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It's time for a new approach to Alzheimer's disease

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Karl Herrup thinks that the national research effort to understand Alzheimer's disease has gone about as far as it can go with its current theories. And that's not far enough.

Alzheimer's disease is an incurable, degenerative, eventually fatal disease that attacks cognitive function. It affects more than 26 million people around the world and is the most common form of dementia among people over the age of 65. Over the last three decades, most Alzheimer's research has been governed by the "amyloid cascade hypothesis." The theory – which holds that the beta-amyloid peptide is the key to the initiation and progression of the disease – has had significant appeal as the peptide is the main ingredient of the disease-related plaques that are common in the brains of those affected.

Indeed, this persistent correlation has led researchers to spend many years and many millions of dollars looking for ways to prevent plaques as a way of treating, curing or preventing Alzheimer's. In recent years, however, dozens of human clinical trials based on this theory have failed.

Herrup, the chair of the Department of Cell Biology and Neuroscience at Rutgers University, suggests an alternative perspective, which he has set forth in a paper published today in the *Journal of Neuroscience*. Pointing out that age is the most important risk factor in the disease, he suggests a new hypothesis with age as the starting point.

Age slows the brain's agility and blunts its responses to change; on their own, however, age-related changes lead only to a slow ‘natural’ decline in cognitive function, Herrup says. He posits that while these changes might increase one’s risk of the Alzheimer’s, they do not cause the disease.

Herrup believes three three key steps that are needed for an individual to progress from this natural path to the full spectrum of Alzheimer’s clinical symptoms: an initiating injury that is probably vascular in nature; an inflammatory response that is both chronic and unique to Alzheimer’s; and a cellular change of state, a one-way cell biological door that permanently alters the physiology of neurons and several other cell types in the Alzheimer’s disease brain.

"The initiating injury might trigger a protective response in the brain cells," Herrup said. "But the real problem is that in the elderly the response doesn't know when to quit. It continues even after the injury itself subsides. In the end, the real damage is done by the persistence of the response and not by the injury, itself."

Herrup hopes his new theory will stimulate discussion and open the way to new experimental and diagnostic advances. “This new hypothesis, for example, emphasizes the value of anti-inflammatory approaches to the prevention of Alzheimer’s disease,” Herrup says.

He concedes that the individual components of the model aren’t entirely new, but points out that by rearranging their order and shifting their priority, his view has enormous implications for modern Alzheimer’s research.

“My hypothesis implies that beta-amyloid aggregation is not a central part of the biology of Alzheimer’s disease,” Herrup says. “It predicts that one can have plaques without having Alzheimer’s and that one can have

Alzheimer’s without having plaques.

“Researchers should be cautious about following up these predictions, but since we’ve gone about as far as we can with our current hypothesis, we may have reached a point where too much caution is ill-advised. It’s time to re-imagine Alzheimer’s disease, so we can think creatively about treating it.”

Provided by Rutgers University