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# UNEXPECTED RESULTS FROM STUDY IN MICE MAY OPEN NEW STRATEGY AGAINST ALZHEIMER'S DISEASE

*In laboratory mice, immune system cells from the bloodstream entered the brain and devoured plaque that is believed to play a major role in Alzheimer's disease.*

LOS ANGELES (May 30, 2008) – Interrupting a signaling pathway in certain immune system cells in laboratory mice had the opposite effect researchers expected but opened the possibility of a new approach to treating Alzheimer's disease, according to an article in the journal *Nature Medicine*.

The intervention targets the sticky plaque buildup that occurs in the brains of patients with Alzheimer's disease, using immune system cells (macrophages) from outside the brain. In the animal study, these cells were attracted to the plaque and able to cross the blood-brain barrier, a natural barrier that prevents most substances from entering the brain from the bloodstream. Plaque deposits were significantly reduced and mice performed better on behavioral tests.

"Attempts to develop therapies for Alzheimer's disease have been difficult because most rely on getting a therapeutic molecule or antibody across the blood-brain barrier. If results from our study in mice engineered to develop Alzheimer's-like dementia are supported by studies in humans, we may be able to develop a drug that could be introduced into the bloodstream to cause peripheral immune cells to target the amyloid plaques," said Terrence Town, Ph.D., first and co-corresponding author of the article.

Town is a research scientist with the departments of Neurosurgery and Biomedical Sciences at Cedars-Sinai Medical Center and with Cedars-Sinai's Maxine Dunitz Neurosurgical Institute. He performed the majority of this work at the Yale University School of Medicine in the laboratory of Richard Flavell, Ph.D., senior and co-corresponding author on the article, Sterling professor and chairman of the Department of Immunobiology and Howard Hughes Medical Institute investigator at the Yale University School of Medicine.

Amyloid plaques, composed of a protein called amyloid-β (Aβ), are thought to damage brain nerve cells (neurons) and stimulate a response in nearby inflammatory cells called microglia. Theoretically, Alzheimer's might be treated by somehow preventing or removing the plaque buildup and calming the inflammation.

"Our group has been working at the interface of the immune system and the brain," said Town. "We believe the kind of chronic, low-level inflammatory response that we see in Alzheimer's disease is deleterious, and we'd like to find a way to turn it around into a therapeutic modality."

Attempts to stimulate a beneficial immune response have been limited not only by access – the blood-brain barrier – but also by the fact that the brain is an "immune privileged" environment, not conducive to a strong immune response from microglia and other brain-resident immune cells.

(more)

Earlier studies have shown that an immunosuppressive molecule called transforming growth factor-β (TGF-β) is upregulated in the brains of patients with Alzheimer's disease. This upregulation may represent the brain's attempt to return to normalcy by quieting the immune response around the amyloid plaques. Town and his colleagues used genetically engineered mice to study the effects in the brain of blocking the TGF-β molecule on immune cells outside the brain (peripheral macrophages).

"We originally thought that if we blocked this TGF-β response in peripheral macrophages we would worsen Alzheimer's-like pathology because we would cause those cells to become hyperstimulated or hyperactivated. They would then enter the brain and likely exacerbate the brain inflammatory and immune response brought on by the amyloid plaques," Town said. "What we found was the exact opposite – which gave us the opportunity to learn something new about the biology of Alzheimer's disease. When we behaviorally tested the mice, we found they were doing better by some measures. And when we looked at the brains of these mice, we noticed that the amyloid plaques were strikingly reduced – by as much as 90 percent by some methods."

Further studies confirmed that macrophages from the blood were coming into the brain and – like PAC-MAN – devouring the plaque.

"Previous studies have suggested that peripheral macrophages may restrict amyloid plaques by entering brains of Alzheimer's mice. We performed a series of experiments in cell culture and were able to find that not only were these cells entering the brain at a higher frequency in our genetically engineered mice, but they also seemed to be able to eat more amyloid plaque on a per-cell basis," Town said. "The peripheral macrophages appeared to be attracted to the plaques, engulfing them, and by virtue of TGF-β signaling blockade, they also appeared to be more voracious in eating the plaque than a wild-type (naturally existing) macrophage would be."

"If these experimental animals are representative of the clinical syndrome of Alzheimer's disease, we may have a therapeutic target that we did not have before – TGF-β on these peripheral macrophages," said Jun Tan, M.D., Ph.D. co-author of the study, professor and Robert A. Silver chair in developmental neurobiology at the University of South Florida. "We're now investigating the molecular mechanisms that allow the cells to cross the blood-brain barrier, but it appears that by blocking TGF-β, we're able to lower their threshold for activation and empower them to enter the brain where they're homing to the amyloid plaques," said Tan.

Collaborators from Cedars-Sinai, Yale University, Saitama University in Japan, Johns Hopkins University, University of South Florida, and University of Michigan were involved in the study. The work was supported by grants from the Alzheimer's Association and the National Institutes of Health.

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