# Immune antibodies penetrate neurons to clear Alzheimer's-linked amyloid

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Researchers at Weill Cornell Medical College have gotten much closer to understanding how immune-based therapies can treat Alzheimer's disease -- by studying how antibodies go inside brain cells to reduce levels of Alzheimer's-linked amyloid peptides that form plaques between neurons.

"This internalization and activity of the antibody within the cell was a big surprise and something we really haven't appreciated in neurological medicine. It gives us new hope for the use of immunotherapy against Alzheimer's, while casting intriguing new light on other disease processes," says senior author Dr. Gunnar Gouras, associate professor of neurology and neuroscience at Weill Cornell Medical College and associate attending neurologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

His team's study will appear as a prestigious "paper of the week" in an upcoming issue of the *Journal of Biological Chemistry*, and was published in the May 1 online edition of the journal.

There are currently no effective treatments to fight Alzheimer's disease, which now affects over 5 million Americans, according to the Alzheimer's Association. Scientists now project that unless new ways are found to prevent or treat the disease, the total could climb to 16 million by 2050.

For years, the idea of an immune-based vaccine therapy against

Alzheimer's has been a Holy Grail of research. In fact, in the past, researchers did have some clinical success with an antibody-directed immune therapy. Those hopes were dampened somewhat after a few subjects came down with a serious, treatment-linked (but nonfatal) meningitis.

"Still, the dream has remained very much alive -- especially since we know that antibodies to the beta-amyloid plaques associated with Alzheimer's can cross the blood-brain barrier, gaining access to the brain," Dr. Gouras explains. He remains one of the leading authorities on beta-amyloid plaques because of earlier work on its deposition and accumulation between neurons.

"One of the things those earlier immunotherapy studies taught us was that antibodies can reduce amyloid plaques, which are a hallmark of the disease," he said. "The next logical question was -- how does it do that?"

Over the past six years, Dr. Gouras' team took advantage of breakthroughs in neuroscience research to help answer that question. They relied on the development of special transgenic mice bred to closely approximate the progress of human Alzheimer's disease.

In their latest study, the researchers exposed amyloid-filled neurons from these mice to immune antibodies similar to those used in clinical trials. They then examined changes in these cells in the lab, using microscopy, immunofluorescence and other high-tech methods.

"What we found astounded us," Dr. Gouras says. "Instead of working outside the cell, we discovered that these antibodies to beta amyloid bind with a specific part of amyloid precursor protein (APP) -- a precursor molecule to beta amyloid -- as it lies on the outside of the affected cell. This complex then gets internalized within the cell, where it works to decrease levels of amyloid peptides, the building block of plaques that

are found outside and between cells."

In fact, the antibodies cut down on intracellular amyloid accumulation by about one-third, the researchers found.

How might antibodies working inside neurons decrease exterior plaque levels" The researchers still aren't sure, but they have already ruled out some of the most obvious answers.

"We found no evidence that the antibody somehow inhibits the activity of either of the two cellular enzymes -- secretases -- that we know help produce beta amyloid," notes the study's lead author Dr. Davide Tampellini, a researcher in the Weill Cornell Laboratory of Alzheimer's Disease Neurobiology. "In fact, if anything the presence of the antibody appears to boost secretase activity," Dr. Tampellini says.

According to the researchers, it's possible that the antibody is affecting key trafficking mechanisms within the cell, thereby increasing the degradation of existing beta amyloid before it makes its way to the surface.

"Most of the data we have supports this degradation model rather than an inhibition of beta-amyloid production," Dr. Gouras says. "More research is needed to clear up that mystery, however."

What is clear from the study is that immune-based therapy does work to rid brain cells of amyloid -- giving new impetus to the search for a safe, effective Alzheimer's vaccine.

"A cure isn't likely as close as we are hoping for" Dr. Gouras cautions, "and new roadblocks to a successful vaccine might arise. But as we better understand how immunotherapy is working, we can better meet those roadblocks head-on."

And the discovery that antibodies work their magic both inside and outside the cell could have profound implications for the investigation of other disease conditions, especially autoimmune disorders where the immune system mistakenly attacks it own tissues.

"Biologists have long understood that antibodies can affect intracellular processes, but it's been woefully underappreciated in medicine," Dr. Gouras says. "Hopefully this will help to change that."

Source: Weill Cornell Medical College