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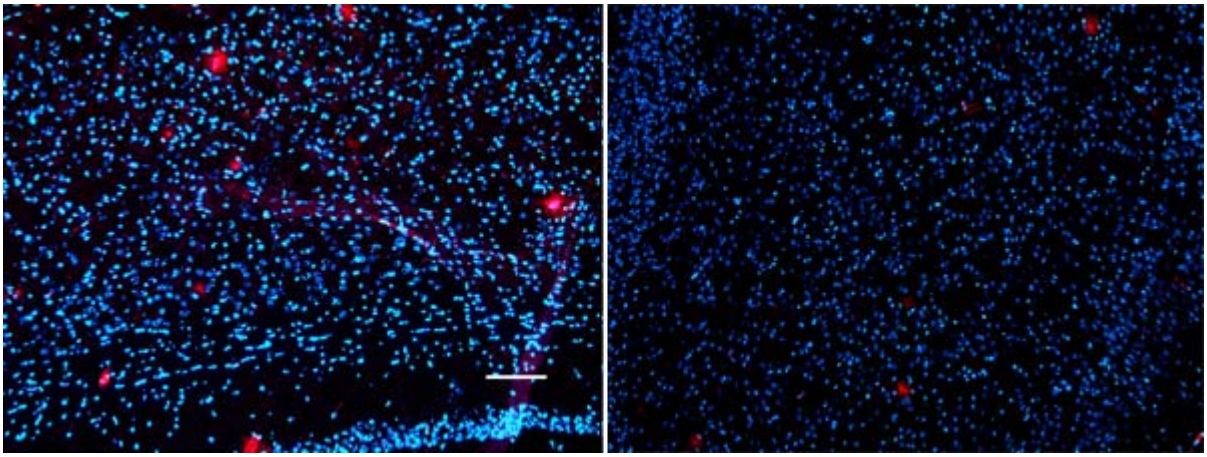
Alzheimer's Disease Symptoms Reversed in Mice

A cancer drug given to mice eliminates brain-damaging proteins, leading to improved cognition within days, but will it work in humans?

By Gary Stix | February 9, 2012

A nearly 13-year-old skin cancer drug rapidly alleviates molecular signs of Alzheimer's disease and improves brain function, according to the results of a new mouse study being hailed as extremely promising. Early-stage human clinical trials could begin within months.

In the study, published online February 9 by *Science*, researchers from Case Western Reserve University in Cleveland and colleagues used mice genetically engineered to exhibit some of the symptoms of Alzheimer's. Most notably, the mice produced amyloid beta peptides—toxic protein fragments that gum up neurons and lead to cell death—and showed signs of forgetfulness.



Amyloid beta (*red areas*) peptides clear from the brain of an Alzheimer's mouse after three days of treatment with a cancer drug (*right image*). *Source: AAAS/Science*

The Case Western team, led by Gary Landreth, decided to try the drug bexarotene (Targretin), approved in 1999 for cutaneous T cell lymphomas. The team chose this drug because of its long experience working with proteins in the nucleus of brain cells that can induce biochemical processes that affect amyloid beta.

Landreth and his colleagues fed bexarotene to the demented mice, and with just a single dose it lowered the most toxic form of the amyloid beta peptide by 25 percent within six hours, an effect that lasted for up to three days. Mice that were cognitively impaired by

the amyloid buildup resumed normal behaviors after 72 hours: They began to crinkle toilet paper placed nearby to make nests, a skill lost as amyloid increased in their brains.

"We have successfully reversed all of the known pathological features and behavioral deficits found in mouse models of Alzheimer's disease," Landreth says. "Never before has anyone observed clearance of amyloid plaques with such speed in mouse models."

Other Alzheimer's researchers hail the work. "I think this is extremely promising," says Samuel Gandy, a professor of neurology and psychiatry at Mount Sinai School of Medicine and associate director of the hospital's Alzheimer's Disease Research Center. "One of the drugs that has been on our wish list for 25 years is a drug that would clear existing amyloid deposits."

"Landreth's paper is impressive," adds Kenneth Kosik, a neuroscientist at the University of California, Santa Barbara. "The effects in mice, including some restoration of cognitive abilities, are dramatic."

Neural sanitation

In a field littered with drug failures, the study offers hope that the strategy of clearing the brain of the toxic peptide can work. **Bexarotene** does not do so directly, however; instead, it activates retinoid receptors on brain cells that increase production of a fat-protein complex, apolipoprotein E, that helps rid excess amyloid in the fluid-filled space between neurons. It also appears to enhance another cleanup process, called phagocytosis.

Bexarotene functions differently than an amyloid-clearance approach using monoclonal antibodies, which are further down the drug development pipeline. These antibodies bind directly to amyloid and then remove it, but they have sometimes caused fluid to fill brain tissue. Bexarotene may be less likely to cause such swelling. "I think the fact that we're inducing a natural process by turning on these receptors doesn't lend itself to water on the brain," says Paige Cramer, Landreth's graduate student who performed much of the research. Unlike bexarotene, which is taken orally, monoclonals are more troublesome to administer, because they must be delivered intravenously, and if they receive U.S. Food and Drug Administration approval, they would likely be significantly more expensive.

The study also provides the most compelling evidence to date of how the biggest risk factor for Alzheimer's later in life—having the so-called *Apolipoprotein E* (*APOE*) gene, identified in the early 1990s—might yield a strategy for new therapies. The gene for apolipoprotein E comes in three versions, one of which, the *e*4 variant, confers a significantly higher risk of getting the disease—a roughly 60 percent chance at age 80 for those who carry a copy from both their mother and father, as against a less than 10 percent overall risk at that age in the general population. The gene variant, known informally as the Alzheimer's gene, is common: about 20 percent of the U.S. population has at least one copy. The *e*4 carriers may be vulnerable to Alzheimer's because they have a diminished ability to clear amyloid, a hypothesis that seems to be reinforced by this Case Western study.

Jumping the gun?

That idea, though, is not universally endorsed. Some experiments have shown that the *e*4 version may also impair the brain in other ways, *perhaps by bollixing the biochemical functioning at the synapses, the connection points between neurons, or by producing toxic fragments of the lipoprotein that damage neurons.* If so, increasing the production of this form of apolipoprotein E could actually worsen the pathology of the disease and would complicate greatly bexarotene's development.

This potential hurdle does not dissuade one researcher experienced in Alzheimer's clinical trials. "I am not particularly concerned" about potential toxic effects of extra *e*4 production, says Paul Aisen of the University of California, San Diego, who heads the Alzheimer's Disease Cooperative Study, which organizes clinical trials for drugs to combat the illness. "If it significantly enhances amyloid clearance and reduces the burden of brain amyloid, there is a good chance it will succeed." David Holtzman, a prominent Alzheimer's researcher from Washington University in Saint Louis, echoes the sentiment about bexarotene's prospects: "I do think it is promising to go into humans."

Landreth and Cramer certainly think so. They have formed a company called ReXceptor Therapeutics that intends to begin a preliminary trial in humans in the next few months to determine whether the drug crosses the blood–brain barrier and clears amyloid, as it does in mice. If those processes occur, clinical trials on the drug's effectiveness in humans could begin even this year, and they would probably last from 18 months to three years. The drug loses patent protection for cancer this year, but Case Western has filed for patents for its use in Alzheimer's.

Many unknowns

Despite their optimism, scientists say it's important not to overplay the progress. After all, drugs that work in mice do not necessarily help humans. Moreover, the genetically engineered version of mice used in this study do not recapitulate every aspect of the human disease. For instance, the mice do not experience the effects of dying neurons (despite having impaired cognition), and they do not go on to develop a hallmark characteristic of a later disease stage in humans—namely, the accretion of so-called tau proteins that seem to abet the killing of nerve cells. "Transgenic mouse experiments have not reliably predicted therapeutic effects in humans," Aisen says, "so caution is essential until human studies confirm target engagement," that is, the removal of amyloid plaques.

And bexarotene does not come without risk: it raises levels of triglycerides, blood fats implicated in cardiovascular disease and diabetes. The Case Western mouse work suggests that Alzheimer's patients may benefit with doses lower than those ingested for cancer treatment, which might produce less of an effect on fat levels. Whether the drug remains effective over time is another question. The levels of amyloid plaques—although not the apparently more toxic soluble form of the peptide—rose after 90 days, a suggestion that the drug may be metabolized differently after ingestion over long periods.

The enthusiasm generated for a mouse study stems from the desperation for new ideas as the number of Alzheimer's cases, now at 5.4 million in the U.S., is expected to more than

double by the year 2050 as the nation's demographic profile continues to gray. A better understanding of the disease process—the knowledge that pathology begins 10 or 20 years before the first symptom—has shifted focus toward earlier drug trials. New technologies that combine brain imaging and spinal fluid tests might identify at-risk patients and test new drugs. A relatively inexpensive drug that can be ingested orally, such as bexarotene, could then be prescribed to at-risk but symptom-free patients, who would take them over the course of their lifetimes, like a cholesterol-lowering drug.

As ReXceptor moves forward with its clinical trial plans, it will inevitably have to contend with the demands of the families of Alzheimer's patients. Landreth emphasizes that calling your physician after reading an article like this one is a bad idea. "Don't try this at home," he cautions, "because we don't know we what dose to give, we don't know how frequently to give it, and there are a few nuances to its administration. So one shouldn't be prescribing it off-label." It is also unclear whether a drug like bexarotene would work at a middle or advanced stage of the disease, when neurodegenerative processes have already set in.

Bexarotene's genesis as an Alzheimer's treatment comes as an outgrowth of Landreth's long-time fundamental work on cell receptors. If it succeeds, it will demonstrate that new ideas for treating this seemingly intractable disease may come from beyond the sometimes narrowly focused strategies of large pharmaceutical companies.