

# NEWS IN FOCUS

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Alzheimer's disease is marked by cognitive decline and the accumulation of proteins in the brain.

## DRUG DEVELOPMENT

# Alzheimer's drugs show progress

*Protein-targeting antibodies succeed after many failures.*

BY SARA REARDON

For years, scientists studying Alzheimer's disease have been frustrated on two fronts. They have struggled to understand whether the amyloid- $\beta$  protein that accumulates in sufferers' brains is a driver of the disease, or just a symptom. And without a clear understanding of the condition's cause, they have searched fruitlessly for effective treatments.

The latest results from clinical trials of two antibody drugs could provide a path forward. For the first time, such drugs — which target amyloid — seem to have slowed the progression of the disease. The findings, released on 22 July at the Alzheimer's Association International Conference, support the idea that amyloid deposits cause the mental deterioration seen in people with Alzheimer's.

"We're creeping in the right direction," says

Samuel Gandy, a neurobiologist at Mount Sinai School of Medicine in New York. "A lot of the euphoria is because things were so negative for so long." Still, many researchers doubt whether the minor improvements reported last week will hold up in larger trials.

Pharmaceutical firm Eli Lilly of Indianapolis, Indiana, says that in a trial with 440 participants, its drug solanezumab seemed to slow the cognitive decline of people with mild Alzheimer's by about 30%. Over 18 months, people in the treatment group experienced a loss of mental acuity equivalent to the deterioration experienced in just 12 months by those in a placebo group with Alzheimer's disease of similar severity.

Lilly snatched this small victory from the jaws of defeat. In 2012, the company reported no difference between patients who had taken solanezumab for 18 months and those who had received a placebo. But when the company reanalysed the trial data, it found a slight improvement in participants whose symptoms were mild when the trial began. Lilly continued the test for six months and began giving solanezumab to the 440-member control group, whose disease was by then more advanced.

The latest results show that cognitive decline in the 'late start' group slowed to match the rate seen in the 440 people who had been treated for the entire study. This suggests that solanezumab targeted the root of Alzheimer's disease.

Drug-maker Biogen, of Washington DC, presented results that show a moderate dose of its drug aducanumab reduced amyloid build-up in 23 people, but did not have statistically significant clinical benefits. In March, the company reported that 27 people who received high doses of aducanumab for one year showed significantly less cognitive decline than people who received a placebo, and had less amyloid in their brains.

Many experts are greeting these results with tempered excitement, given the relatively small size of the clinical trials. But Eric Siemers, an Alzheimer's researcher at Lilly, is more optimistic. "It's surprising to me that [solanezumab] worked so well," he says. "There's a lot of promise to slow progression."

Lilly launched a larger phase III trial of solanezumab in 2013, enrolling 2,100 people with mild symptoms and amyloid deposits in their brains. The study will end in October 2016. And last December, Biogen said that it would launch a phase III trial with 2,700 participants that would run for 18 months. ▶

► Lon Schneider, an Alzheimer's researcher at the University of Southern California in Los Angeles, questions the decision to start large trials before the drugs, and the amyloid hypothesis, have been well validated. "Why are there so many antibodies when none so far have proven efficacy?" he asks, noting that behavioural interventions, such as diet and exercise, have been shown to slow Alzheimer's as much as any drug (A. M. Clarfeld and T. Dzwolatzky *JAMA Intern. Med.* 173, 901–902; 2013).

But not everyone agrees. "This is the time to be bold," says Randall Bateman, a neurologist at Washington University in St. Louis, Missouri. "It seems to me the cost of delay from a human-suffering standpoint is much more expensive than the cost of moving forward."

Bateman is leading a trial that is testing solanezumab and ganetenerumab — developed by Roche of Basel, Switzerland — in 160 people between 18 and 80 years old who have a genetic risk of Alzheimer's, but no symptoms. It is one of several efforts attempting to determine whether the disease can be prevented by destroying amyloid protein before the brain is damaged. That harm occurs over decades (R. J. Bateman *et al. N. Engl. J. Med.* 367, 895–804; 2012), and many Alzheimer's researchers suspect that antibody-drug trials have failed because they have treated people too late.

This hypothesis is supported by Lilly's finding that only people with mild disease benefit from solanezumab. The latest results also demonstrate for the first time in humans that slowing amyloid deposition can slow down cognitive decline, says Eric Reiman, executive director of the Banner Alzheimer's Institute in Phoenix, Arizona.

That is important because the US Food and Drug Administration has said that it will not approve drugs that block amyloid deposits without sufficient evidence of a clinical benefit. If one drug company can prove the cause and effect between amyloid accumulation and Alzheimer's progression, all companies will benefit, says Reiman, who is leading a trial of crenezumab, a Roche drug that has also failed previously in large trials.

If such drugs falter in larger preventative trials, that would be a setback for Alzheimer's research in general, says Gandy. "The main concern is that the pipeline behind amyloid-reducing agents is really pretty spare," he says. However, at least three companies are developing treatments — some of which are antibody drugs — that target a different protein, tau, which destroys neurons in advanced Alzheimer's disease. ■ See [go.nature.com/lathpu](http://go.nature.com/lathpu) for a longer version of this story.



The MV *Cape Race* is using sonar to map the depth of water around Greenland's west coast.

#### GLACIOLOGY

# NASA launches mission to Greenland

*Ship and planes will probe water–ice interface in fjords.*

BY JEFF TOLLEFSON

When the retired fishing trawler MV *Cape Race* sets off along Greenland's west coast this week, it will start hauling in a scientific catch that promises to improve projections of how the ice-covered island will fare in a warming world. The ship's cruise is the initial phase of a six-year air and sea campaign to probe interactions between Greenland's glaciers and the deep, narrow fjords where they come to an end.

Called Oceans Melting Greenland (OMG), the US\$30-million NASA project will help scientists to predict the future of the Greenland ice sheet, which holds enough water to boost sea levels by around 6 metres and already seems to be melting more rapidly in response to increasing air temperatures. But it is not clear how much the oceans affect the rate of melting along the island's edges, which depends on poorly known variables such as how warm, saline water interacts with the glaciers.

"It should be a powerful constraint on our knowledge and ability to model ice loss there," says principal investigator Joshua Willis, an oceanographer at NASA's Jet Propulsion Laboratory in Pasadena, California.

When simulating glacier dynamics, current global climate models consider only ice's

interactions with the atmosphere, says William Lipscomb, an ice modeller at Los Alamos National Laboratory in New Mexico. He is working to incorporate ice–ocean interactions around Antarctica into a climate model being developed by the US Department of Energy. But in Greenland, the intricately carved coastline makes this much more difficult. The department plans to give researchers at the Naval Postgraduate School in Monterey, California, \$466,000 over 2 years to build a detailed model that will link the land ice and oceans around Greenland. OMG data will help to validate that model, says project leader Frank Giraldo.

Work by OMG participant Eric Rignot, a glaciologist at the University of California, Irvine, underscores the importance of detailed data (E. Rignot *et al. Geophys. Res. Lett.* <http://doi.org/6dn>; 2015). Using sonar data from one part of western Greenland, Rignot's team found that existing maps underestimate the depth of three fjords by several hundred metres. It also found that glaciers flowing into all three fjords extended deeper than was thought, far enough below fresh surface waters to reach a warm, salty layer flowing up from the Atlantic Ocean that could accelerate melting and contribute more to sea-level rise than had been believed.

"With OMG, we are going to reveal the depth of these fjords," says Rignot.

MARIA STENZEL/UCI