WHAT FOSSILS AND FRIENDS FROM THE ZOO TELL US ABOUT FIXING HURT KNEES

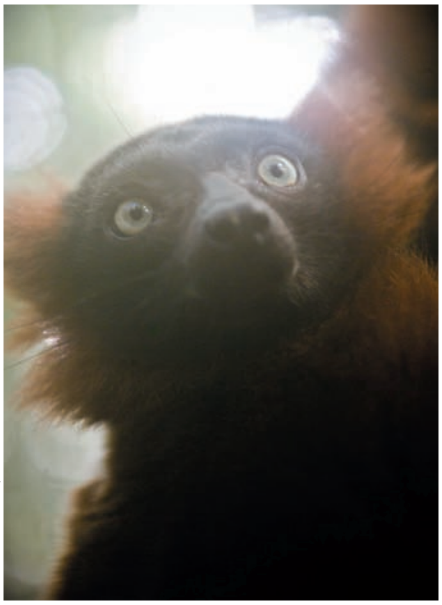
BY JOE MIKSCH

WOBBLY KNEES

How does one make a lemur walk a straight line? The answer: grapes. But the real question being asked is, "What does the evolution of the knee tell us about the best way to repair ours when the anterior cruciate ligaments snap?" That answer is a bit more complicated.

If a layman takes even a very close look at the ACL, it looks like one bundle of fibers connecting the femur to the tibia. The ligament (which is actually two ligaments, the anteromedial and posterolateral—more on that in a bit) stabilizes the knee while allowing for extension of the leg and rotation of the joint. It's a pretty important piece of anatomy, especially for the professional athlete, but also for the weekend warrior and, frankly, anyone who wants to walk without pain. Worldwide, surgeons perform about 800,000 ACL procedures each year.

Freddie Fu (MD '77, Res '82), an MD as well as David Silver Professor and chair of the Department of Orthopaedic Surgery at the University of Pittsburgh, has been repairing ACLs since 1982. More than a quarter-century later, he frets that he—and every other orthopaedic surgeon in the world—might have been doing it wrong.



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Copper the lemur is a valuable, though not always cooperative, research subject.

The bones of one of our earliest bipedal ancestors, Lucy, give Freddie Fu and colleagues insight into how our knees do and don't work.

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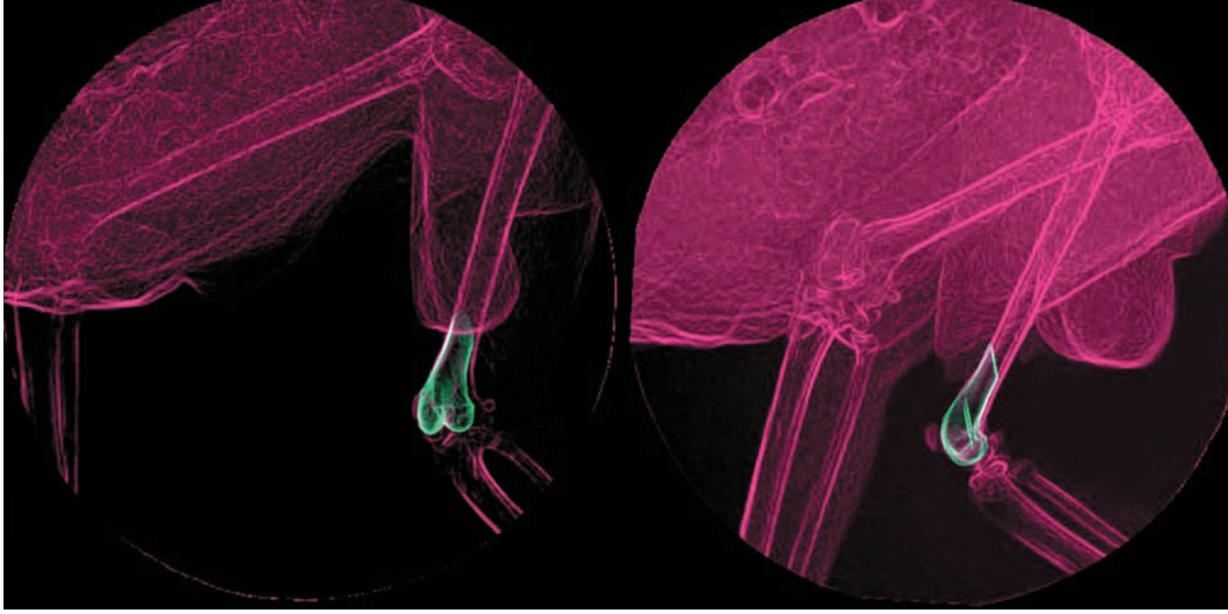

Well, "wrong" may be too strong a word. ACL repair, as it's typically practiced today, does a fine job of getting folks back on their feet. Professional athletes often return to the field cutting, accelerating, and jumping as well as before. The regular guy can walk, jog, or bowl as well as before. In many ways, contemporary ACL surgery is good enough, but Fu is firmly convinced it can be better.

Fu's known as a pretty energetic fellow. He's made surgical "house calls" to Saudi Arabia, Turkey, Brazil, and Hong Kong. He takes care of the joints of University athletes and professional jocks—Steelers, Pirates, and Penguins. He's repaired the anatomies of ballet star Mikhail Baryshnikov and five-time Tour de France winner Miguel Indurain. (Fu himself rides about 100 miles a week and sponsors a professional team—the Freddie Fu Cycling Team of the Allegheny Cycling Association.) Thank-you notes from patients famous and humble decorate his office-suite walls.

He's often pictured, tuxedo-clad, in the society pages of Pittsburgh newspapers. He'll do as many as 12 surgeries a day. And, if a reporter happens to have a small question about something going on in his department—something that any number of Fu's accomplished staffers could answer—it's not unusual for Fu to respond himself, calling from China at 3 a.m. his local time. "I'm worldwide," he says with a shrug and a smile.

Sitting with him at a conference table in his Kaufmann Medical Building office soon turns into a scene of controlled (at least as far as Fu is concerned—it didn't seem so to an overwhelmed visitor) chaos. "Bring me that paper," he shouts to a vacant doorway. Sure enough, the paper, carried by one of his many assistants who had passed by in the hall, arrives. "Where's that diagram?" Same thing. As Fu speaks, it seems as though he might fly out of his chair. It's almost as if he's disappointed that his mind can be in many places at once, but his body cannot. His is a fast-paced world, yet Fu is dedicated to finding a way to slow down ACL surgery.

With all the documentation he wants in hand, Fu begins to elucidate his vision of a more perfect ACL surgery.

"The mainstay of [ACL] surgery was to do it fast and efficiently," Fu says, fast and efficiently.

Then Fu slows down a bit—speaking at a more conversational pace and gesturing less frantically. "We've gotten a false sense of security, because we're used to doing it this way, and it seems to work. But five to seven years after [a procedure], people get a significant amount of wear and tear. If you wait long enough, bad things will happen." These "bad things" include arthritis and joint instability and could require another procedure.

Perhaps if Fu could determine "more scientifically," as he puts it, how nature, through evolution, wants the knee to be structured, he could develop a surgical technique that would fix the ACL as nature intends it to be.

The path to a better understanding and more precise surgery involves the aforementioned lemur, a bear, a tiger, a springbok, a kangaroo, goats, humans, a mandrill, an ostrich, a gorilla, Lucy the famed 3-million-year-old hominid, some 50-million-year-old fossils, and some pretty advanced technology.

In the course of his career, Fu has repaired more than 5,000 ACLs. When he began operating, he'd open the knee, harvest a ligament graft from the patient's hamstring or from a cadaver, and replace the torn ligament. With the advent of arthroscopic surgery, there came to be much less cutting; however, the template remained the same in terms of using just one ligament to replace two and not being particularly precise regarding where the replacement ligament joins the femur and tibia.

Yet two sets of investigators described the ACL as a double-bundled structure in the late 1930s and early 1940s. After that? Not much happened along those lines for a long while.

"Until about five or 10 years ago, nobody actually talked about the presence of these two bundles," says Sheila Ingham, an MD postdoctoral research associate working with Fu. Some people still didn't believe there were two bundles, and those who did failed to see the importance.

The notion that because the healthy knee has two ACL bundles it should again have two after being repaired crept into the operating suite about a decade ago. On a visit to Japan, Fu observed surgeons attempting double-bundle ACL reconstruction.

"When I came back, I started doing the technique," Fu says. "But as I started doing the technique, I realized that I needed to learn more about it. Why it might matter."

Fu set out to confirm that the ACL consists of two bundles and then show that each has important, specific, and separate roles in maintaining the integrity of the knee.

His investigations began with the dissection of knees from cadavers (including a fetus), which unequivocally established that there are two ACL bundles. Fu went back into the annals of human—actually, pre-human—history and examined the knee of the aforementioned Lucy. A model of her fossil is in the care of C. Owen Lovejoy, associate professor of biological anthropology at Kent State University. (Lucy's remains remain in Ethiopia, where she was found.)

Fu contacted Lovejoy after coming across a series of articles the anthropologist published on the knee in *Gait and Posture*. Lovejoy says he wasn't particularly surprised to hear from Fu.

"He's the foremost authority on ACL reconstruction in the world, and as a consequence he's interested in any research that relates to it."

Fu, who keeps a replica of Lucy's femur and tibia in a velvet-lined wooden case in his office, says that examining our distant ancestor went a long way toward confirming his hunch that having a double-bundle ACL is part of what it means to be human.

"She has the double-bundle configuration, and she walked upright," Fu says. "She's similar to a human being, not a gorilla—very similar in the soft tissue."

LEFT: High-speed radiography captures the gait of Copper the lemur and shows his knees at work. ABOVE: Johnny the mandrill, of the Pittsburgh Zoo, gave Fu a chance to peek inside his knee after the monkey injured his ACL. RIGHT: Fu's team, including Sheila Ingham (in bouffant surgical cap), didn't fix Johnny's ligaments, but they did clean out some damaged tissue.

LEMUR RADIOGRAPHY: COURTESY F. FU. MANDRILL: PAUL A. SELVAGGIO / THE PITTSBURGH ZOO. MANDRILL SURGERY: PAUL A. SELVAGGIO / THE PITTSBURGH ZOO

Fu then had to show whether this fact matters—that the use of a joint dictates how nature allows it to evolve. Enter the lemur.

The lemur in question is Copper, a resident of the Pittsburgh Zoo. He's 18, docile—"He's so sweet you can actually go into his cage and pet him," Ingham says—and is one among many who are giving Fu and his team insight into how form follows function.

At 5 one morning, Copper's keepers at the zoo took him to UPMC Presbyterian for a CT scan of his knee. "Five people came with him," Ingham recalls. "They dealt with him, gave him the anesthesia." Then Copper traveled across town to Pitt's Orthopaedic Biodynamics Laboratory on the South Side. There, the plan was to encourage him to walk so that Scott Tashman, PhD associate professor of orthopaedic surgery and director of the lab, could record a high-definition X-ray movie of Copper's gait. (The lemur testing, and examinations of other subjects, was made possible by a grant from the Heinz Endowments.

With zoo personnel at each end of a special runway-like box crafted for Copper, he was coaxed back and forth. "He just had to walk," Ingham says, "to come and go, come and go, but he got stubborn sometimes." He would get started, stop, start again, stop again.

"This went on for a couple of hours," Ingham says. "Finally, he looked at us and kind of said, 'What do you want me to do?' And toward the end, he sort of said, 'Okay, if you want me to walk, I'll walk.'" A gentle poke, coupled with grapes offered by the zoo's vet team, finally got the little fellow moving—long forelimbs stretching out, followed by his red rump and rear legs.

Ingham compares Copper's perambulations to those of a cat. "His gait is similar to most quadrupeds," she says. "He keeps his knees flexed, which makes them a bit different from ours." This bended stance and accompanying ease of rotation, she notes, allows for greater suppleness of movement than humans have. "[Lemurs] are very agile animals when they need to be," she says.

After a couple of hours in Tashman's biodynamics lab, the team had enough data, and Copper was excused. "At the end he got pizza, and that made him happy," Ingham says with a laugh. "We wanted to make him jump, but he wasn't having any of that."

The biodynamics lab lies along the Monongahela River, on South Water Street. Tucked between the Steelers' and University of Pittsburgh football team's practice facility, the UPMC Sports Performance Complex, and the FBI's local headquarters, the lab is kind of a playground for the kinesthesiology set. Tashman has become known as one of the foremost designers of X-ray systems for capturing rapid motion. His Pitt lab includes strobing X-ray machines equipped with video cameras that can record between 180 and 1,000 frames per second. The speed, Tashman says, is vital to producing accurate and clear images. On the floor of the space are two treadmills for studying the gait of human subjects (and, at least one time for Fu's studies, a monkey—"apparently it was already trained to walk on treadmills," Tashman says). In addition to governing the walker's speed, the treadmills are equipped to measure the impact of footfalls. The technology can be used postsurgery to determine whether the repaired knee is working the same way as a healthy one would.

Once the X-ray images are recorded, Tashman and colleagues feed them and all the other data, including a CT scan, into a computer. Various programs take this information, and the result is a blur-free, 3-D, moving image of a knee (or any other joint) at work.

Tashman can start, stop, and rotate the image at will. He can look at how far the ACL stretches and rotates, the structure of condyles (the round, bony projections at the terminus of the tibia and femur in this case), how the bones move in relation to one another, and the degree of force borne by cartilage and the bones during locomotion.

Tashman's examinations of the nature of the knee—with humans and other primates—are at a fairly early stage. "Part of [the investigation] is about understanding the evolutionary development of the knee and why our knees are designed the way they are," he says. "That's more of an intellectual pursuit. But then there's the possibility of understanding why a specific configuration of the knee might be beneficial for certain activities."

For example, the work may one day help explain why some people—such as Pittsburgh Steelers receiver Hines Ward—can participate in sports at the highest level without an ACL in one knee and why others can barely walk with a torn ligament.

"There are a lot of theories running around about how structure relates to risk of injury and as to whether certain knees are better designed for certain activities," Tashman says. "There are a lot of options when it comes to repairing a damaged knee ligament. What we might need to think about is what this person is going to be doing."

All this, Fu says, will help him and other surgeons change ACL surgery from a one-size-fits-all pursuit to a personalized one.

The team's animal investigations—part of a collaboration with the Pittsburgh Zoo that began in 2007—are lending further insight

In their investigations, Fu and Ingham examined a grizzly bear's knee and checked the rotation and flexion of a sedated tiger.

into what the structure of a knee says about what it can, and should, be able to do.

"The animals are critical because we are trying to know why different animals have different sizes of ACL—why some have triple bundles, some have two," Fu says. "How do these things correlate with animal morphology, and how can we translate this knowledge to humans?"

Ingham says it's generally accepted that the anteromedial ligament of the ACL stabilizes the knee as it swings forward and back. The posterolateral provides rotational stability. Typically, she says, single-bundle ACL repair includes only the anteromedial ligament, and the patient tends to have more knee rotation than she should. Not good.

"What you see in ACL reconstruction is that after a few years, you develop osteoarthritis," Ingham says.

"At that point, you either downgrade your physical activity or decide to go swimming [rather than participate in high-impact activities]."

When a zoo animal is anesthetized for any reason, Ingham or her colleagues go to the zoo equipped with a goniometer to measure the rotation and flexion of the creature's knee. When an animal dies of natural causes, the zoo provides the knee to Fu's team for dissection and examination of the ligaments.

When Petya the Siberian tiger, for example, had his annual physical, Ingham had the privilege of examining the 15-month-old, 200-pound cat. Small animals, like Copper, she can do on her own, she notes. The bigger, furrier patients require some help.

"Examining them is challenging enough, because we're trained to examine humans," she says. "And with the larger animals—bears, tigers, gorillas—two of us have to do the examination." One holds the leg at a 90-degree angle while the other manipulates the knee, measuring the rotation and extension. "And it's hard to deal with all that fur and even to find the knee sometimes."

Ingham admits to some trepidation when working with those outweighing her by hundreds of pounds and bearing sharp teeth. But at the beginning of the project, she got some sound advice about what to do if Petya were to wake up while having his knee twisted this way and that: "Basically, it was, 'Get out of the room as quickly as possible!'"

In 2007, the zoo's mandrill, Johnny, was grabbing and poking at his knee. Fu took this opportunity to operate on the living monkey, finding that he had a partial ACL tear and three ACL bundles. Though a full-on fix was impractical, Fu says, he removed some inflamed tissue in Johnny's knee to reduce his discomfort. Today, Ingham reports, Johnny is pain free and has even acquired a girlfriend.

Ingham calls up an image on her laptop. "This is a gorilla knee. You can see that it has three bundles. What we've come to see is that these [three-bundle] animals have more rotation, that animals who live in trees seem to need more rotation than we do."

A tiger, on the other hand, has less rotational range of motion.

"We asked, 'Why is that?'" says Ingham. "Well, gorillas are plantigrades [they walk with the soles of their feet on the ground], they move like we do. But tigers aren't, they move like dogs or cats [on their toes]; they're digitigrades and have much more range of motion front and back. So—aha!—that's where the form and function start coming in."

So if we humans are more like the gorilla than the tiger, yet the gorilla has an extra bundle to help control knee rotation, while we don't, perhaps, Ingham says, it makes sense to consider that excessive rotation contributes to the development of osteoarthritis in humans with bad ACLs.

If that's so, she adds, it's all the more important to repair both bundles in the human knee to ward off degeneration.

Christopher Beard—a PhD, Mary R. Dawson Chair of Vertebrate Paleontology and curator at the Carnegie Museum of Natural History, and an adjunct faculty member in Pitt's School of Medicine—says that his involvement with Fu began several years ago, when the surgeon invited him to Pitt. Beard and a handful of colleagues made short presentations to visiting scholars about the evolution of the knee in primates and other mammals.

Fu's team has since examined scores of fossils in the museum's collection. This work, Beard says, has gone a long way toward confirming Fu's conviction that nature gave humans a double-bundle ACL for a reason.

"The double-bundle ACL is an ancestral condition among a wide variety of primates and other mammals," Beard wrote in an e-mail. "Put another way, this strongly suggests that double-bundle ACLs have been conserved by natural selection for millions of years in a variety of different organisms, including humans. So, [Fu's] surgical technique to reconstruct ACLs in light of this knowledge is obviously the best way forward."

Lovejoy agrees. "The absolute sanity of [the double-bundle procedure] struck me," he says. "Mechanically, of course that's the way you should do it, but it isn't the standard procedure."

Yet. The more knowledge Fu and his team acquire, the more Fu looks to apply it to surgery.

Let's say a mechanic wants to replace a fan belt in a car. The vehicle is designed in a way that, once he opens the hood, it's pretty obvious where the belt should go—see those pulleys there? But what if the mechanic doesn't quite place the new belt into the proper slot on the pulleys? Or, if he does put it in the right place, what if he uses the wrong size belt, fails to tighten it adequately, or over-tightens it? It'll probably work well enough for a while, but sooner or later, the belt will slip off the pulleys or rupture.

Putting the ACL in the proper position—using the double- or single-bundle technique—is a challenge. And this, says Fu, has contributed to the fact that at five to seven years after ACL surgery, many patients report significant pain.

"If you put [the ACL] in the wrong place, the force pulling on it isn't right," Fu says. The bone can expand. There are consequences both mechanically and biologically, and people don't realize it."

So why don't surgeons always place ACL repairs in the right place? There are a handful of reasons: an incomplete understanding of the anatomy (which Fu and colleagues are trying to remedy through their research); the fact that presurgical imaging wasn't so great before 3-D CT scans were used regularly; and the belief that close enough was good enough.

Fu is now convinced that little is more important to successful ACL repair than replicating native anatomy. Close enough won't cut it any more. "With nonanatomical placement, you can have abnormal kinematics of the knee, and that will cause it to wear out," Fu says.

When a surgeon does a single-bundle ACL repair, even if the graft is put precisely where it should be, only 40–60 percent of the native anatomy is replicated, Fu says. If he were to do a double-bundle repair, that percentage would come closer to 90 percent.

The thing is, this type of ACL surgery takes more time, requires a defter surgical touch, and, at the end of the day, might not be for everyone. And, frankly, says Fu, he's not entirely sure that it will improve patient outcomes enough to justify the difficulty. Of course, one reason for this uncertainty is that double-bundle surgery hasn't been around long enough to do long-term studies.

Fu's dedication to the idea of anatomical reconstruction applies regardless of whether single- or double-bundle reconstruction is appropriate for a patient. In either case, lack of attention to detail—typical ACL repair surgery has been so mechanized that it can take less than a half-hour to complete—can result in surgeons placing the anteromedial bundle in the insertion site where the posterolateral bundle belongs and vice versa.

Putting tab A into the wrong slot C can have unfortunate consequences for those assembling IKEA furniture. It's no better for an ACL patient.

"We did a study with a goat," Fu says. "We matched it right, and we matched it wrong. We saw osteoclasts [cells that destroy bone] much more when we put it in the wrong place. That makes sense. You have the wrong tunnel, and you put [the bundle] in the wrong place, and the function will not be right. It's simple."

Fu has taken steps to ensure greater accuracy in the placement of ACL bundles as well as in how much graft to use.

"It takes time to change bad habits. I had to shed bad habits, but right now I would say that I'm pretty anatomical," he says.

Several elements factor into deciding where the new ACL bundles ought to be inserted in the femur and tibia. Looking for the remnants of the torn bundle is a good first step toward finding out where the new one should go. Once the insertion sites are defined, Fu breaks out—get ready for this high-tech tool—a ruler. He then measures the length and width of all four (if it's a double-bundle procedure) insertion sites.

"I guess it's not hard to do this," Fu says. "But in every case we use the ruler and take about five more minutes to do these measurements. It helps us make decisions about what to do." Otherwise, range of motion will be limited, bone may impinge on tendon, and tension on the tendon will be stronger than normal. For all these reasons, the graft can fail.

Accounting for precise variations in individual knee anatomy—how large the insertion sites are, as well as how far apart they are—allows Fu to customize the tunnel and graft size for each bundle. It also makes notchplasty—the shearing of bone to prevent tendon from rubbing on bone—a thing of the past. "The truth is that if you put an ACL exactly where God gave you an ACL, there will be no impingement." And the native anatomy won't be distorted.

So, during your surgery—a procedure that mimics native anatomy if Fu has his way—how about a sandwich?

The Pittsburgh sandwich does not include fries and coleslaw; rather, it has healthier components like growth factors and an intracellular matrix—helpers in the healing process.

During his knee-oriented investigations, Fu found that stem cells are present in the septum that separates the posterolateral and anteromedial bundles. Thinking that stem cells and healing are coconspirators of the highest order, he decided to put these cells to work.

"What we do is take 50 ccs of blood from the patient—at no extra charge, okay?" he says, laughing. "Then we put it in a jar and use a glass rod to stir it for 30 minutes. In a half-hour, you get 3 to 4 ccs of clot, and it's got growth factors and a little matrix, too. I take the clot and put it between the bundles, like a sandwich. We need to do an outcome study on this."

So, there Fu is with one foot in the zoo, one in the natural history museum, one in the operating room, one in the lab, one in the past, and one in the future. Not bad for a guy with only two feet. Fu says that it's all part of a big picture: relying on nature to shape surgery rather than surgeons doing their best to reshape nature.

"I want all orthopaedic surgeons to think like scientists, not technicians. No knee is the same," Fu says. "There are so many variables, and I want people to think in a way that makes orthopaedics multidisciplinary. I want orthopaedic surgeons to think more, beyond what they operate on."

He concedes that there's a long way to go—justifiably so—before anatomical double-bundle surgery is fully understood and fully accepted.

"The question is, 'Is it better?' I don't know," says Fu. "But what I'm saying is that I believe it is. It makes sense. It's logical. I almost want them to prove me wrong."

C. Owen Lovejoy, Fu, and Lucy share a moment together.

KODIAK GRIZZLY BEAR: PAUL A.SELVAGGIO / THE PITTSBURGH ZOO. TIGER EXAM: COURTESY F. FU. LOVEJOY AND FU: COURTESY F. FU