Clearing Out Problem Proteins

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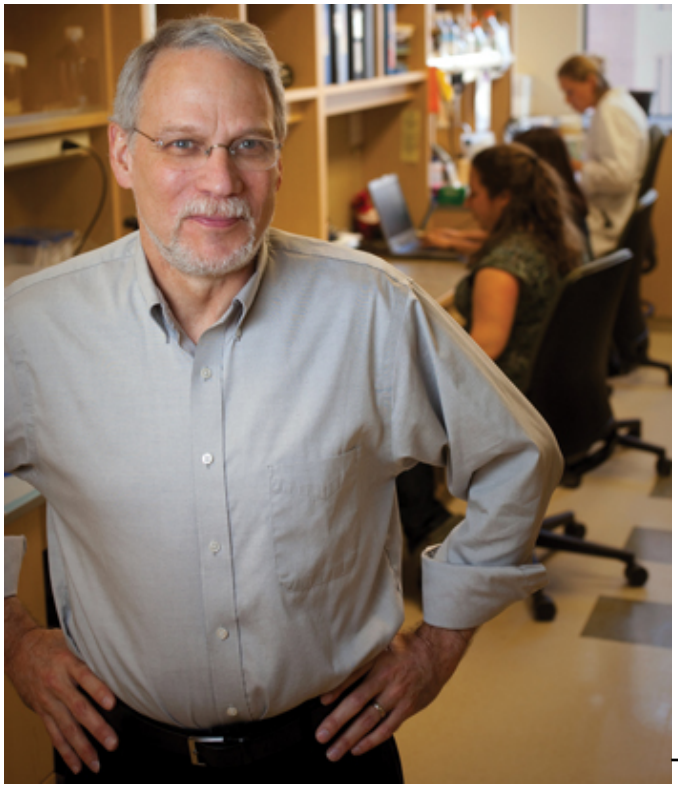 Treatments for Alzheimer’s disease have eluded researchers for decades. A major reason for this is because researchers have not pinned down a clear mechanism for the disease. Without knowing what causes Alzheimer’s, researchers have not been successful in developing effective treatment regimens to combat it.

Instead, many of the first Alzheimer’s drugs worked only for a short time and addressed the diseases’ symptoms, rather than its core. Over the years, several once promising drug candidates failed in late-stage human trials, adding to the gloom of the disease.

Nobody knows this better than Dr. Gary Landreth. Landreth, a professor of neuroscience and neurology and the director of the Alzheimer Research Laboratory at Case Western Reserve University School of Medicine, Cleveland, has been pioneering a new tack in the fight against Alzheimer’s. Landreth, who lost his mother to Alzheimer’s disease last year, knows first hand the devastating effects of this insidious disease.

“This is the disease of the 21st century,” he says.

Landreth is exploring the use of an agonist to change the behavior of a cholesterol carrying protein called apolipoprotein E (ApoE), by targeting a protein that regulates it. Earlier studies had shown that ApoE helps break down amyloid-beta, a protein formed in the brain.

While the exact cause of Alzheimer's remains unknown, one of the leading theories involves the formation of clumps of the protein amyloid-beta in the brain. Everyone's brain produces amyloid-beta, Landreth says, but when people are young, they also produce sufficient amounts of ApoE to clear out the amyloid beta before it becomes a problem.

The Apo-E acts as sort of a "garbage disposal unit," helping to degrade the amyloid beta proteins, cutting them into smaller pieces and clearing them out. With age, however, the ApoE-dependent clearance mechanisms become less efficient. The buildup of amyloid beta continues until it is believed to result in impaired learning and memory loss.

So Landreth reasoned that if he could stimulate the ApoE, the natural protein clearance of the brain would be enhanced. Their goal, he says, is to "help Mother Nature do what she normally does" in clearing out the amyloid-beta fragments.

Landreth's research has focused on nuclear receptors since 1998. They selected a drug that activates retinoid X receptors, or RXR.

"It wasn't a big leap to choose a RXR agonist, although there were a zillion reasons why this probably wouldn't work, which is why we didn't try it sooner," he says.

As they looked around for a drug that would stimulate this receptor, they found a FDA approved drug called bexarotene. Bexarotene is a drug used in skin caner treatments, but they found it also helps to activate the ApoE gene.

When Landreth had a graduate student give the drug to "Alzheimer's mice," he says, "we got remarkable results."

They found that in three days the amyloid beta protein had largely disappeared in the mice. They further reported that up to half the plaques present in the mice were removed after 72 hours of treatment.

In an additional trial, collaborator John Cirrito at Washington University, St. Louis, used an *in vivo* microdialysis in the brain of an Alzheimer's mouse. This allowed the researchers to sample the fluid between the cells and measure how much amyloid was circulating in the brain at any given moment. Results showed that within six hours of treatment the levels of amyloid in the brain fell about 30 percent.

Behavioral tests on the mice also showed cognitive improvements. For example, healthy mice typically gather paper strewn about their cage and build a nest. Alzheimer's mice stop doing that. When the drug was administered to diseased mice, they made nests once again.

Landreth says that since these tests, the team has been working to optimally administer the drug to mice. He adds that they have also begun tests on a different mouse model, one that exhibits frank neuronal loss to determine if it can arrest neuronal death.

The work, he adds, will be a test to see if the bexarotene can be used for patients with more advanced states of Alzheimer's.

"We have no data yet," he adds. "But our expectation is that we can clear out the amyloid, and that these neurons will not be distressed and will not die. We can

reduce the level of intra-neuronal amyloid with some speed. It is our hope and expectation that is going to be read out in sustained neuronal survival."

Landreth says that his team began phase 1b clinical trials in January. This trial is in 12 normal subjects and is a proof of mechanism trial to determine if bexarotene works in the expected way in the normal human brain, he adds.

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