**A sporting chance**

This month, athletes from all over the world will gather in Beijing to compete for the gold. Some will win, some will lose and some will undoubtedly get injured. Cassandra Willyard explores the advances in biomedical research that might help get injured athletes back on the field faster in the future.

In contact sports such as American football, hardly a game goes by without a sprain, strain or break. Just before the Super Bowl championship, however, is a terrible time for a team to lose one of its star receivers. Yet that was the situation the New York Giants faced last February, when a swollen knee and sore ankle sidelined the team’s wide receiver Plaxico Burress—just two days before his team was set to face the then undefeated New England Patriots in the biggest game of the year.

Lucky for the Giants, Burress felt strong enough to play on game day despite his injuries; he caught the winning touchdown pass with just 35 seconds left on the clock.

Scott Rodeo, a knee and shoulder specialist and one of the Giants’ physicians, breathed a sigh of relief from the sidelines. He knew just how close Burress had come to sitting out the game. “For you and me, it’s probably not a big deal to lose time from sports,” Rodeo says. “But for a professional athlete, the stakes are high.”

The thrill of the game lies in the unknown. But when it comes to healing, Rodeo would like to leave more to science and less to chance. So he spends a good deal of his time in the lab trying to understand how the body heals itself and searching for ways to speed the process. And the therapies that Rodeo is testing—everything from stem cells to growth factors—are a far cry from the orthopedic screws and bolts of yesteryear. “We’ve entered a biologic era,” Rodeo says. “I think there’s real potential.”

**Soft sell**

The Hospital for Special Surgery, where Rodeo spends most weekdays, lies on the banks of the East River, on Manhattan’s fashionable Upper East Side. “It’s a smallish place. We just do orthopedics and rheumatologic disease,” Rodeo says. “We’re not a 2,000-bed city hospital.”

The hospital may be small by New York standards, but, according to the ranking source U.S. News & World Report, it’s the country’s number one hospital for orthopedic medicine. Rodeo, a lean, clean-cut man with an immaculate lab coat and an easy smile, is co-chief of the sports medicine department. He and nearly two dozen other surgeons take care of New York’s major-league teams, including the Mets (one of...
New York’s major-league baseball teams), as well as New Jersey’s basketball team the Nets and a bevy of Olympic athletes. Eli Manning’s jersey, a gift from the Giants quarterback himself, hangs behind the reception desk in Rodeo’s waiting room.

When Rodeo isn’t fixing athletes’ shoulders, ankles, knees and elbows, he’s in the lab. As a physician-researcher, Rodeo is a big believer in taking problems from the bedside to the bench and coming back with solutions. “A clinician can wear both hats,” he says. “We can understand and participate in the science, but we also take care of patients.”

Rodeo’s interest in regenerative medicine began more than a decade ago, when he was in medical school. During his residency, he started studying the basic biology of tendon-to-bone healing in dogs, trying to understand both the mechanisms and the timeline.

Today Rodeo is going a step further: he wants not only to understand the healing process, but also to improve it. “A lot of the work has initially been in bone, but the more exciting area is the soft tissues,” he says. “We know even less, and we’re having bigger problems.” The soft tissues that cushion and hold joints together—tendons, ligaments and cartilage—heal slowly, if at all. Part of the problem is that the blood that helps other tissues heal after injury hardly reaches them.

Every day, Rodeo sees patients with blown-out knees and aching elbows—injuries that occur as a result of sudden stress or years of repetitive motion. As a surgeon, he can only do so much. Tendons that rip can be sewn back together, and those that pull free of the bone can be reattached. But without biological healing, these surgical repairs aren’t likely to last.

The same holds true for a torn shoulder, one of the most complex and versatile joints in the body. The stability that allows athletes to throw balls and swing racquets comes in part from the rotator cuff, a group of muscles and tendons that ensure that the upper arm bone stays affixed to the shoulder blade. Hard falls or sudden movements—a too-fast pitch, for example—can cause the tendons to peel painfully away from the bone, leaving the shoulder wobbly.

Left to their own devices, rotator cuff tendons will not reconnect with bone. And over time, small tears can grow larger. “Healing is very slow and very imperfect,” Rodeo says. “In fact, there’s a distinct failure rate.”

In healthy shoulders, the junction between tendon and bone is filled with strong, flexible tissue called fibrocartilage, which is harder than tendon but softer than bone. But fibrocartilage doesn’t regenerate. The best a physician can hope for after rotator cuff surgery is for weakened scar tissue to develop where supportive fibrocartilage once was. Rodeo has spent the past decade looking for tools that will help the body regrow healthy fibrocartilage. And he may finally have found one—BMP-12.

Growth factors
Bone morphogenetic proteins (BMPs) are growth factors. Usually they spur formation of bone, as their name suggests. In fact, within the past few years the FDA has approved BMP-2 and BMP-7 to help fuse vertebrae in people with severe back pain and to mend hard-to-heal shinbones. But some of these proteins, such as BMP-12, can also help form tendon and fibrocartilage. Scientists are still uncertain which types of cells get activated by BMP-12 and go on to form new tissue, but Rodeo’s best guess is that they come from bone marrow. The cells that do respond probably carry special BMP-12 receptors, he suggests.

Rodeo tested whether BMP-12 could help healing after rotator cuff surgery in sheep (J. Shoulder Elbow Surg. 16, S191–S197; 2007). Sheep shoulders aren’t quite the same as human shoulders—rat shoulders are actually anatomically closer—but they are roughly similar in size. (And, because of their size, the sheep live in Colorado, not in Rodeo’s Manhattan laboratory.)

At extremely high doses, BMP-12 risks promoting the formation of bone instead of soft tissue. But a more real challenge of using growth factors is that, because they are
proteins, they break down easily in the body. “They have a half-life of only two hours *in vivo,*” says Edward Schwarz, a professor of orthopedics at the University of Rochester in New York and the president of the biotechnology company LAGeT. “Typically [healing] is a process that occurs over weeks.” The body solves this conundrum by sending cells that can churn out growth factors over long periods of time to the site of the injury.

To ensure that a growth factor has time to work, researchers have to make sure the proteins persist. So Rodeo and his colleagues tested two modes of long-term BMP-12 delivery: a thick paste and a biodegradable collagen sponge, about the size and thickness of a postal stamp. These were sandwiched between the tendon and bone before surgical reattachment.

After eight weeks, sheep that received the collagen sponges laced with BMP-12 had shoulders that were about three times as strong as those that received only surgery. Strength was measured by determining how much force was required to pull the tendon off the bone after the animals were sacrificed. Whereas it took only 0.6 kilonewtons in the sheep that received surgery alone, it took 1.8 kilonewtons in those sheep that received the collagen sponge plus surgery (compared with 3.7 kilonewtons for a healthy sheep shoulder).

“We’re excited because we’ve probably been ten years in development,” Rodeo says. “It has real promise.” In fact, BMP-12 has shown so much promise that Rodeo and his colleagues plan to test it in humans next year. It will be the first growth factor available for soft tissue repair, he says.

Some researchers are skeptical, however. Schwarz says he believes that introducing the genetic code for proteins through gene therapy is a better way to provide growth factors. “It’s a much more sustained delivery,” he says.

But gene therapy comes with its own challenges. Researchers have to figure out not only how to safely transfer the necessary genes from the lab into the right cells, but also how to switch them on once they’re inside.

**Joint ambition**

Gene therapy treatments and growth factors aren’t the only techniques being explored for joint healing. In his lab, Rodeo is investigating whether stem cells might be able to eventually help athletes who tear either the rotator cuff or the anterior cruciate ligament, better known as the ACL.

A torn ACL doesn’t mend well, even if surgeons manage to sew the ends back together. It typically must be replaced. The graft can come from a cadaver, but often the doctors use a piece of the patient’s own patellar tendon or hamstring, which are located at the front and the back of the knee, respectively.

In a typical ACL surgery, physicians drill holes in the thighbone and shinbone, thread the graft through and screw it in place. Again, the tendon-to-bone attachment site is the weak link. Full recovery takes at least six months. For most sports, including basketball, that’s a full season. And for Mitzel, bouncing back from an ACL injury proved difficult. Not only would there be no comeback, there would be no possibility of a scholarship.

Rodeo is running experiments in rats to determine whether stem cells might hold promise for both ACL and rotator cuff repair. For the ACL, rats are a good model because their knees are similar to human knees, he says.

As with growth hormones, one of the challenges with stem cells is determining the best way to get the cells into the body. Rodeo and his colleagues use a gooey toothpaste-like material made from fibrin—the substance that helps blood clot. The cells get suspended in the fibrin and injected at the time of the surgery.

After reconstruction: A knee after anterior cruciate ligament (ACL) reconstruction. The screws fix the graft to the bone tunnels
“The cells might contribute in a lot of ways,” Rodeo says. They might start producing the chemical signals that call other cells to the scene. Or they might start producing tissue-healing proteins. The response depends, at least in part, on where they’re placed. Cells introduced into the liver might behave differently than cells placed in the knee. “It’s a bit of an act of faith. You put them in and see if something happens,” Rodeo says. “Generally it does. You can spend the next decade saying, ‘OK, what is the mechanism?’” In the knee, the cells seem to do some good, but Rodeo has yet to tag them to see how exactly how they function.

Gregory Altman, president of biotechnology company Serica Technologies in Medford, Massachusetts, is trying a different tack. Replacing a patient’s torn ACL with tissue taken from elsewhere in the body, such as the patellar tendon, is still “robbing Peter to pay Paul,” he says. Altman would know. He tore his ACL playing football for Tufts University in the fall of 1996. “Overcoming the loss of my patellar tendon was the number one hurdle in rehabilitation,” he says.

Altman’s company has developed a biodegradable scaffold. It’s a piece of woven silk (from silkworms) designed to act as an ACL until the body rebuilds its own. The idea is that cells will migrate to the scaffold, colonize it and slowly digest it as they form a new ligament. He and his colleagues plan to start their first human trial next year. “Intelligent scaffolding is here today,” Altman says. “I think gene therapy and stem cells, while they are certainly the future of regenerative medicine, are a few years out.”

Rodeo agrees that the research must proceed cautiously. Not only are regenerative techniques risky, they could potentially enhance performance as well as speed healing. And that means the World Anti-Doping Agency will be watching new developments closely. Because there is so much potential to heal damaged tissue, however, Rodeo expects to see some of these techniques available in the next decade. And that could be a boon for injured professional athletes.

Come August of this year, Rodeo will be in Beijing. He’s been asked to join the US Olympic Committee medical staff to oversee US athletes involved in water sports—swimming, diving, water polo and much more. He’s there to take care of sprained ankles and broken bones, as well as to deal with upset stomachs, runny noses and insomnia.

The Olympics is neither the time nor the place for surgery, but Rodeo’s research may eventually lead to cells or proteins that he could use on the field. He and his colleagues are already investigating whether a shot of BMP-12 might help athletes with tennis elbow. Such therapies probably wouldn’t work fast enough to get an athlete back in the game, but they could speed recovery and help the athletes avoid surgery. “If we’re really good at what we do, we’ll put ourselves out of business,” Rodeo says. “That’s the ultimate goal.”

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