A Vaccine for Alzheimer's Disease?

Stunning, unexpected results from experiments with mice have given scientists cautious optimism that simple injections can prevent or slow the development of Alzheimer's disease. Such therapy might even reverse some of the brain damage in people already afflicted with the devastating disorder.

Scientists at Elan Pharmaceuticals in South San Francisco, Calif., injected mice with beta-amyloid, the very protein fragment suspected of causing Alzheimer's disease. This immunization, they found, generated antibodies that prevented the accumulation of beta-amyloid within the mouse brain and even cleared existing amyloid deposits, known as plaques.

"This is the first time that anyone has stopped the development of amyloid plaques in a mouse model of Alzheimer's," says Marcelle Morrison-Bogorad of the National Institute on Aging in Bethesda, Md. "This is a major step forward. Conceivably, you could immunize people against Alzheimer's disease."

"It's wild and amazing," agrees Sangram S. Sisodia of the University of Chicago.

Several years ago, Elan's Dale Schenk wondered whether the immune system could be aroused to clear the amyloid deposits seen in the brains of people with Alzheimer's. To test Schenk's idea, Elan scientists turned to genetically engineered mice that develop large numbers of plaques because they harbor a mutant version of the human gene for the protein that forms beta-amyloid. The researchers began injecting these mutant mice with human beta-amyloid and an immune-stimulating agent called an adjuvant.

Starting at 6 weeks of age, the mice received the injections once a month for nearly a year. At the end of the immunization, the scientists examined the rodents' brains and found that seven out of nine had virtually no amyloid deposits. Both of the two remaining mice had significantly less beta-amyloid than untreated animals, Schenk's team reports in the July 8 NATURE. The treated mice also lacked other brain alterations associated with amyloid deposits, such as misshapen nerve connections.

Taken aback by their findings, the investigators then gave a similar series of injections to 11-month-old mice that had already developed amyloid plaques. The shots prevented additional amyloid deposits and even triggered clearance of some existing plaques, the scientists found.

The immunizations create large amounts of antibodies that bind to beta-amyloid, prompting Schenk to speculate that some of the antibodies circulating in the blood sneak into the brain and latch onto any plaques. That may alert the brain's immune cells, microglia and monocytes, to clear the beta-amyloid.

"It's as if the microglia and monocytes are garbagemen and the antibodies act as signposts stuck on the garbage," says Schenk. He notes that Elan has found beta-amyloid inside those immune cells in the brains of treated mice.

The immunization strategy may resolve the great debate in Alzheimer's disease research. Most neuroscientists believe that the accumulation of beta-amyloid within the brain somehow causes the cell death and resulting memory impairment seen in people with the illness. Other investigators suggest accumulations of a protein called tau are the real villains in Alzheimer's disease.

If the beta-amyloid shots prevent plaques in people as well as mice, "we're going to test the amyloid hypothesis very thoroughly," says Schenk.

While the benefits of a vaccine for Alzheimer's are obvious, it's less clear whether the immunization strategy will serve people already impaired. "Even if you get rid of the amyloid deposits, what will happen to the patients? Will they level off or actually get better?" asks Sisodia. Eliminating amyloid deposits may not prevent accumulation of the tau protein, he notes.

Still, Sisodia marvels at Elan's novel strategy. Almost all scientists would have dismissed the immunization approach, he notes, because of the "dogma" that the so-called blood-brain barrier keeps circulating antibodies out of the brain.

The immunization tactic may also prove useful for the other diseases in which amyloids accumulate in the brain or elsewhere, notes Peter H. St. George-Hyslop of the University of Toronto. The approach might even tackle Huntington's and Parkinson's diseases, both of which involve abnormal brain aggregations of other proteins, he speculates.

While the mice given the beta-amyloid injections suffered no obvious ill effects, scientists caution that the shots could trigger an autoimmune response to the beta-amyloid precursor protein, which is present throughout the body.

By the end of the year, Schenk and his colleagues plan to begin testing the immunization approach on people with mild to moderate Alzheimer's disease. Their initial goal is to confirm the strategy's safety, but they'll also monitor the people for cognitive improvement or slower-than-normal decline. Elan would then like to quickly launch a prevention trial in people known to have a high risk of developing Alzheimer's disease.

"If it does work, it would stand as one of the great scientific success stories of all time," says Morrison-Bogorad. —*J. Travis*

Drug to treat flu also protects against it

For 3 decades, scientists have been experimenting with medications that stifle the influenza virus. Two drugs, amantadine and rimantadine, can impede the disease and limit symptoms. However, neither works against one of the two major strains of influenza, and both can be eluded by the evolving virus. In addition, amantadine causes some disagreeable side effects, including confusion and nightmares.

A new antiviral—zanamivir—seems to ease or eliminate many symptoms of either flu strain if taken within a day or two of the disease's onset, and the viruses seem powerless to develop resistance to it. Now, researchers find that the medication also works as a preventive against both strains of influenza when taken for 4 weeks during the height of flu season. In the July 7 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, they also report that zanamivir shows no side effects.

The two classes of disease-causing influenza virus are dubbed A and B. "The potential of having access to a new class of antiviral agents that can be used in the prevention of both influenza A and B is very exciting," says Linda C. Lambert of the National Institute of Allergy and Infectious Diseases in Bethesda, Md.

To test the drug, researchers gave each of 1,107 people in Michigan and Missouri an inhaler that dispensed a powder and instructed them to take one dose per day. Half of the people received an inert substance, or placebo; the rest got zanamivir. Neither researchers nor participants knew which was the placebo.

Of 554 people getting the placebo, 34 subsequently came down with the flu, and 19 of them also ran a fever. Of 553 getting zanamivir, only 11 got the flu and just 3 had a fever.

About 14 percent of each group had already received a flu shot. Among these people, zanamivir imparted additional protection and didn't hinder the vaccine's effectiveness, says study coauthor Arnold S. Monto, of the University of Michigan in Ann Arbor. Zanamivir is made by Glaxo Wellcome of Durham, N.C.

"This is a noteworthy piece of science," says Fred Y. Aoki, of the University

of Manitoba in Winnipeg. "It confirms... that drugs for prevention of the flu are an important adjunct to vaccine."

Flu virus consists primarily of RNA molecules wrapped in proteins. Once a virus has invaded a cell and multiplied, new virus particles emerge from the cell bound together. One viral protein, an enzyme called neuraminidase, is required for the bundle to unglue itself so that individual virus particles can infect other cells.

Zanamivir foils the flu by binding to neuraminidase and deactivating it. The virus particles then stay bundled. The molecular docking site the drug uses to attach to neuraminidase doesn't vary much among different strains of flu virus, so scientists call it a conserved site.

In earlier laboratory efforts intended to induce the virus to become resistant, it didn't find a way to substitute an enzyme impervious to the drug, Aoki says.

This gives zanamivir an advantage over the flu vaccine. The immunization, which uses a disabled virus to elicit an antibody response to the active flu virus, aims at a moving target. The vaccine-triggered antibodies recognize the flu virus less often as it spreads in a population, mutating rapidly. Even in young adults, a flu shot is at best 70 to 90 percent effective. Indeed, the vaccine used in the 1997-1998 flu season, when the scientists conducted the new study, proved only marginally effective.

Many scientists believe it's only a matter of time before doctors will be up against a highly lethal flu, such as the 1918 strain that killed tens of millions of people. In such a pandemic, zanamivir may work against the virus even as flu shots fail because it will still be able to dock to neuraminidase's conserved site, Monto says.

"There's no doubt this has the potential to become a really important stopgap measure in case of a new pandemic," Aoki says. "The limiting factor is in the logistics of having enough drugs readily available to distribute in such a circumstance."

The drug may initially prove most valuable to people who are allergic to flu vaccine or those whose immune system has been compromised by anticancer medications or drugs that limit rejection after an organ transplant, says W. Paul Glezen, of Baylor College of Medicine in Houston. Among elderly people, whose immune response is weakened, the vaccine is only 30 to 50 percent effective.

Researchers still need to test zanamivir on high-risk patients, elderly people, and those with asthma, he says. The participants in Monto's study averaged 29 years old. "These were [mostly] healthy young people," Glezen notes.

Zanamivir might also be useful as an interim measure among people who are exposed to the virus before getting a flu shot. Daily doses may fend off the disease while the vaccine mounts its antibody response, Glezen says. —*N. Seppa*

Seabed yields mark of nearby supernova

A stellar explosion rocked Earth's neighborhood about 5 million years ago, according to German researchers who have uprooted the first direct evidence of a supernova so recent and so close.

Such an explosion would have shone 10 times as brightly as the full moon for months, and a star remnant that appeared the size of 20 moons would have smoldered for millennia. Had the supernova been much closer to Earth, its energy would have caused mass extinction, the researchers say. "What was over the years only a subject of speculation—namely, that a stellar explosion could happen very close to the solar system—now seems to be a reality," says study coauthor Wolfgang Hillebrandt of the Max Planck Institute for Astrophysics in Garching, Germany.

Hillebrandt's team sampled and dated three thin layers of a deep-sea sediment called a ferromanganese crust. The researchers sought particles of iron-60, a radioactive iron isotope produced abundantly in supernovas but having few other sources in the solar system. The group used a method known as accelerator mass spectrometry to isolate iron-60 from elements and molecules of different masses. A gas-filled magnet then teased iron-60 apart from nickel-60, another isotope of the same mass.

The handful of iron-60 ions that emerged was enough to point to a supernova, the group says. The newest layer in the sample contained 14 iron-60 ions; the middle layer, 7 of the ions; and the oldest layer, only 2, the team reports in the July 5 PHYSICAL REVIEW LETTERS. The researchers used the layers' known ages to take into account radioactive decay. They conclude that the quantity of iron-60—especially in the 4- to 6-million-year-old middle layer—indicates a massive stellar explosion, probably a type II supernova, about 5 million years ago.

Although there are other explanations for iron-60 on Earth, such as cosmic ray bombardment, the group says that none accounts for the samples' high concentration. "Everything hangs together on just those few ions," notes physicist Louis Brown of the Carnegie Institution of Washington (D.C.). Nonetheless, he says, "my impression would be that these people know what they're doing."

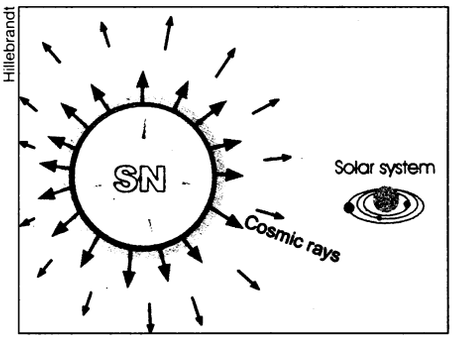
The German researchers say that after the stellar explosion, gaseous iron-60 condensed on dust particles, probably from inside the star. Hitching a ride on these particles, the iron-60 had enough velocity to pierce the solar wind and reach Earth. From the amount of iron-60 in the samples, the supernova must have been within about 90 light-years, they calculate.

"It's not exact, but it's a pretty close window on when and where such an event happened, so in that sense I think it's quite exciting," Hillebrandt says. He adds that further tests must confirm the results. His team is searching for iron-60 elsewhere and for other supernova products, such as plutonium-244.

Astrophysicist Stanford E. Woosley of the University of California, Santa Cruz says that the group's data are compelling but additional confirmation is essential, given the importance of the discovery.

"If this holds up, it's so astonishing that it's going to spur a tremendous amount of research," says astronomer Donald D. Clayton of Clemson (S.C.) University. "The scientific tentacles of this are very deep." —*S. Carpenter*

Hillebrandt



A nearby supernova (SN) sends stardust (blue) toward the solar system.

Vitamin C's stretch

Healthy blood vessels expand slightly with each pulse of blood pumped by the heart, and they temporarily stretch even more during bouts of exercise. This dilation occurs in response to nitric oxide produced by the vessels themselves. The nitric oxide–induced dilation diminishes in persons with coronary artery disease, but vitamin C supplements can help restore it, a new study finds.

A normal vessel can dilate up to 15 percent in diameter. Having found that a single, large dose of vitamin C can temporarily increase a vessel's ability to dilate appropriately, Joseph A. Vita of the Boston University School of Medicine and his colleagues wondered whether that responsiveness would persist after longer term and more moderate vitamin C supplementation. They gave 500 milligrams daily of either the vitamin or a placebo to 46 heart-disease patients.

In the June 29 CIRCULATION, the researchers report that vessels that initially dilated on average just 6.6 percent could, after a month of treatment, expand some 9 percent. No similar improvement resulted from the placebo. Vita suspects that vitamin C works by restoring the ability of a blunted vessel enzyme to produce nitric oxide. —*J.R.*