Deborah Franklin is based in San Francisco and has reported on science and medicine for *NPR*, the *New York Times*, *Fortune* and *Health Magazine*.

A Dangerous Game

Some professional athletes' enthusiasm for certain stem cell treatments outpaces the evidence

In 2005, at the age of 32, then Los Angeles Angel Bartolo Colón won the American League Cy Young Award for best pitcher, one of professional baseball's top honors. He stumbled through subsequent seasons, however, after a series of rips and strains in the tendons and ligaments of his throwing arm, shoulder and back. In 2009 he all but quit baseball. Desperate to reclaim his career, Colón flew home to the Dominican Republic in 2010 for an experimental procedure not vetted or approved by the U.S. Food and Drug Administration. Doctors centrifuged samples of Colón's bone marrow and fat, skimmed off a slurry containing a particular kind of stem cell—immature, self-renewing cells that can turn into a variety of tissues—and injected it into his injured shoulder and elbow. Within months of the procedure the then 37-year-old Colón was once again pitching near the top of his game for the New York Yankees—commanding a 93-mile-per-hour fastball.

Whether the injected stem cells rejuvenated his arm is an open question. The FDA and the International Society for Stem Cell Research warn that no rigorous studies have demonstrated that such treatments safely and effectively repair damaged connective tissue in people. The results of related animal studies, though promising, have raised more questions than answers. "The term 'stem cell' makes it sound cutting edge and exciting," says Paul Knoepfler, a cell biologist at the University of California, Davis, who also writes frequently on policy surrounding stem cells. "But the role of these cells in sports medicine is essentially all hype."

No matter, apparently, to the aging, injured athletes who have followed Colón's lead. Lefty pitcher C. J. Nitkowski, who underwent the same procedure in 2011, told readers of his personal blog that he did not mind the lack of carefully controlled research. "My attitude is I don't have the time to wait for the five- or 10-year study to come out," the then 38-year-old relief pitcher wrote, "so I'm taking a chance now." Besides, Nitkowski figured, even if the treatment did not work, any health risks ought to be slight because the cells involved were his own.

That might not be such a safe bet. Numerous studies suggest that Colón, Nitkowski and others trying untested stem cell treatments may be risking more than they think. Even a syringe of one's own stem cells taken from one part of the body and squirted into another "may multiply, form tumors, or may leave the site you put them in and migrate somewhere else" the FDA warns on its Web site. More clinical research is needed to define safety procedures, as well as how many cells of which types and what other tissue factors produce the desired results. In some animal studies, for example, the regenerated tissue is not as strong or flexible as the original. In other cases, an overgrowth of scar tissue makes the injected tendon or ligament adhere to the overlying skin. By preventing different tissues from gracefully sliding past one another, these adhesions sometimes pull an even bigger tear in an already serious wound.

In addition, Knoepfler worries that high-profile sports testimonials by Colón, Nitkowski and others will encourage joggers with blown-out knees and the parents of sore-armed Little Leaguers to demand the procedure before it has been thoroughly tested. "When celebrities take to a new treatment, many other people follow suit," he says. Such premature enthusiasm—or an unforeseen tragedy that results from proceeding too fast too soon—could also prevent serious researchers from

Illustration by Peter Ryan

getting funding to do the kinds of careful experiments that might eventually lead to safe and reliable treatments.

SEEDS OF REPAIR

THE NEED FOR BETTER WAYS to reknit damaged tendons and ligaments is painfully apparent to the roughly two million Americans in a given year who seek medical help for tears in their shoulder's rotator cuff, for example, or the 100,000 patients in the same year who undergo surgery in the U.S. to repair a ripped or ruptured anterior cruciate ligament (ACL) of the knee. Tendons and ligaments are tough, fibrous bands, made mostly of collagen, that anchor networks of muscles to a bone or link bones and cartilage across crucial joints. They lend strength, flexibility and stability to your daily twists and turns, whether you are rocketing a baseball across home plate or hefting a suitcase into an overhead bin. Once frayed or snapped, they can take many months or longer to mend—even with surgery.

Healing is slow in part because tendons, ligaments and cartilage lack the interlaced blood vessels that other organs rely on for quick delivery of cells involved in repair and growth factors that encourage cells to thrive and divide. Under these circumstances, the rationale for stem cell therapy seems straightforward: bathe the injury in a healing, concentrated wave of tissue-mending cells, and the body will repair itself that much more quickly.

As so often happens in biology, however, applying a simple idea can quickly become more complicated once you start dealing with the details. For starters, the term "stem cell" describes several different types of cells with different capabilities. Embryonic stem cells, for example, can readily give rise to any type of cell found in the body under the right set of circumstances—and when plied with the right set of biochemical signals. In contrast, a more specialized group of stem cells found in the bone marrow generally begets blood cells and immune cells exclusively. These so-called hematopoietic stem cells (from Greek meaning "to make blood") have been reliably used over the past 40 years to seed bone marrow transplants in the treatment of some cancers and immune disorders.

By the 1970s researchers had recognized another type of progenitor cell in the adult bone marrow, which they named the mesenchymal stem cell. In a laboratory dish—and, presumably, also inside the body—these cells readily multiply and give rise to various structural cells, such as fat, muscle, bone, tendon, ligament and cartilage. Studies in animals suggest that mesenchymal stem cells play important roles in the body's ability to heal after an injury, although researchers are still working out the signals and steps required to steer their differentiation into one type of tissue or another.

It turns out, for example, that mesenchymal stem cells do not regenerate tissue in isolation. They depend on other cells and growth factors that may or may not be present in a particular region of inflamed tissue, says Rocky Tuan, who directs the Center for Cellular and Molecular Engineering at the University of Pittsburgh School of Medicine. "You can inject all the best cells," Tuan says, "but if you don't have the right combination of healing goodies around them, it's useless."

Lab studies are also finding that mesenchymal stem cells extracted from different parts of the body can have different attributes. Those found in fat, for example, though relatively plentiful and easy to extract, do not seem to form cartilage as readily as those that come from bone marrow, Tuan says. Other studies suggest that mesenchymal stem cells also modulate the immune system and may have some part in the spread of tumors. Gathering much more basic information about how these cells behave is a vital first step before any safe and broadly reliable treatment can be developed for people, Tuan and other leading stem cell scientists argue.

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GALLOPING AHEAD OF THE SCIENCE

UNDETERRED, advocates for the immediate use of stem cell therapy in human athletes point to successes with racehorses as the best evidence that the treatment works. Yet some experts say that the same hype that makes human testimonials unreliable has enveloped company-sponsored studies of competitive horses, too.

In the July 2012 issue of *Equine Disease Quarterly,* Wesley Sutter of Lexington Equine Surgery and Sports Medicine in Kentucky cautioned: "To date, no published controlled clinical studies show efficacy in use of stem cell treatment for any of the conditions being treated."

Carol Gillis, a longtime veterinarian and researcher who specializes in soft-tissue injuries in racehorses, says that the more than 22,000 ultrasound images she has captured in her studies and clinical practice have convinced her that with a tightly regimented exercise program, tendons and ligaments will heal, producing strong, well-organized fibers—all without the use of stem cells. The reason that many soft-tissue injuries end a horse's racing career, Gillis explains, is because most owners allow the animal to run free too soon, when the pain from the initial injury has faded but the tissue is still fragile.

The ebbing summer of 2012 found Nitkowski working on a new sidearm delivery with a Minor League Mets team, still hoping to return to the Majors as a 40-year-old in 2013. Meanwhile the professional story of Colón, now an Oakland Athletic, entered a darker chapter on August 22, 2012, rendering his experiment with stem cells moot. The 39-year-old's season ended that day when Major League Baseball officials suspended him for 50 games—because he tested positive for the performance-enhancing drug synthetic testosterone. On November 3 the Oakland A's gave Colón a $3-million, one-year contract extension, which begins as soon as his suspension ends. SA

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