

# Elbow, Knee, and Ankle Grease

BIOENGINEERS DELVE INTO WHAT JOINTS NEED TO FUNCTION.

To get up and go, we need our joints. But what happens when they give out? Joint replacement surgery is an option, but one day scientists hope to regenerate failing joint tissue. Getting a step closer to this goal is HHMI professor Robert L. Sah from the University of California, San Diego, who with a team including undergraduate students designed a bioreactor capable of growing cartilage tissue within whole joints.

Due to aging and normal wear and tear, the smooth surface of cartilage at the ends of bones in joints erodes and synovial fluid is unable to effectively lubricate the joints, which can lead to the painful condition known as osteoarthritis. The damaged joints can be replaced with artificial ones, but doctors would rather be able to resurface existing joints with a patient's cartilage.

Sah's team found that applying shear load to a joint, as is done with the machines that gently flex patients' knees to help them recover from joint surgery, causes cartilage cells at the edge of the joints to produce a molecule called proteoglycan 4. Like oil in an engine, proteoglycan 4 appears to be a necessary component in synovial fluid for normal joint lubrication and function.

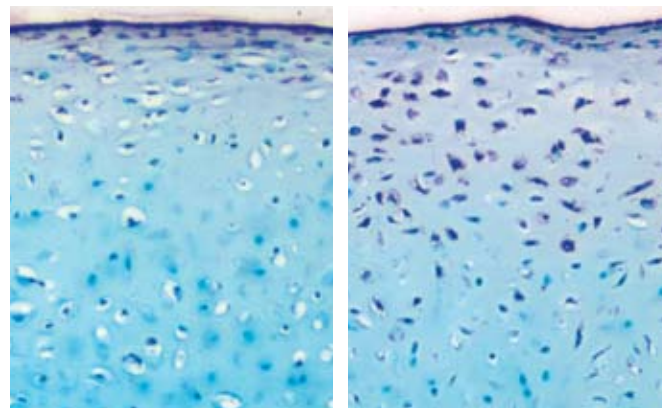
The results are reported in a December 8, 2006, advance online article of *Osteoarthritis and Cartilage*.

Sah hopes one day to be able to culture pieces of joint tissue from arthritic patients back to a healthy form, and then reimplant them. For this to occur, he and others need to figure out what

factors are needed to grow cartilage and create the synovial fluid that flows between the joints.

"Like an enzymatic cascade, there may be a mechanical cascade of events that needs to occur for cartilage to grow and mature," says Sah. "If we can dissect the mechanobiologic process into distinct components, then we could potentially reengineer the process to regenerate cartilage and joints." ■

—JACQUELINE RUTTIMANN



Compared to joints grown alone in a bioreactor (left panel) those additionally exposed to joint-flexing machines (right panel) increase their cartilage cells' production of proteoglycan 4 (purple), a key component in synovial fluid.

## IN BRIEF

most challenging aspects of this work is that proteins can be notoriously difficult to crystallize. Now, HHMI investigator Stephen R. Quake of Stanford University and colleagues have developed a systematic way to speed up protein crystallization. The technique analyzes the solubility of minute amounts of protein in a range of solvents and conditions. With that information in hand, researchers can generate so-called phase diagrams for proteins, thereby creating customized crystallization "recipes" for each one.

Details of the method were described in the November 7, 2006, issue of the *Proceedings of the National Academy of Sciences USA*.

### GENETIC MUTATION EXPLAINS FORM OF BRITTLE BONE DISEASE

A newly identified gene mutation helps explain a subset of cases of osteogenesis imperfecta, or brittle bone disease. Identifying the mutation is important because children with the disorder, whose bones break easily, are sometimes mistaken as victims of child abuse.

Most cases of brittle bone disease are known to be caused by a structural change

in a particular collagen protein or a change in the amount of collagen the body produces. The mutation—responsible for up to 15 percent of cases of osteogenesis—has a different effect; it prevents collagen proteins from being properly modified after they are produced. In the October 20, 2006, issue of *Cell*, HHMI investigator Brendan Lee at Baylor College of Medicine and colleagues report how mutations in a gene called *cartilage-associated protein (CRTAP)* can affect bone formation. The team produced mice that lacked *CRTAP* and found that they developed deformed and brittle bones similar to those of patients with the disease. The researchers next analyzed *CRTAP* in two families who had brittle bone disease but lacked the pattern of inheritance commonly associated with it. They found that partial loss of function of the *CRTAP*-encoded protein caused mild brittle bone disease, while profound loss caused a more severe form of the disease.

### A FLY'S-EYE VIEW OF EVOLUTION

HHMI researchers have found that mutations in a single structural protein can determine whether an insect develops the

highly organized, light-harvesting eye that flies have or the optically simpler compound eye of a beetle or bee. Working with the fruit fly *Drosophila*, the researchers explored the formation of rhabdomeres, transparent rod-like structures in the compound eye.

Rhabdomeres feed light to the bundles of photoreceptors in each of the 800 units in a fly's compound eye. Flies have evolved a more advanced "open rhabdom" structure, in which the rhabdomeres are separated, but beetles, bees, and some mosquitoes have a more primitive "closed rhabdom" structure in which the rhabdomeres are fused.

The fruit fly also has a primitive closed version of an eye found in the ocelli, light sensors located on the top of the head and used for navigation. The researchers engineered fruit flies that expressed the Spacemaker protein in their ocelli and found that the ocelli reorganized into the more advanced open rhabdom system.

These findings "help illustrate the beauty and power of evolution—how small changes can have such an incredible impact," says HHMI investigator Charles S. Zuker of University of California,