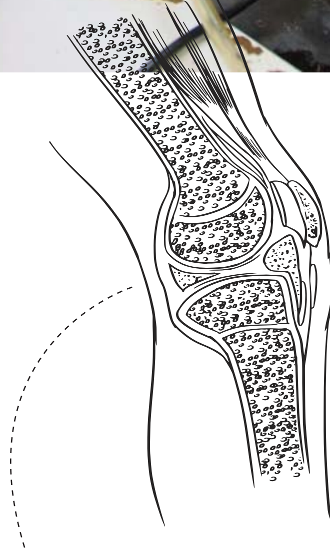
Fixing Up the Joint

BETTER WAYS TO FIND AND TREAT OSTEOARTHRITIS
BY LESLIE FRIDAY



AN ESTIMATED 27 MILLION AMERicans suffer from osteoarthritis, a degenerative disease that destroys cartilage and underlying bone in knees, hips, fingers, and spine. Those living with the condition endure daily pain and stiffness.

While pain medication, physical therapy, and weight loss all help to alleviate symptoms, there's no known cure for this most common form of arthritis. The best solution for patients in late stages of the disease is a hip or knee replacement, but those replacement parts typically last only about 15 years. With increasing numbers of people living into their 80s, those who develop osteoarthritis at midlife face an unpleasant choice: either forego surgery and live with pain, or opt for a joint replacement and hope that it won't wear out before they do.

It's the type of medical challenge Mark Grinstaff and his lab, the Grinstaff Group, enjoy tackling.

"The more challenging a problem is, the more it drives us to think about it in the most critical and creative ways that we can," says Grinstaff, a College of Arts & Sciences professor of chemistry, a College of Engineering professor of biomedical engineering, and a member of the ENG Division of Materials Science & Engineering. "If we can develop therapies that will address the early and middle stages of osteoarthritis, that can be very valuable."

As we live longer, more people will suffer from arthritis and treatment costs will climb.

Chemistry postdoctoral fellow Cynthia Ghobril is developing synthetic high molecular weight polymers that act as biolubricants for cartilage. When injected into a joint, they stick to the cartilage surface and restore some degree of lubrication between long bones.

Since he arrived at BU 11 years ago, Grinstaff and his graduate students have spun three biotech companies out of their bench research. Flex Biomedical is one of them. Grinstaff and Michel Wathier, one of his former postdoctoral fellows in chemistry, cofounded the company in 2008, after creating a viscous polymer that when injected into animals' joints improves lubrication and lasts longer than one of the leading osteoarthritis products on the market, Synvisc-One, made by Genzyme. Grinstaff hopes to get their polymer into clinical trials and receive the US Food and Drug Administration's stamp of approval within three years.

Meanwhile, 5 of the Grinstaff Group researchers—a cadre of more than 20 graduate students and postdoctoral

PHOTOGRAPHS BY CYDNEY SCOTT

fellows with expertise in chemistry, pharmacology, and biomedical and mechanical engineering—are attacking osteoarthritis from other angles. While some members are investigating various polymers for their lubrication and creating a new polymer that reinforces diseased cartilage, others are developing a more accurate method to diagnose osteoarthritis. They split their time between Grinstaff Group headquarters at the Metcalf Center for Science & Engineering and the Beth Israel Deaconess Medical Center labs of their clinical collaborator, Boston Children's Hospital orthopedic surgeon Brian Snyder.

WEB EXTRA
Members of the Grinstaff Group discuss how they are developing new ways to diagnose and treat osteoarthritis in a video at bu.edu/bostonia.

With osteoarthritis, degradation manifests itself in two ways: synovial fluid, a joint's natural lubricant, loses its slipperiness, and cartilage fails to retain water and "becomes more like a leaky sponge than a resilient tissue," explains biomedical engineering doctoral candidate Benjamin Lakin (ENG'14).

Chemistry postdoctoral fellow Cynthia Ghobril is addressing the first hurdle by developing synthetic high molecular weight polymers that act as biolubricants for the cartilage. When injected into a joint, they stick to the cartilage surface and restore some degree of lubrication between long bones. Theoretically, this strategy would allow the polymers to remain in the joint longer. Ghobril hopes that eventually her polymers will stay in place for several months, instead of the several days currently observed. Ideally, she says, patients would require injections only a couple of times a year.

Chemistry doctoral candidate Benjy Cooper (GRS'16) is tackling the second problem by developing a polymer that helps cartilage retain its mechanical integrity. He has tested his molecules on cartilage and bone cores from cows. After refining his polymer in cellular assays and in small animals, he plans to test it in large animal studies.

Biomedical engineer Mark Grinstaff and one of his former postdoctoral fellows created a viscous polymer that when injected into animals' joints improves lubrication and lasts longer than one of the leading osteoarthritis products on the market.

X-RAYS AND GUESSTIMATION

Grinstaff researchers are also working on a better early diagnostic tool for osteoarthritis. Currently, most physicians rely on X-rays and patient-reported pain to diagnose the disease, but because scans don't show soft tissues like cartilage, doctors look carefully at the distance between a patient's long bones. "If the distance is large, they say, 'You're healthy and don't have osteoarthritis,'" Grinstaff says. "If the distance is really small and the bones are close together, they say, 'You have osteoarthritis.' That's very limiting. It would be great if we had a quantitative way to assess the stage of the disease."

Neel Joshi believes he may have developed one. The former Grinstaff Group postdoctoral fellow, now an assistant professor of chemical and biological engineering at Harvard, created a positively charged small molecule, called CA4+, that attaches to negatively charged molecules called glycosaminoglycans, or GAGs. Under a CT scan—which combines a series of X-ray views taken from multiple angles—Joshi's contrast agent glows to reveal the presence (or relative absence) of GAGs, which retain water and maintain cartilage's strength and durability. A low GAG count indicates the onset of osteoarthritis.

Benjamin Lakin (ENG'14) performs an assay to determine the amount of weight-bearing glycosaminoglycans, or GAGs, within the cartilage.

By using Joshi's contrast agent during CT scans of cow knee cartilage and rabbit knees, the team can quantitatively measure how thick and firm the tissue is. They believe physicians could eventually use the tool to more accurately diagnose and treat osteoarthritis in humans.

Lakin and Rachel Stewart (ENG'14), another biomedical engineering doctoral candidate, are testing CA4+ on larger joints, including the knees of racehorses and human hips and knees.

The biomarker is among the group's suite of contrast agents that may someday include a small molecule and nanoparticle used with MRIs. While CT scans are cheaper, faster, and more commonly found in hospitals nationwide, MRIs are the preferred imaging technology of physicians for assessing soft tissues. "The idea is ultimately to have the best early-stage diagnostic that we can," Lakin says, and to produce it within the next decade. That could spell relief to the one-third of Americans 65 and older who, according to the US Centers for Disease Control and Prevention, are affected by osteoarthritis. ■