In June 2018, Jonathan Gray left the field after a USA Rugby Club Championship match at Infinity Park in Glendale, Colorado with an unwelcome companion: severe pain in his left knee.

The discomfort was as emotional as it was physical. Gray loved rugby. Now 41, he had been a top-level player since his high school days in Seattle. He was a two-time All-American at the University of Arizona and regularly competed after graduation overseas and on United States club teams.

Gray was no stranger to injuries he sustained playing the high-contact sport. The list includes a dislocated collarbone, broken ribs and fingers, lacerations, and a badly torn hamstring. But the knee injury had slowed his game since 2014. The 2018 pain ultimately forced him off the field for a year and a half – and threatened his ability to play rugby again.

"The injury had been a sticking point," Gray said. "When I came out low, made a hard cut or squatted, the pain was unbearable. It held me back for a long time."

The problem was badly damaged cartilage in the knee that forced pressure on his femur (thighbone). The result: a hairline fracture and a bone bruise. Gray tried a battery of treatments to ease the pain: cortisone shots, plasma-rich platelet injections, lubricating gel, "massive" physical therapy, massage, and transcutaneous electrical nerve stimulation – all to no avail.

"Nothing seemed to work," Gray said.

As the pain worsened, he had to ease his way down the stairs sideways. If he took a wrong step or tripped, the leg gave out.

"It was like a knife went through it," Gray recalled.

Two-and-a-half years after his dispiriting trudge off the Infinity Park field, Gray is back to playing with USA Rugby, relying on a left knee that he says feels like new. He owes the reversal to reconstructive surgery last summer at <u>UCHealth Steadman Hawkins Clinic – Denver</u>. His recovery may also have gotten an assist from cells in his own body that show tantalizing promise for boosting the body's healing power.

In the operating room, Gray's surgeon, <u>Dr. Jason Dragoo</u>, Professor and Vice Chair of Academic Affairs for the Department of Orthopedics at the University of Colorado School of Medicine, worked to redistribute force in Gray's knee joint away from the femur injury. He then turned to regenerative medicine, one of his specialty areas.

Dragoo used liposuction to harvest fat tissue from Gray's abdomen. Still in the OR, he separated from the fat tissue mesenchymal stem cells (MSCs), the kind that give rise to connective tissue, bone and fat, and injected the cells into the knee joint.

It was no wild experiment. Dragoo explained that MSCs can help to decrease pain by naturally <u>activating</u> <u>opioid receptors</u> and also <u>reduce inflammation</u> by stimulating the body's immune response. In Gray's case, the strategy appears to be an unqualified success.

"His knee exam is now normal," Dragoo said.

He's now putting MSCs to a further test. In a <u>trial</u> underway at the Steadman Hawkins Clinic – Denver, Dragoo is conducting surgery on two groups of patients with knee osteoarthritis. On both groups, he makes surgical repairs, such as removing loose cartilage and fixing meniscal tears. He then harvests MSCs from a layer of tissue under the kneecap called the fat pad. One group gets an injection of the cells, while the other gets a placebo injection of saline. It's a randomized double-blind study, meaning neither the patient nor Dragoo know who received which treatment.

Two years of observation, including independent review of functional MRIs, will follow to answer the question of whether or not these MSCs derived from fat tissue can unleash the body's power to regenerate new cartilage.

The notion of the body self-healing is hardly revolutionary, Dragoo noted. Think cuts, scrapes and broken bones that repair over time. Damaged cartilage is another story. If it could regenerate itself after injury, athletes wouldn't agonize over losing their careers to anterior cruciate ligament tears.

"Why can the body heal one area and not the other?" Dragoo said. "That is what is behind the science we are pursuing. We are learning and understanding how we can use the body's own resources to heal parts of that body where it doesn't otherwise do so."

Yet a rigorous clinical trial like the one he is conducting is the only way to definitively answer the question. He's also <u>openly worried about clinics that make unsubstantiated claims about the ability of stem cell treatments to heal musculoskeletal injuries</u>.

"We're trying to prove if these cells can actually lead to restoration of cartilage tissue," Dragoo said. "As of now, we just don't know."

Dragoo said the clinical foundations for the trial stretch back to his residency in orthopedics at UCLA Medical Center, where he was part of a team that discovered MSCs within fat tissue. He and his colleagues began studying how they might be useful in treating musculoskeletal disease. That work led to examinations of the fat pad – a heretofore poorly understand part of the anatomy – that yielded an important finding. The pad, it turned out, contains "huge numbers" of MSCs, Dragoo said.

With this new knowledge in mind, Dragoo said he and others began looking at cartilage damage in the knee from a surgical perspective. They noticed that the fat pad grew around injured areas.

"We saw the body's response, which was to grow local tissue over the injury," Dragoo said.

That observation suggested the healing power of MSCs in the fat pad. But the fat pad contains a variety of cells. How to harness the stem cells for surgery?

"We realized that MSCs are not necessarily accessible to the joint without freeing them up," Dragoo said. While at Stanford University Medical Center, he and a colleague <u>described a method for harvesting</u> the cells from the fat pad so they could be used in regenerative procedures.

A subsequent trial demonstrated that the processed cells could be used to heal cartilage damage in animals, setting the stage for the current clinical trial of human osteoarthritis patients.

Jonathan Gray was not part of the trial, but his experience with cell therapy offers at least anecdotal evidence of the healing power of cell therapy. The surgery has also restored his ability to play the game he loves.

"It feels again like I can play week in and week out," Gray said. "That's invigorating."

Rugby is more than just a game for him, he added. He was born in the United States, but his family is from New Zealand, where rugby is huge. Gray spent a few formative years there before returning to the States, settling in Seattle, taking up the sport seriously and forming enduring bonds around it.

"A lot of my social network and my friends, I met through rugby," Gray said. He recalled his coach at the University of Arizona addressing him and about 60 other rookies and asking them to look around.

"He said, 'You may not know any of these people, but one day you'll be at one another's weddings and funerals and you will be there when one another's babies are born.' That's the rugby culture. It's a very tight community."

Thanks to the surgery and cell therapy, Gray has been able to renew that connection.

"To be able to go back and reunite with friends and those still playing and have tournaments to go to or travel on weekends and practice is a great outlet for me," he said.

Gray said after steady work rehabbing and strengthening his knee, he's now able to work out with local rugby teams. He's practiced tackling without pain and steps from his truck without fear of wincing.

"I no longer have to be extra careful," he said.

He credits Dragoo and his team for being upfront with him about his care options, the most extreme of which was a one-quarter knee replacement and six months of recovery. Gray said he was interested in the cell therapy option, but Dragoo did not push it.

"He told me the jury is still out on it, there are no guarantees, and that I should do my own research," Gray said.

With a knee that now feels like it's 30 years old again, he feels he made the right surgical decision.

"I was put back together by science," he said.