



RESISTANT TO DAMAGE

ON CONQUERING ARTHRITIS

AND OTHER BATTLES

BY DOTTIE HORN

ABOVE: The key to avoiding osteoarthritis is keeping these cartilage cells, called chondrocytes, healthy. Constance Chu has devoted herself to finding treatments to deter the debilitating disease.

It was Constance Chu's first day as a new cadet. Her hulking first sergeant lined up his company—all men except for Chu. The United States Military Academy at West Point had opened its doors to women three years earlier. The sergeant's voice boomed: "If you want to get through these Beast Barracks in plebe year, you have to walk, talk, look, think, and act like the man next to you." He strode up to the lone woman in his ranks. "Miss, what's your name?" he said.

"New cadet Chu, sir."

"Chu? What kind of name is that?" He turned away from her and then came back. "Well, I got news for you, Chu. I have a plane ticket home for you in my locker box anytime you want it."

It has been almost 25 years since Chu, now an assistant professor of orthopaedic surgery at the University of Pittsburgh School of Medicine, started at West Point. But even now, as the accomplished surgeon thinks back to those days, she pauses to compose herself before saying, in a level tone: "People told me every single day my first year at West Point, *We don't want you here. You will never make it. You can't do this.* And it's actually very emotional, because my gosh, when you're 17 years old, to have people say, *We don't want you here.* You have to dig deep and say, *I want to be here.*"

Chu, whose grandfather was a general in the Chinese army, became the first Chinese American woman to graduate from West Point. (Better, she ranked among the top 5 percent of her class in terms of cumulative military, athletic, and academic prowess.) If she had it to do over, she would, without hesitation, choose West Point again. The reason? "Because of that deep-down, gut-level absolute confidence that no matter what happens, no matter how dark it might look, I can do this."

Pretty much anyone with cartilage that's being worn away can be thankful for Chu's resolve. She's tackling osteoarthritis on a number of fronts, and won't let anyone tell her it's too difficult to advance the basic science behind the debilitating disease while also pursuing a demanding clinical practice. "As a surgeon, I love it when I see a patient who has a problem I can fix. As a basic scientist, the person who motivates me is the patient who comes in with a problem that I can't fix," says Chu.

But being well-known and respected within a community as an orthopaedic surgeon requires seeing a lot of patients. After all that time spent in the clinic and OR, there's little left over for the laboratory. With cutbacks in budgets at academic medical centers, there is often less money to support orthopaedic surgeons who want to pursue basic science. For these and other reasons, some of Chu's mentors discouraged her from pursuing her dual path. But Freddie Fu, chair of the Department of Orthopaedic Surgery, was impressed by Chu's unusual background and

her work on cartilage—leading him to recruit her while she was a fellow at Harvard University (where she was encouraged by Henry Mankin, MD '53). "She knows what she wants to do," says Fu. "She is also in a very hot research field—cartilage. She's definitely out of the box. I think she's outstanding."

After joining the Pitt faculty in 1999, Chu forged ahead with her professional plans, restricting her surgery practice to the knee so that she'd have more time for the lab.

"It's within my reach, doing basic science research to make a contribution that would impact many more people than I could personally treat myself," says Chu. She is ever mindful of those who suffer from arthritis, particularly the millions who can't find relief from current treatments.

Theresa Lach burst into tears the first time she visited Chu at her clinic. After teaching special education students for three decades, Lach, who was approaching retirement age, had stopped teaching because of the pain in her knees. The

prior joint injury.) For Lach, whose joint was destroyed by the disease, a knee replacement was a good option. Lach had the operation on her left knee in March 2003 and is glad she did; she is able to stand longer and walk farther than before, though she still has arthritis in her right knee.

But for others with end-stage arthritis, a total joint replacement is far from optimal. An artificial knee, which is made of metal and plastic, lasts about 15 years. As it wears out, bits of the synthetic material break off. Immune cells respond to the synthetic particles by attacking the bones to which the knee is attached and killing the bone cells. When the first knee wears out, doctors can often replace it again. Eventually, however, so much leg bone is destroyed that it is impossible to put in a new knee. A knee replacement is ideally suited for someone who is 10 to 15 years from the end of his or her expected life span.

But increasingly, arthritis is affecting younger people. One reason may be the growing corps of women participating in sports. Research suggests that the female

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four-minute walk from her car to the school building had become a struggle, and once inside, she had another 10-minute walk to reach her classroom. But retiring was not easy. "I was emotionally a wreck," says Lach. "I really liked my job, and I thought I could have put in many more years."

Throughout the previous decade, the pain in her knees had gotten progressively worse. A year before she retired, her left knee had buckled inward, and she was unable to straighten it.

Her knee problems affected most areas of her life. Lach loved to cook, but standing in the kitchen to prepare meals took her three times longer than before—she had to keep stopping to rest from the pain. "If I had to stand in line in the grocery store, it was excruciating," she says. "It was emotionally draining to be in constant pain. You lose all joy for life."

Lach is one of 21 million Americans who have osteoarthritis, arthritis that results from cartilage becoming frayed and worn. The incidence of this disease is expected to rise as the baby boomers get older. (Osteoarthritis is associated with age, as well as obesity, and a

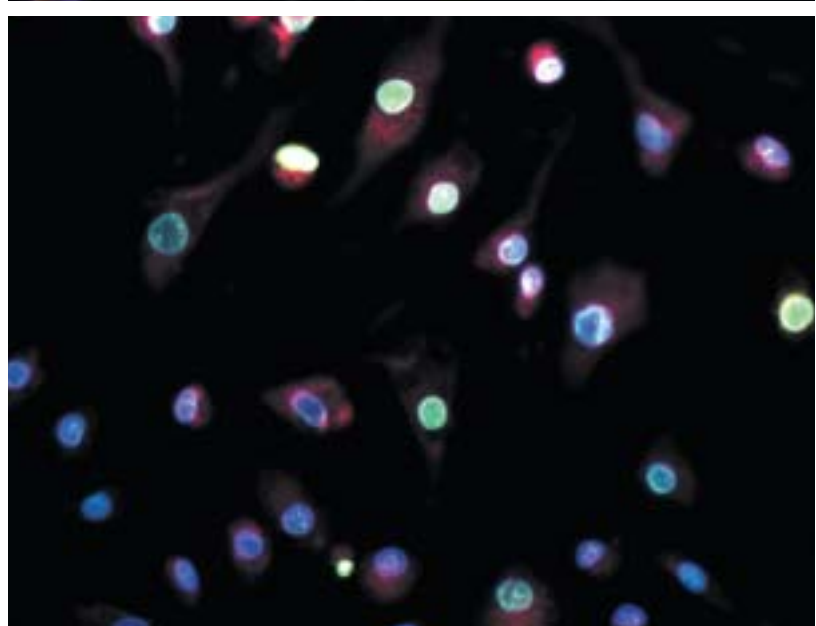
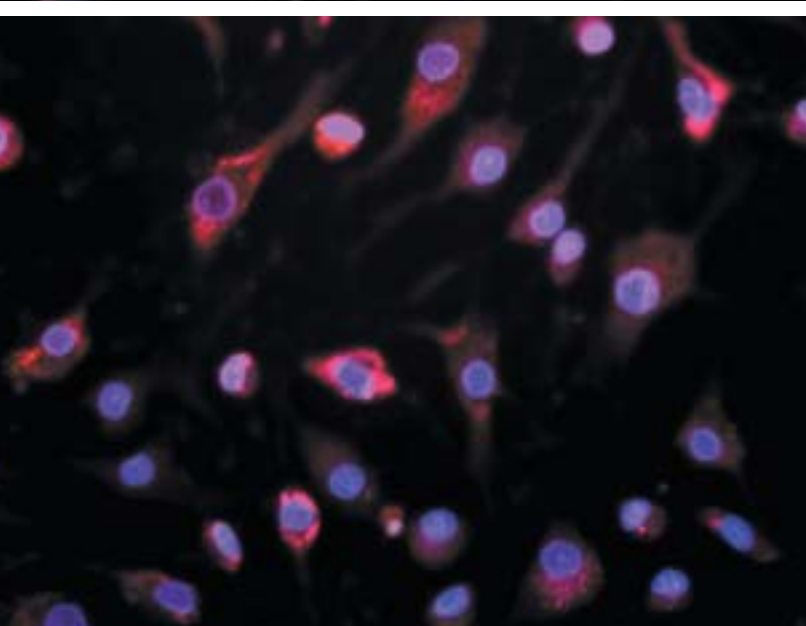
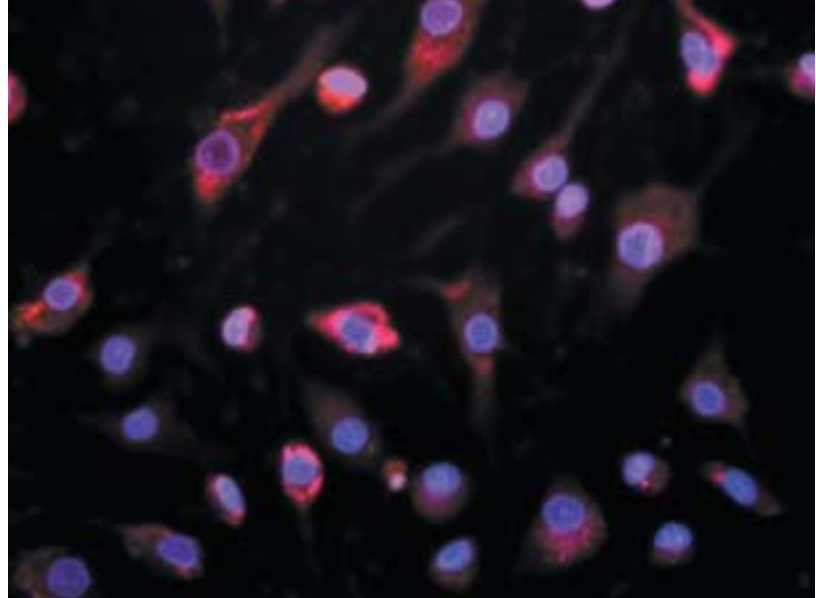
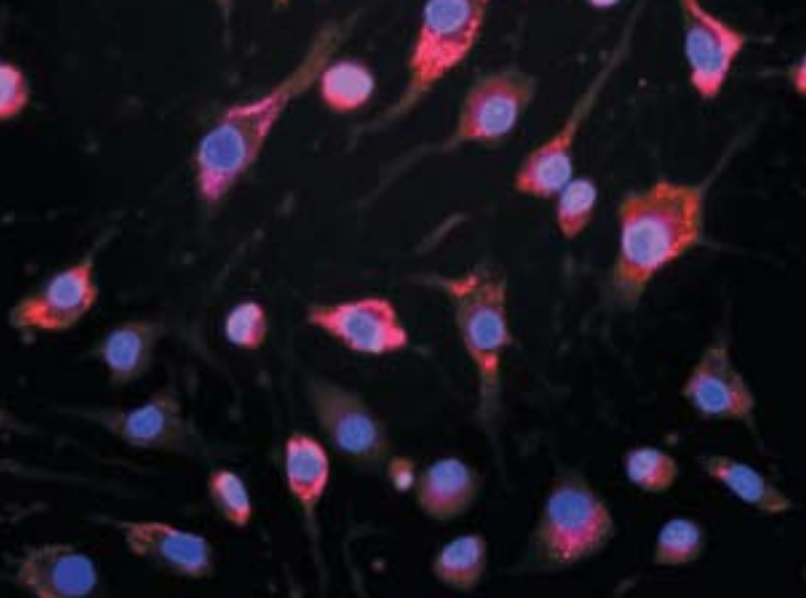
knee—perhaps because of gender-based differences in training or a different anatomy—is more susceptible to injury than the male knee. Another contributing factor may be the epidemic of obesity in the United States.

More and more, orthopaedic surgeons are encountering patients in their 40s with end-stage arthritis in their knees. "I have replaced knees in people as young as 40," says Chu. She tells young patients considering total joint replacement surgery that they could be in a wheelchair or lose a leg by the time they're 65. Chu won't perform a knee replacement in patients that young unless they're severely debilitated. "When you see that, it makes you more determined to find something for the 22-year-old who comes into your office, who has twisted a knee or had an injury, so that [he or she doesn't] show up at age 40 needing a knee replacement."

Whenver two bones meet, cartilage at the end of each bone cushions the junction. The cartilage, which has a slippery surface, allows the ends of the

Anyone susceptible to osteoarthritis (which is an increasing fraction of the American population) can be thankful for Chu's resolve. She's shown here relaxing at home with Sid.





COURTESY C. CHU

Using heat and other stress tests, Chu looks for ways to help cartilage cells survive injury. UPPER LEFT: Healthy cells at normal body temperature. Then Chu turns up the heat. UPPER RIGHT AND LOWER LEFT: At 113 degrees Fahrenheit and hotter. LOWER RIGHT: By 140 degrees, the cells are most likely dead. Their nuclei (formerly blue) have turned greenish-white, indicating that the cell's membranes are no longer working normally; most of their mitochondria (stained red) can no longer be seen, because they're not functioning.

bones to glide smoothly over each other. Cartilage is 10 percent cells and 90 percent matrix (water and proteins secreted by the cells). It is the matrix that gives the cartilage its characteristic glassy smooth surface, stiffness, and ability to absorb shock. The cells, scattered here and there throughout the matrix, are like custodians: Their job is to renew and sustain the matrix. These specialized cells, found only in cartilage, are called chondrocytes.

The sudden impact of an injury or the chronic stress of excess weight can kill or damage chondrocytes. Instead of maintaining the matrix, an injured cell may release chemicals that break it down. Or the cell may simply die and be unable to perform its usual role. Once chondrocytes are dead or dysfunctional, there is nothing to renew the matrix. Little by little, over the course of years, the matrix wears away. The joint may become stiff and painful. Eventually, there will be no matrix left, and the ends of the bones will scrape against each other when the joint moves. This is end-stage arthritis, a realm in which debilitating pain like that experienced by Lach is the norm.

The degeneration of matrix causes arthritis and makes it an often silent disease as it encroaches. Let's say a rugby player is tackled, propelled into the air, and lands on her knee. She immediately suffers from pain and swelling in the joint, but in a few weeks, her knee feels fine. Yet inside, chondrocytes may have died, setting in motion the silent, decades-long breakdown of matrix.

Chu wants to know if there is a way to make those chondrocytes heartier, more likely to recover and become normal again after they are damaged. She has received a developmental National Institutes of Health grant to pursue this question. In the lab, Chu grows chondrocytes in small glass containers. First, she takes the chondrocytes and exposes them to stress—simulating an injury to a joint. One of the stressors she uses is interleukin 1, which is produced by cartilage cells in an arthritic knee. Chu is studying the effects of a number of substances that she hopes will protect the cells. She's hoping to find compounds that allow more cells to survive and preserve their ability to sustain a healthy matrix. Although she does not yet have definitive results, the studies are encouraging. For example, it appears that the COX2 inhibitors, anti-inflammatory drugs currently used to treat arthritic pain, do improve the ability of the cell to maintain the matrix. Chu wonders, if the drugs were administered in the early stages of the disease, before symptoms ever occur, would they help

prevent the breakdown of matrix?

She is one of many scientists seeking ways to make cartilage more durable. “There are many drug companies and biotech companies that are interested in developing drugs, or biologic agents, that protect the cartilage from damage or that accelerate repair processes,” says John Klippel, president and CEO of the Arthritis Foundation. “So, we do believe that in the future, it’s quite likely we’re going to see drugs that are called chondroprotective drugs.”

Let’s say such a class of drugs were developed and our rugby player came into Chu’s office shortly after falling on her knee. Chu knows she’s at risk for developing arthritis, but there’s no practical way to assess, for example, what percentage of the chondrocytes in her knee are dead or injured after the fall. The only way to get detailed cellular information would be to biopsy the cartilage. But that

moved it, and sometimes lock unexpectedly.

To repair an isolated defect like a “pothole” or a dent, orthopaedic surgeons have several options. One is to use cartilage from human cadavers to fill in the damaged area. As a resident at the University of California, San Diego, Chu studied patients who’d received knee cartilage transplants; she followed them for up to 10 years after the procedure. She found that 75 percent of the patients showed improvement in knee pain and function. In her study, the cartilage was transplanted after testing showed that it was not infected with bacteria or viruses—but it was always transplanted within three to seven days after the donor died.

Based in part on Chu’s studies, tissue banks began offering cadaver cartilage for sale. One problem: Tissue banks take three weeks to complete the testing that ensures the carti-

chondrocytes derived from stem cells. She takes stem cells from human bone marrow, treats them with growth factors in the lab, and turns them into cartilage. For her studies, she uses rats that have been bred so that they will not generate an immune response against human cells. She makes a hole in the cartilage in the rat’s knee. She then implants her lab-generated cartilage into the hole. After eight weeks, she has found that the implanted cartilage is still alive and is helping to repair the defect in the knee. When compared to rats that received the knee hole but not the implant, the implanted rats show less evidence of arthritic changes in the cartilage surrounding the hole.

While such results are promising, there are challenges to overcome before a similar treatment might be used in humans. Chu and others studying stem cells can generate enough cartilage to patch up a tiny rat knee.

But so far, no one has been able to grow a piece big enough to, say, fill in a big defect in a human knee. Normal cartilage is firm (firmer than garlic, says Chu), but a large piece of cartilage derived from stem cells is so soft

it often can’t stand on its own. Lab-made chondrocytes don’t organize themselves into the structure of natural cartilage. And as the Arthritis Foundation’s Klippel notes, “One wants the cell produced [to be] as identical as possible to a normal, healthy human cartilage cell in terms of how it functions and the products it produces.”

Chu will keep at it. After all, this was the woman who chose West Point over Stanford and Harvard. (She calls that choice a “no-brainer” because she thought that West Point would be a more well-rounded experience.) Chu is not one to be dissuaded—unless Valerie Brisco-Hooks is involved. Growing up in Los Angeles, Chu wanted to be a track star. She was the fastest runner in her elementary school. But there came a day when Chu’s track dreams came to an end. Up until that point, she’d won most of her races. But one day in high school, Chu was the final runner in a relay and had a nice lead. Then, a girl she didn’t know (Brisco-Hooks) came up from behind and passed her, winning with a huge lead. “She didn’t just beat me. She creamed me. So at that point, I definitely knew: She’s a track star. I’m not,” recalls Chu. “I didn’t quite recover from that until the 1984 Olympics, when Valerie Brisco-Hooks won the 200- and 400-meter gold medals.” ■

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would cause further damage to the joint.

So Chu and colleague Yingtian Pan have modified the minimally invasive surgical tool known as the arthroscope. Normally, it is inserted into a joint through a small tube, allowing the surgeon to see and do surgery inside of the joint. Chu and Pan have added optical coherence tomography to the arthroscope, enabling them to see what’s happening at the microscopic level without damaging the cartilage. Chu has recently published two studies that show that the images obtained using the modified arthroscope provide the same detailed information you would get if you did a biopsy and then examined the tissue under the microscope. The new device may allow doctors to diagnose arthritis years before symptoms arise. If treatments are developed, doctors could then administer them to patients early—and hopefully slow down or prevent the progress of the disease.

For some people who develop arthritis, there is nothing silent about the onset of the disease. If a man were in a car accident, for example, and his knee were propelled into the dashboard, the force of the impact might dent the cartilage. It’s likely that bits of cartilage would then begin to flake off. The knee would hurt, swell, click when he

lance is not infected. Chu has shown that after three weeks of refrigerated storage, all the chondrocytes are dead. She now limits her use of the procedure and counsels patients that grafts from tissue banks will deteriorate over time. But she hopes to identify substances that, if they are placed in the storage fluid, might help chondrocytes survive. Her research suggests that, even if only 50 percent of the cells were alive at three weeks, the matrix could be maintained.

Another option for repairing an isolated defect is to take a biopsy of the cartilage, extract the chondrocytes, grow them in culture until there are millions of cells, and then re-implant those cells at the site of injury. This procedure results in improved function (though not a perfect knee) in about 75 percent of patients. Yet it is an appropriate therapy only for patients with small, discrete injuries. “I can only take a little bit of cartilage out of a person’s knee, about 200 grams, and that’s about half the size of a thumbnail,” says Chu. The chondrocytes in the extracted cartilage can be induced to divide only a certain number of times before they will cease being chondrocytes. So, the number of cells that can be generated for repairing the defect is limited.

In the hope of overcoming this problem, Chu is exploring the possibility of implanting