee Ligament Graft Replacement Market Forecast
The Search For Graft Alternatives

It’s not for the lack of trying by device makers that no alternative has proved entirely successful so far. In the 1980s, several prosthetic soft-tissue replacement technologies reached the market. All shared similar faults of failing as biomechanical equivalents to normal human tissue, potentially inducing foreign body reactions and causing infection. The need for too many surgical revisions forced withdrawal of the products from US markets. Holdover products sold now primarily in Europe include Surgicraft Ltd.’s (UK) LockDown, Neoligaments’ (UK) JewelACL device, LARS ligament (France), and the Telos GMBH (Germany) Trevira. “The concept of a synthetic or artificial ligament is a good one,” says Bedi, who has worked with several of the available products. “The surgery cost is less expensive. It would in principle be safer.” However, none of the attempts stuck – except for use in rare cases in which neither autograft nor allograft is a suitable option. “To work,” says Bedi, “a synthetic graft device needs to be structurally and mechanically strong enough, and you want it to be around long enough to incorporate yet not so long that a foreign body reaction ensues.” Those requirements have proved insurmountable to date.

Given the past problems, investors and entrepreneurs have largely shied away from the soft-tissue field, despite the potentially large market opportunity. Stephen Bloch, MD, a partner at the VC Canaan Partners, finds, “Time and costs to market are substantial and technical risks are high. We’re looking for projects that are three to seven years maximum to exit. We’re cautious about devices because exits have been weak relative to capital required.” Nonetheless, a few companies – as well as academic labs – are continuing to develop soft-tissue repair technologies, but a review of the space found just four with existing products or products in development for surgical repair of tendons or ligaments. As a result of the sorts of concerns expressed by Bloch, some of them have needed to be creative in their financing or business structure in order to survive with little outside investment.

Fibralign Corp., in Union City, CA, does not produce tendon or ligament products of its own. Instead, through Advanced BioMatrix, an affiliated distributor, the firm sells its collagen, fibrin, silk, and other biomaterial matrices for creating three-dimensional (3-D) nanostructures tailored for specific tissue-engineering research and medical applications. Some of those matrices have gone into efforts to generate soft-tissue repair and regeneration devices. Fibralign acquired the assets of CollEngin, a firm that was developing nanoscale three-dimensional biopolymers, composed of collagen and extracellular matrix components that potentially functioned as ligament and tendon replacements. Fibralign seems to have halted development of those devices.

Another pathway to overcome shortfalls in soft-tissue reconstruction technologies has been to find better sources of allograft tissue. In Europe particularly, human tissue banks remain inadequate to meet demand for allografts. San Antonio’s Aperion Biologics Inc. developed what it calls Z-Process, a proprietary method for deactivating both alpha-gal and non-gal antigens on xenograft tissue to prevent transplant rejection. The company is seeking to process and sterilize animal tissue applicable to a variety of human needs, including orthopedic ligaments, meniscus, and other soft-tissue grafts for augmentation and repair. The company’s lead product for knee ligament reconstruction, the porcine xenograft Z-Lig ACLR Device, began a 60-subject clinical study at centers in Europe and South Africa in early 2011 and announced completion of enrollment in March 2012. The company has not yet reported results, which would presumably lead to its filing for CE mark for an off-the-shelf allograft alternative product in Europe.

Two companies have focused on finding ways to encourage the body’s soft tissue to regenerate on its own. They both have developed tightly woven, synthetic biodegradable mesh matrices that serve as scaffolds to provide strength while the natural tissue recovers. Soft Tissue Regeneration Inc. (STR), a largely virtual
firm with offices in New Haven, CT, and San Diego’s **Synhasome Inc.** employ proprietary fiber, braid, and mesh designs comprising poly (L) lactic acid (PLLA), a resorbable polymer with a long and proven history of use in implantable medical devices. Both companies already have products: US Food and Drug Administration 510(k)-approved surgical polymer mesh jackets that provide additional strength and stability to aid in the repair of sutured tendons, ligaments, and other soft tissue. They compete with numerous FDA-approved transplant products. These include **Wright Medical Group Inc.**’s *GraftJacket*, which utilizes cadaveric skin; **DePuy Orthopaedics Inc.**’s (a division of **Johnson & Johnson**’s **DePuy Inc.**) *Restore*, made of proline small intestine submucosa; **Stryker Corp.**’s *Stryker Orthopaedics’ TissueMend*, composed of fetal bovine dermis; and several others. Also in the space, **Allergan Inc.** acquired *SeriScaffold*, a silk fiber mesh soft-tissue repair product when it bought the American firm Serica Technologies in 2010. [See Deal] At the time Allergan acquired Serica, the smaller firm was spinning out its **Tufts University School of Medicine** silk mesh ligament scaffold technology into a new firm. However, it no longer appears to be active.

Unlike artificial and synthetic soft-tissue prosthetic products, intracellular meshes composed of PLLA, silk, collagen, fibrin, and other 3-D nanostructure matrices are designed to capture migrating cells and slowly bioresorb in parallel with neovascularization and native tissue ingrowth. This regenerative process eventually replaces the scaffold with native tissue. As bioresorption occurs, load-bearing responsibility transfers to the new tissue ingrowth while mechanical integrity at the site is maintained. According to Synhasome, PLLA degrades following implant over a 12- to 18-month period, maintaining approximately 80% of its strength after a year.

Synhasome is a five-person company that grew out of the 2002 bankruptcy of Advanced Tissue Sciences (ATS). That company developed one of the first FDA-approved cell-based products, *Dermagraft*, a bioabsorbable human dermal substitute for diabetic foot ulcer wound healing, now sold by **Organogenesis Inc.** Anthony Ratcliffe, PhD, and other former ATS employees formed Synhasome. Their first PLLA mesh product, *X-Repair*, received US FDA 510(k) clearance in 2009 for surgical repair of tendon, ligaments, and other soft tissue. Ratcliffe, now president and CEO of Synhasome, says that the company is focusing the product on rotator cuff and foot-and-ankle repair. According to the firm, depending on the size of the rotator cuff tear, sutured repairs fail frequently, 60% of the time in the case of very large tears. The ultrathin – 1.4 millimeter – X-Repair can be compared to a patch: during surgery, surgeons drape this biodegradable construct over the tendon that sits on the shoulder bone, anchoring it with sutures to keep it in place while the tendon, bones, and nearby tissues heal. Ratcliffe says, “To do this effectively the repair device has to have the same critical mechanical properties as native tendons and ligaments, and X-Repair has those. It is bio-mimicry of tendons and ligaments.”

Previous efforts to bolster soft-tissue surgical repairs with synthetics haven’t worked well. Ratcliffe says that led to “a cautious attitude to new products coming to the market.” The company has so far relied entirely on internal funding sources and **National Institutes of Health** grants to develop its products.

Ratcliffe won’t reveal annual sales, but Synhasome has a small sales force that is currently expanding nationally. He adds: “We’re considering getting some outside funding to help with the growth of the company.” That will include a second generation of mesh products that enhance the biological response at the injury site. “You want to speed the repair,” Ratcliffe says. “That’s where we see the next need.”

He shies away from the ACL graft space. “While we do consider it,” he says, “ACL replacement is difficult to do technically, and to motivate from a return on investment stance.” The regulatory hurdles are significantly higher for replacement technology as opposed to repair devices. “Nevertheless,” Ratcliffe says, “a well-designed product with compelling long-term clinical performance would be a valuable addition to the treatment options of ACL tears.”

Few investors are willing to take the risk, and most previous firms that have sought to develop biomimetic devices for soft tissue have disappeared. Like other firms such as CollEngin and Serica, Orthomimetics – a UK firm that was working on an ACL replacement graft, *LigaMimetic*, composed of a porous, resorbable tissue-regeneration scaffold that mimicks the composition and structure of ligaments and their bony insertions – was sold (in 2009) to **TiGenix NV.** [See Deal] The Belgian firm has since focused the core
technology’s development on cartilage repair and appears to have dropped efforts to develop the LigaMimetic device.

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- Joseph Reilly, CEO, STR

Currently considering possible soft-tissue repair company investments outside the ACL space, Jeffrey Barnes, a partner at the VC BioVentures Investors, agrees that the ACL remains thorny for investors. “The ACL,” he says, “is by far and away the most challenging soft-tissue injury in terms of being able to affect a healing process. It has been really, really hard to find the right characteristics of tension, flexibility, safety, and regulatory compliance.” Given that present solutions are less than ideal, he still believes, “If there were a way to restore the ACL without autograft or allograft and it didn’t have discomfort and pain in recovery and returned the patient to full function, then you have a winner. I view that as being well worth it.”

Given the high risk and the recent low returns on medtech venture investments, STR seems alone in seeking to develop an ACL reconstruction device. Founded in 2008, the company grew out of a PLLA braiding technology developed by textile engineers at Drexel University together with the bioengineering expertise of the company’s scientific founder, Cato T. Laurencin, MD, PhD, director of the Institute for Regenerative Engineering at the University of Connecticut Health Center. The company’s PLLA bioresorbable scaffold, the L-C Ligament, is composed of two tightly braided outer segments, which are anchored to the bone much like standard ACL graft implants, and a more loosely braided central portion. The mesh’s tight intracellular braid captures cells in its sock-like weave that regenerate the ACL while the L-C Ligament provides support to the knee. “All prior synthetic devices were nonresorbable prosthetics designed to replace the ACL, while our device regenerates the ACL,” says Joseph Reilly, co-founder, president, and CEO of STR. “Our product shows no drop in mechanical strength while the patient’s natural tissue regenerates. That means you can rehabilitate sooner and stronger.”

After three years’ study in almost 150 sheep, the company started a 15-patient clinical trial of the L-C Ligament in Europe in March 2013. According to STR board member Konstantine Drakonakis, a partner in the New Haven office of LaunchCapital, a Pritzker-Vlock family office venture fund and investor in STR, “The first patient is more than nine months out and doing well.” The company anticipates one-year data from all enrolled patients by March 2015. According to Reilly, the company will start enrolling an additional 60 patients after September 1 of this year. He says, “We believe when we have data for a total of 75 patients we can apply for CE mark,” which he projects for the second half of 2016. In mid-2016 he anticipates starting a 250-patient US clinical trial to win approval for an American product.

That large trial will be very costly and risky. To date, the company has raised $13.2 million, according to Reilly, enough cash to carry its development program through to the second half of 2016. Extraordinarily, Reilly was the sole employee of the company until this past February. “I have a lot of talented consultants,” he says. Reilly has a general business background, including having started up a previous high tech composites company and a proteomics diagnostics firm. “A traditional start-up,” he says, “would have taken a $25 million to $30 million investment to reach this point.”

Drakonakis is optimistic about the very lean company’s prospects for venture-level returns. “Devices which do not have larger markets and do not require the more robust regulatory requirements have been the majority of exit comps for the last four to five years,” he says. “This class of technology companies is not able to demand the higher, biotech-like, returns that VCs are looking for. The real disruptive – game changing – large market technologies tend to require the more rigorous regulatory pathways, and can still command the larger exit values from strategics which have limited differentiation across their product lines.” BioVentures’ Barnes agrees: “If they can get the ACL to regenerate without allograft or autograft, it’s a big deal.”
For more than a century now, though, orthopedic scientists have been trying to get to that big deal. The “Holy Grail” of orthopedics continues to elude their grasp. But, perhaps, a braided bioresorbable mesh may eventually change that.