**Three Biotech Solutions for Knee Repair**

*New techniques in orthopedic surgery aim to unleash the body's own healing power*

By [Claudia Wallis](http://www.scientificamerican.com/author/claudia-wallis/) on March 1, 2015: *Scientific American*



If you look very carefully at the C-curved squiggle taking shape on a 3-D printer at Columbia University Medical Center, you just might spot the future of knee repair. Layer by layer, the machine's tiny needle squirts out a bead of white polymer, matching a virtual blueprint of a meniscus—the semicircular band of tough, fibrous cartilage that serves as the knee's shock absorber. A bioprinter in the laboratory of Jeremy Mao can churn out three menisci in just under 16 minutes.

These particular parts are destined for sheep, the test animal for a new method of correcting a torn meniscus, one of the most common of all human joint injuries. Surgeons will substitute the manufactured part for a sheep's own damaged meniscus to serve as a scaffold for healing. Once the device is in place, specialized proteins embedded in it will attract stem cells that will rebuild the meniscus as the polymer breaks down. A study published in December 2014 found it took just four to six weeks to restore a sheep's meniscus using this method. If successfully developed for humans, the new approach would be far superior to what physicians can offer today, which in most cases is simply to remove the ripped tissue if it is causing pain or disrupting knee function. “What we are shooting for is true joint regeneration,” Mao explains.

The sheep experiment is part of a broader trend in orthopedic surgery to find ways to trick the body into healing joints in ways that are more functional and durable than current surgical interventions. Although modern orthopedic surgery does a good job of getting people back on their feet and, in the case of professional athletes, performing at exalted levels, it does not restore an injured knee to its original condition and generally fails to stop—or even exacerbates—the long-term deterioration of the joint.

For reasons that are not entirely clear, damage to the key stabilizing structures of the knee joint often triggers a degenerative process that leads to the worn-out cartilage and chronic pain of osteoarthritis. The goal of next-generation treatment is to return the knee to its full function in as natural a way as possible, which may also slow or stop the runaway cycle that leads to arthritis. “Its repair and regeneration, rather than removal and replacement,” says orthopedic surgeon Martha M. Murray, who heads the Sports Medicine Research Laboratory at Boston Children's Hospital.

The need is huge. Every year an estimated 5.5 million people in the U.S. visit orthopedic surgeons for a knee problem. About a million undergo outpatient knee surgery, and that figure does not include another 700,000 annually who have reached the end of the line with one or both of their own knees and wind up with artificial replacements.

**Why Can't These Joints Just Heal?**
Much of the new thinking about joint repair is rooted in research into the perplexing question of why connective tissues in the joints—tendons, ligaments and cartilage—do not necessarily heal the way other tissues do. A big part of the problem in many of these structures is a relatively poor blood supply; blood contains cells and proteins that are essential to healing.

Tendons, the flexible ropes of fibrous tissue that connect muscles to bone, and ligaments, the slightly stretchy bands that link bone to bone, are less well nourished by blood vessels than are most other tissues. As for cartilage—such as the supersmooth white material on the end of bones (think chicken legs) that helps joints glide—most of it has no blood supply. “So cartilage has virtually no capacity to heal,” says Scott Rodeo, an orthopedic surgeon and researcher at the Sports Medicine and Shoulder Service at the Hospital for Special Surgery in New York City and a team physician for the New York Giants.

Although surgeons can sometimes stitch together a torn meniscus—especially if the tear is in the outer region, which has its own supply of blood vessels—most of the time they can do little more than cut away the frayed pieces—a procedure that a major study in 2013 found was of questionable, long-term value. Nor can surgeons sew up a tear in the anterior cruciate ligament (ACL), located in the middle of the knee and the site of many sports injuries. Instead they remove the torn ligament and replace it with a graft from a cadaver or from the patient's own body.

In addition to a paltry blood supply, the ACL's central location in the joint capsule, which is filled with a lubricant called synovial fluid, is another reason the band will not heal on its own. Wound repair normally begins with bleeding and the formation of a blood clot. Cells in the clot called platelets release certain proteins that promote healing, whereas the sticky clot itself serves as a temporary scaffold for reconstruction with new cells. In joints, however, synovial fluid dissolves clots, “so there's never that early bridge that gives healing a place to happen,” says Murray of Boston Children's Hospital. This is why a tear in the ACL does not heal, but a rip in the nearby medial collateral ligament, which runs along the side of the knee beyond the synovial fluid, slowly knits itself together.

**Secrets of Self-Repair**
Orthopedic surgeons have long made attempts to lure the body into doing a better job of healing cartilage, ligaments and tendons. In recent years they have turned to what they call “biologics”—substances made from the patient's own blood and other tissues. One of the most popular is called platelet-enriched plasma (PRP), which was first used by oral surgeons to help regenerate bone and soft tissue in the jaw.

PRP is simple to produce and deploy: extract some blood from the patient, spin it in a centrifuge to concentrate the platelets, and then inject the resulting fluid into an injured joint or use it in combination with surgery. PRP is replete with growth factors and other substances that promote healing. Studies have so far shown that it can help heal inflamed tendons, such as “tennis elbow,” and relieve pain in an arthritic joint, but whether it can effectively address the wide variety of problems for which it is used is not yet clear.

A newer biologic is made of bone marrow instead of blood and is richer in stem cells than PRP. It, too, is extracted from the patient (through a thin needle in the hip, under local anesthesia) and concentrated using a centrifuge. Bone marrow aspirate concentrate, or BMAC, can be turned into a dense clot that serves as a blood-red spackle that surgeons use to fill gaps in cartilage and to surround and nurture grafted tissue. Veterinarian Lisa Fortier of Cornell University developed the stuff to help racehorses get back on track after a cartilage injury. It offers what she calls “the trilogy of tissue repair”: a thick clot that serves as a short-term scaffold, stem cells to generate new tissue and growth factors to guide that regeneration. Studies in both humans and horses show that cartilage healed with BMAC has a more normal structure than cartilage repaired in other ways.

Because PRP and BMAC come from the patient and go right back into the patient, they did not need to be approved by the Food and Drug Administration, and their use has spread rapidly without a lot of testing. “They are hard to study,” Rodeo notes, because they vary from person to person, making results uneven. With additional research, he predicts, “we will probably turn to a more refined approach—where we'll identify the factors in bone marrow aspirate and PRP that we want to keep and factors we want to take out” and modify accordingly.

Although the biologics appear to promote healing, they cannot generate a sturdy enough scaffold to repair a torn meniscus or ACL. That is why researchers are trying out 3-D printing and other innovations. At Boston Children's Hospital, Murray is testing a small cylinder of sponge-like material—made of proteins such as collagen that are found in connective tissue—as a scaffold for repairing a torn ACL. The sponge is soaked in the patient's blood and then sutured between the two torn ends of the ligament, creating a temporary bridge for healing, much the way a blood clot would. It has worked so well in pigs that Murray and her associates have received FDA approval to try it in humans this year. One especially hopeful finding in pigs: those treated with the new technique developed far less arthritis than those given traditional ACL reconstruction.

Despite the promise of these and other regenerative techniques on the horizon, it is, of course, always a good idea to try to avoid surgery by protecting your knees as best you can. But for those unfortunate enough to damage this complex joint, the future is looking stronger and a lot less painful.

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1. What serves as the knee’s shock absorber? How is it described in the article?
2. What is the manufactured meniscus made of?
3. How does the manufactured meniscus aid in the healing of a sheep’s joint?
4. What is the current approach that physicians offer for a problematic meniscus?
5. How many people visit an orthopedist for knee problems in the United States each year?
6. Why don’t tendons, ligaments, and cartilage heal the way other tissues do?
7. How do surgeons typically do for a torn ACL (anterior cruciate ligament)?
8. How does synovial fluid interfere with the body’s attempt at healing the ligament?
9. What does PRP stand for? How is it ‘made?’
10. What does BMAC stand for? Why is it a promising treatment for the future?