# 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*

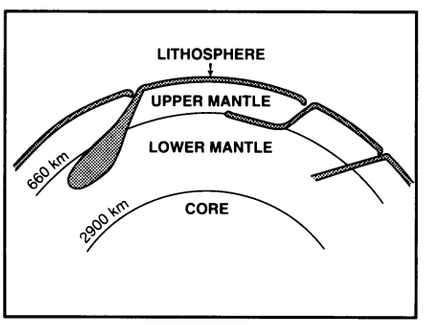
# Hitting a barrier deep within the planet

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.*