Multiple research teams unable to confirm high-profile Alzheimer's study

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Teams of highly respected Alzheimer's researchers failed to replicate what appeared to be breakthrough results for the treatment of this brain disease when they were published last year in the journal *Science*.

Those results, presented online Feb. 9, 2012, suggested that the drug bexarotene (marketed as Targretin) could rapidly reverse the buildup of beta amyloid plaques (A?)—a pathological hallmark of Alzheimer's disease—in the brains of mice. According to the authors of the 2012 report, drug treatment quickly removed most of the plaques and brought rapid reversal of the pathological, cognitive and memory deficits related to the onset of Alzheimer's.

However, the new reports from extensive and carefully controlled studies did not show any reduction in the number of plaques or total area occupied by the plaques during or after treatment. These results are described in three "technical comments"—one of which comes from researchers at the University of Chicago, Northwestern University, Massachusetts General Hospital, Washington University in St Louis and University of Tubingen in Germany—to be published in the May 24, 2013, issue of *Science*.

"The drug has no impact on plaque burden in three strains that exhibit A? amyloidosis," according to that group's comment. "We have failed to support earlier findings by Cramer et al that Targretin is efficacious in reducing plaque burden in transgenic mouse models of cerebral A? deposition."

Comment co-author Sangram Sisodia, PhD, professor of neurosciences at the University of Chicago, said he and his colleagues were curious about the initial report in 2012.

"We were surprised and excited, even stunned, when we first saw these results presented at a small conference," said Sisodia. "The mechanism of action made some sense, but the assertion that they could reduce the areas of plaque by 50 percent within three days, and by 75 percent in two weeks, seemed too good to be true."

"We all went back to our labs and tried to confirm these promising findings," Sisodia added. "We repeated the initial experiments—a standard process in science. Combined results are really important in this field. None of us found anything like what they described in the 2012 paper."

The researchers found no effects on plaque burden in three different strains of mice that were treated with bexarotene.

The discrepancy, besides being disappointing, also raises concerns about patient safety. The Food and Drug Administration approved bexarotene in December 1999 for a very specific use: treatment of refractory cutaneous T-cell lymphoma, a type of skin cancer. Once approved, the drug became legally available by prescription for "off-label" uses as well.

"Anecdotally, we have all heard that physicians are treating their Alzheimer's patients with bexarotene, a cancer drug with severe side effects," said co-author Robert Vassar, PhD, professor of cell and molecular biology at Northwestern University Feinberg School of Medicine. "This practice should be ended immediately, given the failure of three independent research groups to replicate the plaque-lowering effects of bexarotene."

Bexarotene has never been tested as a treatment for Alzheimer's disease in humans, not even to determine the optimal dose or duration of treatment. This drug has significant side effects, including major blood-lipid abnormalities, pancreatitis, liver function test abnormalities, thyroid axis alterations, leucopenia, headaches, fatigue, weight gain, depression, nausea, vomiting, constipation and rash.

The two other technical comments came from research teams led by Kevin Felsenstein, Todd Golde, David Borchelt and colleagues at the University of Florida and by Bart DeStrooper and colleagues at the University of Leuven, Belgium.

There is no cure or effective treatment for Alzheimer's disease, which is a progressive type of dementia that occurs when nerve cells in the brain die. When Alzheimer's was first identified in 1906, it was considered a rare disorder. Today, Alzheimer's is the most common cause of dementia. An estimated 5.3 million Americans have the disease.

More information: "Comment on 'ApoE-Directed Therapeutics Rapidly Clear ?-Amyloid and Reverse Deficits in AD Mouse Models,'" by I. Tesseur, *Science*, 2013.
"Comment on 'ApoE-Directed Therapeutics Rapidly Clear ?-Amyloid and Reverse Deficits in AD Mouse Models,'" by A.R. Price, *Science*, 2013.
"Comment on 'ApoE-Directed Therapeutics Rapidly Clear ?-Amyloid and Reverse Deficits in AD Mouse Models,'" by K. Veeraraghavalu, *Science*, 2013.
"Comment on 'ApoE-Directed Therapeutics Rapidly Clear ?-Amyloid and Reverse Deficits in AD Mouse Models,'" by N.F. Fitz, *Science*, 2013.
"Response to Comments on 'ApoE-Directed Therapeutics Rapidly Clear ?-Amyloid and Reverse Deficits in AD Mouse Models,'" by G.E. Landreth, *Science*, 2013.

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