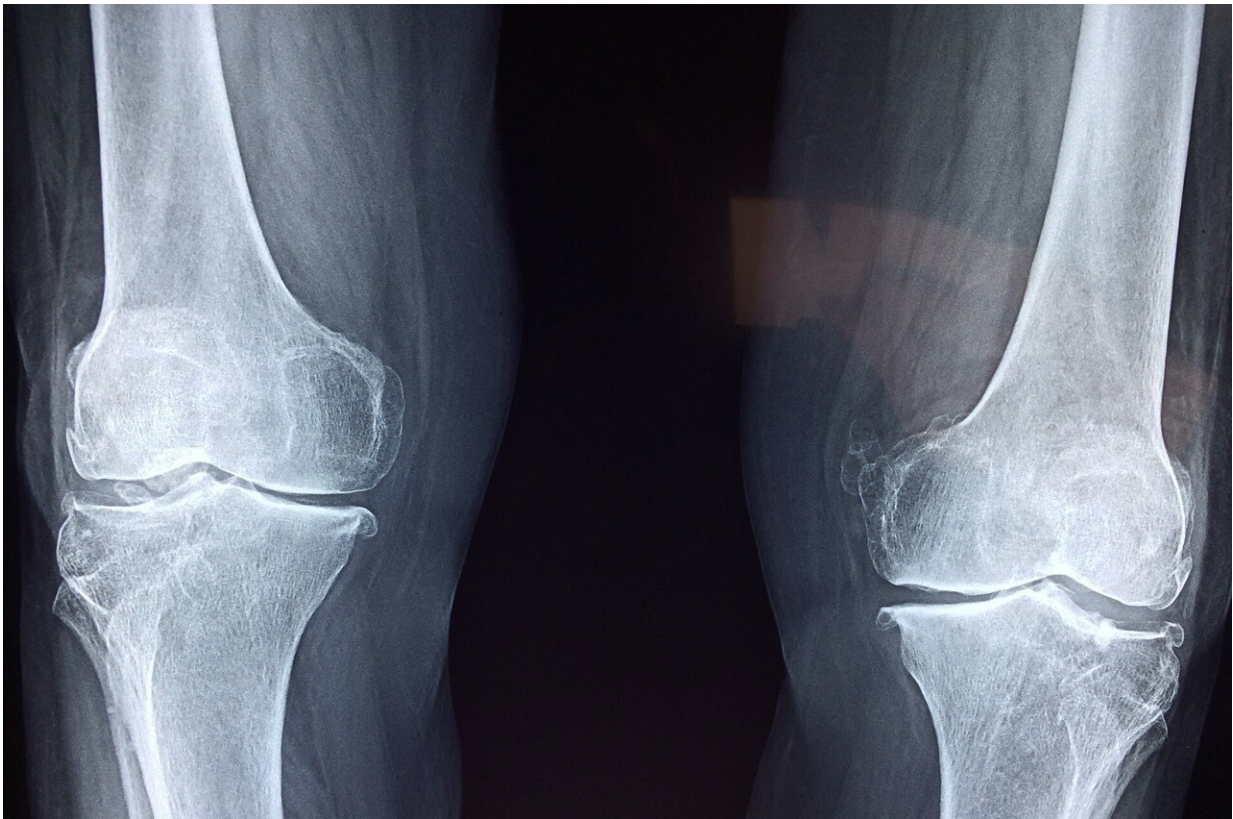


Researchers find method to regrow cartilage in the joints

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Researchers at the Stanford University School of Medicine have discovered a way to regenerate, in mice and human tissue, the cushion of cartilage found in joints.

Loss of this slippery and shock-absorbing [tissue](#) layer, called [articular cartilage](#), is responsible for many cases of [joint pain](#) and arthritis, which afflicts more than 55 million Americans. Nearly one in four adult Americans suffer from arthritis, and far more are burdened by joint pain and inflammation generally.

The Stanford researchers figured out how to regrow articular cartilage by first causing slight injury to the joint tissue, then using chemical signals to steer the growth of skeletal stem cells as the injuries heal. The work was published Aug. 17 in the journal *Nature Medicine*.

"Cartilage has practically zero regenerative potential in adulthood, so once it's injured or gone, what we can do for patients has been very limited," said assistant professor of surgery Charles K.F. Chan, Ph.D. "It's extremely gratifying to find a way to help the body regrow this important tissue."

The work builds on previous research at Stanford that resulted in isolation of the skeletal stem cell, a self-renewing cell that is also responsible for the production of [bone](#), cartilage and a special type of cell that helps blood cells develop in [bone marrow](#). The new research, like previous discoveries of mouse and human skeletal stem cells, were mostly carried out in the laboratories of Chan and professor of surgery Michael Longaker, MD.

Articular cartilage is a complex and specialized tissue that provides a slick and bouncy cushion between bones at the joints. When this cartilage is damaged by trauma, disease or simply thins with age, bones can rub directly against each other, causing pain and inflammation, which can eventually result in arthritis.

Damaged cartilage can be treated through a technique called microfracture, in which tiny holes are drilled in the surface of a joint.

The microfracture technique prompts the body to create new tissue in the joint, but the new tissue is not much like cartilage.

"Microfracture results in what is called fibrocartilage, which is really more like scar tissue than natural cartilage," said Chan. "It covers the bone and is better than nothing, but it doesn't have the bounce and elasticity of natural cartilage, and it tends to degrade relatively quickly."

The most recent research arose, in part, through the work of surgeon Matthew Murphy, Ph.D., a visiting researcher at Stanford who is now at the University of Manchester. "I never felt anyone really understood how microfracture really worked," Murphy said. "I realized the only way to understand the process was to look at what stem cells are doing after microfracture." Murphy is the lead author on the paper. Chan and Longaker are co-senior authors.

For a long time, Chan said, people assumed that adult cartilage did not regenerate after injury because the tissue did not have many skeletal stem cells that could be activated. Working in a mouse model, the team documented that microfracture did activate skeletal stem cells. Left to their own devices, however, those activated skeletal stem cells regenerated fibrocartilage in the joint.

But what if the healing process after microfracture could be steered toward development of cartilage and away from fibrocartilage? The researchers knew that as bone develops, cells must first go through a cartilage stage before turning into bone. They had the idea that they might encourage the skeletal stem cells in the joint to start along a path toward becoming bone, but stop the process at the cartilage stage.

The researchers used a powerful molecule called bone morphogenetic protein 2 (BMP2) to initiate bone formation after microfracture, but then stopped the process midway with a molecule that blocked another

signaling molecule important in bone formation, called vascular endothelial growth factor (VEGF).

"What we ended up with was cartilage that is made of the same sort of cells as natural cartilage with comparable mechanical properties, unlike the fibrocartilage that we usually get," Chan said. "It also restored mobility to osteoarthritic mice and significantly reduced their pain."

As a proof of principle that this might also work in humans, the researchers transferred [human tissue](#) into mice that were bred to not reject the tissue, and were able to show that human skeletal stem [cells](#) could be steered toward bone development but stopped at the cartilage stage.

The next stage of research is to conduct similar experiments in larger animals before starting human clinical trials. Murphy points out that because of the difficulty in working with very small mouse joints, there might be some improvements to the system they could make as they move into relatively larger joints.

The first human clinical trials might be for people who have arthritis in their fingers and toes. "We might start with small joints, and if that works we would move up to larger joints like knees," Murphy says. "Right now, one of the most common surgeries for arthritis in the fingers is to have the bone at the base of the thumb taken out. In such cases we might try this to save the joint, and if it doesn't work we just take out the bone as we would have anyway. There's a big potential for improvement, and the downside is that we would be back to where we were before."

Longaker points out that one advantage of their discovery is that the main components of a potential therapy are approved as safe and effective by the FDA. "BMP2 has already been approved for helping bone heal, and VEGF inhibitors are already used as anti-cancer

therapies," Longaker said. "This would help speed the approval of any therapy we develop."

Joint replacement surgery has revolutionized how doctors treat arthritis and is very common: By age 80, one in 10 people will have a hip replacement and one in 20 will have a knee replaced. But such joint replacement is extremely invasive, has a limited lifespan and is performed only after arthritis hits and patients endure lasting pain. The researchers say they can envision a time when people are able to avoid getting arthritis in the first place by rejuvenating their cartilage in their joints before it is badly degraded.

"One idea is to follow a 'Jiffy Lube' model of cartilage replenishment," Longaker said. "You don't wait for damage to accumulate—you go in periodically and use this technique to boost your articular [cartilage](#) before you have a problem."

More information: Matthew P. Murphy et al. Articular cartilage regeneration by activated skeletal stem cells, *Nature Medicine* (2020). [DOI: 10.1038/s41591-020-1013-2](https://doi.org/10.1038/s41591-020-1013-2)

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