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Taking another shot at RAGE to tame Alzheimer's

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Researchers have taken another crack at a promising approach to stopping Alzheimer's disease that encountered a major hurdle last year. In research published this week in the *Journal of Clinical Investigation*, scientists have developed a compound that targets a molecular actor known as RAGE, which plays a central role in mucking up the brain tissue of people with the disease.

Scientists at the University of Rochester Medical Center and the University of Southern California synthesized a compound that stops RAGE in mice – reversing amyloid deposits, restoring healthy blood flow in the brain, squelching inflammation, and making old, sick mice smarter. But the scientists caution that the work has a long way to go before it's considered as a possible treatment in people.

A phase 2 study in 399 people of another compound designed to stop RAGE – which stands for Receptor for Advanced Glycation Endproducts – was halted prematurely in November when scientists had questions about the compound's safety at high doses, and after early results indicated that the compound was not helping patients with Alzheimer's disease.

Nevertheless, developing an effective RAGE inhibitor continues to lure scientists like Berislav Zlokovic, M.D., Ph.D., a neuroscientist formerly with the University of Rochester Medical Center and now at USC. Zlokovic headed the Rochester team that published its results in *JCI*.

"RAGE remains a phenomenally attractive target for Alzheimer's therapy," said Zlokovic.

"The benefits of blocking RAGE are even greater than has been realized. RAGE is central to many mechanisms that wreak havoc in the brains of people with Alzheimer's disease. It turns out that when you inhibit RAGE, you block molecules central to creating inflammation in the brain, and that is a major problem with Alzheimer's disease," added Zlokovic, who is now director of the Center for Neurodegeneration and Regeneration at the Zilkha Neurogenetic Institute at USC.

Zlokovic was one of the first scientists to describe RAGE's involvement in Alzheimer's disease. Nearly a decade ago, in a paper in *Nature Medicine*, he showed that RAGE acts as a shuttle, ferrying amyloid beta from the blood into the brain. Since then, stopping RAGE has been an attractive but elusive goal for scientists seeking to create a new line of medications to treat Alzheimer's disease.

In the latest work, Zlokovic and colleagues screened thousands of compounds for anti-RAGE activity and identified three that seemed promising. Then the team turned to chemists Benjamin Miller, Ph.D., and graduate student Nathan Ross. The pair analyzed the compounds' molecular structures, then used that knowledge to create dozens of candidates likely to have activity against RAGE.

Several show promise, with one in particular, FPS-ZM1, especially robust at blocking RAGE. Crucially, it's a very small molecule that crosses the blood-brain barrier and gets into the brain, where it's needed. That's not true of many potential RAGE inhibitors, including the three candidates that Zlokovic's team had identified from the initial screen.

"It's a very small molecule, but with a very big effect, which is just what you want," said Miller. "And it's easy to synthesize."

The team tested FPS-ZM1 and other compounds in older mice, 15 to 17 months old, which are specially designed to accumulate amyloid beta in their brains quickly. Mice that received the compound:

- Had much lowers levels of amyloid beta in the brain – 70 to 80 percent lower – because of the reduced effect of RAGE on amyloid beta;
- Had much lower levels of inflammatory cells known as activated microglia – again, levels were reduced approximately 80 percent;
- Had improved brain blood flow, almost back to the level of healthy mice.
- Had improved learning capabilities that approached the levels of healthy mice.

The researchers were not surprised at the lower levels of amyloid beta, since RAGE allows amyloid beta to cross the brain/body barrier. But the scientists note that FPS-ZM1 affected RAGE's operations in a number of important additional ways. The molecule lessened the activity of a molecule called NF kappa B, which causes inflammation like that seen in the brains of Alzheimer's patients, and it reduced the activity of beta secretase, which plays a key role in the creation of amyloid beta.

Most important, the compound shows no evidence of toxicity in mice, even when used at concentrations hundreds of times higher than what would be used in a person.

The research is the culmination of several years of work by more than a dozen scientists at Rochester. The *JCI* paper has two co-first authors. Rashid Deane, Ph.D., research professor in the Center for Translational Neuromedicine, who headed the studies of blood flow in the brain, and Itender Singh, Ph.D., now a research assistant professor in the Department of Pediatrics, who headed the analysis of beta secretase

activity and neuroinflammation. Singh also observed that the compound reduced oxidative stress in the brain, a process central to Alzheimer's disease.

Provided by University of Rochester Medical Center