

Is everything we think we know about Alzheimer's wrong?

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If you've followed the news about Alzheimer's disease research in the past few months, you might find yourself wondering what else could go wrong.

First, a much-anticipated new drug called Aduhelm got approval from the Food & Drug Administration—but its actual effect on patients was so small that insurance won't cover it for most patients.

Then, several other [promising drugs](#) in development by [pharmaceutical companies](#) got sidelined or showed less-than-impressive results in clinical trials.

And then a scandal broke: New evidence came to light in *Science* that researchers had faked images in a paper published 16 years ago—a paper that other researchers had trusted and relied on as they did their own work.

And what do all of these developments have to do

with one another?

They're all tied to the molecule beta-amyloid, the plaque-forming sludge that gums up the outside of brain cells. The molecule that decades of research has focused on as an important factor in the disease and potential treatments to reverse it.

But in fact, scientists at the Michigan Alzheimer's Disease Center and elsewhere have spent years looking beyond amyloid for answers to the roots of dementia and ways to prevent or treat it.

"It's true that amyloid plays a role in the brain and dementia, but Alzheimer's disease is complicated and there's much more to it than one molecule," says Henry Paulson, M.D., Ph.D., who directs the center and has devoted his own laboratory's research at Michigan Medicine and his clinical care to dementia and other [neurodegenerative diseases](#) for decades.

The paper at the center of the scandal has to do with a specific form of amyloid, AB*56, that was put forth as an important "toxic oligomer" encouraging plaque formation.

But Paulson says he and many of his colleagues have not paid much attention to it for many years, because researchers haven't been so successful at achieving the same results that the original researchers claimed.

"I'm more worried about what this news might do to the public's perception of science than to our ability to make progress against this disease," he says. The long delay in uncovering the alleged fakery isn't ideal, and shows the importance of scientists speaking up and publishing results even when their experiments fail to prove another team's claim."

This kind of publishing of "negative results"—papers that don't give good news about a potentially promising idea—is not always encouraged, because

scientists have more reason to leave those results on the shelf and spend time writing papers about things that do work.

But if no one knows that an effort to reproduce a scientific discovery has failed, then other scientists could spin their wheels driving down a blind alley.

Paulson notes that it is still important to study the protein that gets cut up, or cleaved, in order to make different forms of beta-amyloid, and the consequences of that process.

But he's not necessarily surprised by the failure of Aduhelm, the much-talked-about drug that got approval last year, to produce a sizable effect even in the patients it was tested in.

The drug is not available at the clinics or hospitals of Michigan Medicine, and Medicare will only cover its high cost for people taking part in clinical trials. Other drugs in the pipeline at drug companies that focus on beta-amyloid should be scrutinized carefully before getting any approval, he adds.

"We believe much more attention needs to be paid to other factors and proteins underlying various dementias, ranging from environmental factors, to the [immune system](#), to specific molecules like tau, which is the other hallmark protein of Alzheimer's disease," he explains. "In my view, the Aduhelm story underscores the importance of continuing to look for other therapeutic targets in Alzheimer's disease and related dementia."

Targeting amyloid for treatments may be like trying to saddle up a horse that has already left the barn, he says—too much has happened in the disease process by the time the plaques begin to form for a treatment to make a difference.

Working upstream in the process, and doing more with modern tools to understand the process by studying people in the early stages of memory loss, could prove more important.

That's why the Michigan Alzheimer's Disease Center is always seeking people to take part in studies involving everything from brain scans to surveys. Anyone who wants to get involved can

start the process by making an initial inquiry.

Alzheimer's and other forms of dementia are complicated diseases, and likely result from multiple things going wrong in the brain over time, not one rogue molecule, Paulson explains. So it may end up that we need to treat patients with multiple treatments at once, targeting several aspects of their disease—just like cancer or HIV-positive patients receive today.

But in the meantime, research has already shown another important upstream effect that many people may not realize, Paulson says.

There's plenty of evidence that middle-aged and [older adults](#) who want to reduce their risk of dementia, or slow its onset, should focus on healthy habits like sleep, nutrition, exercise, social engagement, and controlling blood pressure and cholesterol. The role of lifelong education and learning—whether informal or formal—is also clear

"If you're 70 years old, I can't tell you to go back in time and eat healthier or get more years of school, but I can tell you to do more to get a good night's sleep as often as possible, and connect socially with other people," says Paulson, a professor of neurology.

For the millions of families dealing with a loved one's dementia today, the hope of new treatments may seem like a faint light on the horizon that's fading as their loved one gets further into their disease.

That's why it's also important to focus on supporting caregivers and understanding their needs through research that could impact public policy and insurance coverage—another focus of the center's programs and research.

Research takes time, which today's patients may not have a lot of. But with help from patients and families willing to volunteer for research studies, including tests of new drugs, it can move as quickly as possible, with safeguards in place to make sure it's happening safely and honestly.

More information: Charles Piller, Blots on a

field?, *Science* (2022). DOI:
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