Antibody Combo Nixes Graft Rejection

A combination of two antibody treatments, each of which has been tested separately in humans, can completely prevent the rejection of tissue grafted from an unmatched donor, according to a new study involving mice.

The strategy could prove particularly beneficial in treating human heart-transplant recipients for whom physicians cannot find a perfectly matched donor organ. Currently, two-thirds of such recipients die after the immune system rejects the donor heart as foreign. The new approach might also prevent rejection of other transplanted organs, such as kidneys.

The mouse study used two sets of monoclonal, or identical, antibodies to block two facets of the immune system's tissue rejection process. One set of antibodies sticks to a cellular receptor called leukocyte function-associated antigen-1 (LFA-1), which helps stimulate certain white blood cells, called leukocytes, to kill foreign cells. The other set of antibodies binds to intercellular adhesion molecule-1 (ICAM-1). Most body cells produce this receptor to summon leukocytes to their defense when injured or exposed to foreign cells.

Researchers in Tokyo and Boston, led by Mitsuaki Isobe of the University of Tokyo, tested antibodies against LFA-1 and ICAM-1 in mice given heart transplants. All of the mice had received hearts taken from totally unmatched donor mice, whose tissues the recipient mice would quickly reject under normal circumstances.

Isobe and his co-workers treated nine mice with both LFA-1 and ICAM-1 antibodies immediately after transplantation. They left six mice untreated and gave only one of the two antibodies to two other groups of six mice.

In the Feb. 28 SCIENCE, the team reports that all of the mice treated with only one of the two antibodies died within one month; those receiving no treatment died within 10 days. But the nine mice that received both antibodies were still alive after six months, and their new hearts showed no signs of tissue rejection at that time, Isobe says.

To determine whether the antibody combination had prevented the nine mice from recognizing the transplanted hearts as foreign, the researchers gave five of the mice two skin grafts each — one from the heart donor and another from a different, unmatched mouse. All of them accepted the heart-donor skin grafts but rejected the third-party skin, Isobe's team found.

Isobe concludes that the double antibody treatment caused the mice to permanently view the heart donors' tissue as their own. "I'm very optimistic about the applications of this mode of immunosuppression in individuals [humans] undergoing organ transplantation," he told SCIENCE NEWS.

Several U.S. biotechnology and pharmaceutical companies are now developing ICAM-1 and LFA-1 antibodies for clinical use, Isobe says. In human trials conducted in the 1980s, each antibody appeared safe but yielded mixed results in preventing graft rejection. One group, led by Benedict Cosimi at Massachusetts General Hospital in Boston, tried ICAM-1 antibodies as a treatment for kidney transplant rejection, "but the [efficacy] results were not so great," Isobe says. Similarly, French physicians reported limited success in using antibodies against LFA-1 to prevent graft-versus-host disease following bone marrow transplants.

"I'm expecting the combination will work much better," Isobe asserts.

J. Harold Helderman, director of the transplant center at Vanderbilt University in Nashville, agrees. "It's clear from the experimental animals that [ICAM-1 and LFA-1] molecules are important ... so blockage of these molecules appears an innovative way to block graft rejection."

One monoclonal antibody treatment for preventing transplant rejection, called OKT3, is already on the market, but it has been linked to non-Hodgkin's lymphoma (SN: 6/2/90, p.343). OKT3 blocks a different receptor on white blood cells. Isobe says unpublished mouse studies by his group show that the new antibody combination is several times more effective than OKT3.

Isobe plans to test the safety of his antibody combination in larger animals soon. Although he saw no side effects of the therapy in his mice, disrupting the binding of ICAM-1 with LFA-1 might slow wound healing, he notes.

"Once I establish the safety of the treatment in larger animals, I will turn to patients, probably within the next year," says Isobe. He expects to start by treating heart transplant patients, because of their high mortality, and he plans to collaborate with several U.S. transplant centers. — *C. Ezzell*

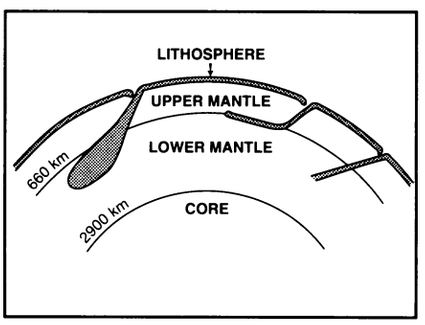
Hitting a barrier deep within the planet

Earthquake waves can reduce a city to rubble in seconds. But when the same vibrations pass deep through Earth's interior, they lose their destructive power and turn into valuable scientific data. By studying thousands of distant tremors, two seismologists have now uncovered important clues concerning Earth's internal recycling system.

For two decades, geoscientists have debated what happens to the ocean floor when it subducts, or dives down into the Earth's mantle, the region whence it came. While some researchers believe the oceanic plates sink all the way to the top of the iron core, others think the slabs of ocean floor get trapped in the upper mantle. The new data cannot resolve the question of how low slabs go, but they do reveal that the boundary between the upper and lower mantle presents a formidable barrier to sinking slabs.

Peter M. Shearer and T. Guy Masters of the Scripps Institution of Oceanography in La Jolla, Calif., analyzed waves from earthquakes that reflect off the 660-kilometer-deep boundary between the upper and lower mantle. By analyzing 3,000 seismograms from shocks around the world, they produced the first global map of the boundary's topography, which they discuss in the Feb. 27 NATURE.

The mantle, which makes up 84 percent of Earth's volume, extends from a depth of 2,900 kilometers all the way up to within 70 kilometers of the surface. The boundary between the upper and lower mantle is defined by a discontinuity in the speed of seismic waves. As earthquake waves pass down through the mantle, they speed up abruptly at a depth of 660 kilometers. Geoscientists think this acceleration arises mainly from a physical change in the crystal structure of mantle rock. High-pressure experiments indi-



Three possible fates for subducting plates. New seismic evidence indicates that these slabs do not pass easily into the lower mantle (right). They either become trapped at the boundary (center) or slow down and widen as they sink (left). In either case, these slabs depress the seismic boundary between the upper and lower mantle.

cate that the rock above the boundary has a more open crystal configuration, whereas the crystals in the lower mantle are squeezed into a denser arrangement. Rocks in the upper mantle might also contain chemicals that differ from those in the lower mantle.

Shearer and Masters report that their topographic map shows broad depressions in the seismic boundary beneath plate subduction zones. The low spots measure about 1,500 kilometers across and extend as much as 30 kilometers below other parts of the boundary. The clearest depression appears northwest of the Kuril-Kamchatka region, where the Pacific plate dives under the Asian plate.

These results suggest that the sinking Pacific slab does not pass cleanly down into the lower mantle, according to the researchers. Instead, they believe, the plate bends at the boundary and moves horizontally across it, forming the depression that appears on their map.

"It's clear that there is resistance to slab penetration at the 660-kilometer boundary," Shearer says.

It is not clear, however, what happens after the slab deflects horizontally and slows its descent. The cold oceanic rock could form a thick blob that continues to sink deep into the lower mantle at a much slower rate, or it might just pile up along the boundary and remain stuck in the upper mantle.

"Its ultimate fate is still in question," says Thorne Lay, a seismologist at the University of California, Santa Cruz.

The answer has important ramifications because it indicates what kind of heat engine drives the motion of the lithospheric plates forming Earth's outer shell. If slabs sink all the way to the core, then the mantle resembles a pot of boiling soup, with hot material rising from bottom to top and cold material sinking from top to bottom. Conversely, if subducting slabs do not descend much below 660 kilometers, then the mantle would resemble a double boiler, with very little mixing across the boundary between lower and upper mantle.

While seismologists in the 1970s generally thought that subducting slabs could not make it into the lower mantle, researchers discovered seismic evidence in the late 1970s and 1980s suggesting that subducting plates in fact penetrated deep into the lower mantle. In the last few years, seismic studies have grown equivocal: Some show deep slabs, while others show deflected ones.

The data collected by Shearer and Masters provide a new approach to the perennial problem, Lay says.

"Trying to understand the deep structure of the Earth and the processes in the Earth is a formidable and challenging problem. We have better knowledge about the interior of the sun than about the interior of the Earth," he notes.

– R. Monastersky

Smokers suffer impaired bone healing

Cigarette smoking has been linked with a laundry list of ills, including heart disease and a variety of cancers. During the last 20 years, a number of research groups have demonstrated that smoking harms the body's ability to heal skin wounds. Now, for the first time, scientists have documented slower bone healing among smokers.

From November 1988 to August 1990, orthopedic surgeon George Cierny III of Emory University in Atlanta and his coworkers studied 29 men and women who suffered from osteomyelitis, a bacterial infection of the bone and bone marrow that can develop after a wound or fracture.

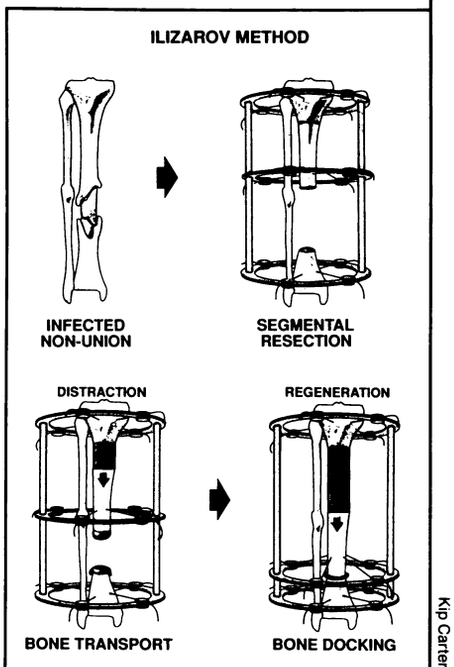
At the study's start, the researchers obtained a detailed smoking history from each participant and tested urine and blood samples for telltale markers of a smoking habit, such as cotinine, a metabolite of nicotine. Many of the recruits denied a smoking habit until their test results came back. The researchers identified nine nonsmokers, nine ex-smokers and 11 people who continued to smoke during the study.

All 29 patients underwent an operation in which surgeons cut through the skin and tissue and remove the infected segment of the tibia (shinbone). This procedure left each patient's tibia with a gap ranging from 4 to 10 centimeters in length. The surgeons then closed the incision and attached an external, circular device to the leg. This device, known as an Ilizarov apparatus, has wires that fasten to each end of the tibia, creating tension. Over time, the tension spurs one end of the tibia to regenerate, so that the bone ultimately heals.

Using X-rays to monitor bone growth, Cierny's group discovered that nonsmokers formed new bone within two months of the operation, whereas smokers showed minimal bone growth at the two-month point. Cierny presented the new findings at the annual meeting of the American Academy of Orthopaedic Surgeons, held last week in Washington, D.C.

The time from the operation until the recruits could resume normal activities ranged from eight to 18 months. When the researchers looked closely at the data, they found that smokers spent more time recuperating. On average, smokers took 2.98 months to manufacture 1 cm of new bone, while nonsmokers took 2.32 months. For nonsmokers with a 5-cm bone gap, that translates to a 10-month recuperation period, Cierny notes. For smokers, the same 5-cm gap would take 15 months to close.

"So you essentially had another half-year of disability if you were smoking during treatment," Cierny told SCIENCE NEWS.



Kip Carter

Surgery for tibial osteomyelitis: After removing the infected bone segment, surgeons attach the Ilizarov apparatus to the leg. This device puts tension on the tibia, which then starts to grow (shaded area). Finally, the two bone ends meet. New research suggests smokers who undergo this procedure can expect slower bone growth than nonsmokers.

Although ex-smokers also showed impaired bone regeneration, kicking the habit paid off: Ex-smokers took about 2.72 months to grow 1 cm of bone. Osteomyelitis patients who quit smoking before undergoing surgery can expect to recover much faster than if they continued to puff away, Cierny says.

Cigarette smoke contains thousands of harmful substances, but Cierny believes nicotine plays a key role in this drama of poor bone healing. Thomas K. Hunt of the University of California, San Francisco, agrees. In recent years, Hunt has found evidence that cigarette smoke can reduce the amount of oxygen reaching body tissues, probably through the activity of nicotine. The lack of oxygen impairs the body's ability to make collagen, a protein used to form new bone, he says.

Cierny's study demonstrates impaired bone regeneration among smokers who undergo surgery for osteomyelitis. But what about smokers who have simply broken an arm, finger or leg? Cierny believes they, too, would experience delayed healing. However, additional research must verify that suspicion, he adds. *– K.A. Fackelmann*