

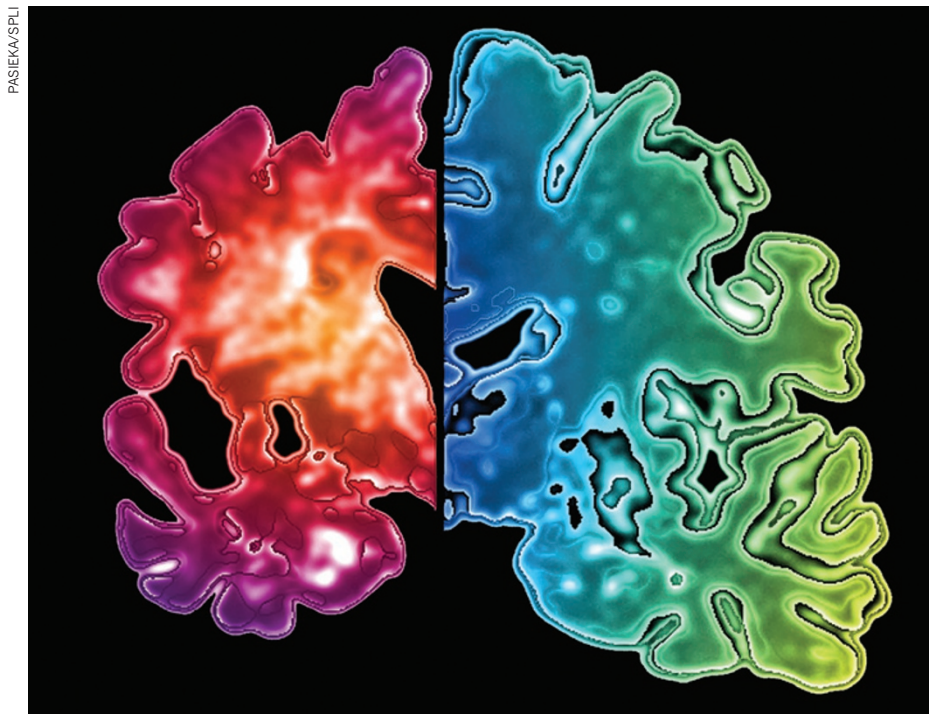
# NEWS IN FOCUS

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Amyloid plaques accumulate in the brains of Alzheimer's patients (left), but not in unaffected brains (right).

## MEDICAL RESEARCH

# Alzheimer's drugs take a new tack

*Hopes pinned on pre-emptive clinical trials after latest setbacks.*

BY EWEN CALLAWAY

After a summer marred by disappointing clinical-trial results in patients with Alzheimer's disease, drug developers are regrouping to plot a fresh course in the battle against the devastating disorder.

The bad news began in July and August, when Johnson & Johnson and Pfizer learned that their biological drug bapineuzumab had failed to show any benefit in two large trials. Then, on 24 August, Eli Lilly said that its drug solanezumab had not hit its goal of significantly slowing the memory decline and dementia

that characterize Alzheimer's disease.

Both of the failed drugs targeted amyloid- $\beta$ , a protein that forms plaques in the brains of patients with the disease and that has long been the prime suspect for causing it. But rather than abandoning the amyloid hypothesis, scientists are pinning their hopes on innovative clinical-trial designs and new diagnostics that would allow them to test compounds earlier in the disease and gauge their efficacy more quickly.

Many worry, however, that investors spooked

by the hundreds of millions of dollars spent on failed trials will be reluctant to support a continuing search for effective treatments for Alzheimer's and other dementias, which affect an estimated 36 million people worldwide. "Money is tight," says Hussein Manji, global therapeutic area head in neuroscience at Johnson & Johnson in New Brunswick, New Jersey. But "we're still very committed. We think this is a major societal problem that needs tackling."

Amyloid- $\beta$  plaques are thought to cause Alzheimer's disease by killing neurons and severing their connections to their neighbours. But the evidence is circumstantial. Autopsies of patients show that larger numbers of plaques occur in more severe cases of the disease. Also, mutations in the gene responsible for amyloid- $\beta$  seem to have either a risk-enhancing or a protective effect. Yet despite all the money invested in amyloid-targeting drugs, "we need to confirm or refute the amyloid hypothesis", says Paul Aisen, a neuroscientist at the University of California, San Diego.

The first results for solanezumab, released by Eli Lilly, which is headquartered in Indianapolis, Indiana, seem to support the hypothesis. The drug is meant to recognize and block amyloid- $\beta$  before it forms plaques. In patients with mild and moderate forms of disease, however, solanezumab failed to meet its main goals of slowing the decline in memory and other cognitive measures, or in the ability to perform tasks such as eating and maintaining personal care. But other analyses suggest that the drug slowed cognitive decline in patients with milder forms of Alzheimer's. No data have been released on the magnitude of these improvements, though, so it is unclear whether they are enough to make a difference to patients' lives.

"From a purely scientific standpoint, we're pleased at the results," says Eric Siemers, medical director of Lilly's Alzheimer's team. "These are the first clinical-trial data that would also support the amyloid hypothesis." Investors and scientists will get a clearer picture this autumn, when further data from this summer's trials of more than 2,000 patients will be presented at conferences.

The bapineuzumab trials seem to have been more of an unqualified failure. This antibody drug targets the amyloid- $\beta$  plaques, in hopes of awakening the immune system to clear them from the brain. But two trials in approximately 2,400 patients failed to show any benefit ►

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## TACKLING ALZHEIMER'S EARLY

Three studies aim to assess the effects of trial drugs on asymptomatic people.

Trial name	Aim	Length	Size	Cost
Alzheimer's Prevention Initiative	To test crenezumab in people who have mutations in the presenilin 1 gene and other genes that cause Alzheimer's in middle age.	5 years	~ 300 people	\$100 million
Dominantly Inherited Alzheimer Network	To test three drugs on asymptomatic people with Alzheimer's-linked mutations in genes for presenilins 1 and 2, and amyloid precursor protein.	5 years	160 people	\$60 million for 2 years
Anti-amyloid treatment in asymptomatic Alzheimer's disease	To test a drug in asymptomatic people who have high levels of amyloid- $\beta$ , and some who have a gene variant that increases their risk of Alzheimer's.	3 years	1,000 people	\$110 million

► compared with a placebo, although this may have been because the drug was administered in lower doses than solanezumab, owing to its higher toxicity. Johnson & Johnson and its partner Pfizer, headquartered in New York city, say that they will vastly scale back development of bapineuzumab.

Increasingly, researchers think that the problem lies not so much with the strategy of targeting amyloid- $\beta$  as with the timing of treatment. "The major conundrum in the field is: 'are we just treating people too late?'" says Ronald Petersen, director of the Alzheimer's Disease Research Center at the Mayo Clinic in Rochester, Minnesota. Like the fatty plaques in coronary arteries, amyloid- $\beta$  plaques accrue over a lifetime, says Petersen. And so, just as cholesterol-lowering statins are prescribed for patients in middle age to stave off heart disease in later life, amyloid-blocking drugs given in middle age may prevent Alzheimer's, Petersen says.

But no one knows when amyloid-blocking drugs would need to be taken to prevent the disease, and researchers might have to track tens of thousands of people for decades to determine whether a preventive drug worked. "You can't take every 30-year-old off the street and try a prevention study," says Manji.

Nonetheless, three studies are set to begin by next year that will test whether anti-amyloid

drugs can forestall early symptoms of Alzheimer's and arrest cognitive decline in patients who, on the basis of genetic predisposition or amyloid levels, have been identified as being at increased risk of developing the disease (see "Tackling Alzheimer's early").

The Alzheimer's Prevention Initiative will test crenezumab, a drug developed by Genentech, based in South San Francisco, California, in a large Colombian family that has a rare mutation predisposing members to develop Alzheimer's in middle age. The

US\$100-million trial will focus on asymptomatic family members for up to five years to see if the drug can stave off their inevitable cognitive decline. The trial will also seek to identify biomarkers, such as amyloid levels from brain scans and in cerebrospinal fluid, that could be used to assess whether crenezumab and other drugs are effective.

"We need to launch a new era in Alzheimer's-prevention research to set the stage to rapidly evaluate treatments," says Eric Reiman, executive director of Banner Alzheimer's Institute in Phoenix, Arizona, who is co-leading the Colombia trial. With such markers

identified, drug companies could quickly get a sense of whether or not a drug is preventing Alzheimer's, saving precious money and time, he says.

Drug agencies, including the US Food and Drug Administration and the European Medicines Agency, are keeping a close watch on those efforts. In theory, approval for preventive drugs could be assessed on the basis of clinical trials measuring changes in biomarkers, or surrogates, instead of traditional measures of cognitive improvement. However, regulatory agencies are likely to set a very high bar for what constitutes a proven surrogate, says Siemers.

Reiman's study is already bankrolled. But the two other imminent trials — one led by the Alzheimer's Disease Cooperative Study, a US government-funded programme, and the other by researchers at Washington University School of Medicine in St Louis, Missouri — are still looking for money. Many Alzheimer's experts hope that this summer's bleak news will not scare off investors.

"We've had this concern for quite some time," says Reiman, "that if these trials were negative we would see some major stakeholders and investors abandon amyloid-modifying treatments. We think that would be throwing the baby out with the bath water, and abandoning Alzheimer's disease." ■

**"The major conundrum in the field is: 'are we just treating people too late?'"**

## CONSERVATION

# India's forest area in doubt

*Reliance on satellite data blamed for over-optimistic estimates of forest cover.*

BY NATASHA GILBERT

To judge from India's official surveys, the protection of its forests is a success. Somehow, this resource-hungry country of 1.2 billion people is managing to preserve its rich forests almost intact in the face of growing demands for timber and agricultural land.

But a senior official responsible for assessing the health of the nation's forests says that recent surveys have overestimated the extent of the remaining forests. Ranjit Gill of the Forest

Survey of India (FSI) claims that illegal felling of valuable teak and sal trees has devastated supposedly protected forests in the northeast of the country. He and other experts also say that an over-reliance on inadequate imaging by an Indian satellite system is making such destruction easy to overlook.

In February, the FSI, part of the government's Ministry of Environment and Forests, released the *India State of Forest Report 2011*. This biennial survey used images from India's remote-sensing satellite system and estimated

that forest covered 692,027 square kilometres of the country — roughly 23% of India's land area — a decline of just 367 km<sup>2</sup> on the tally reported in 2009, and a much smaller loss than in Brazil, for example, where more than 13,000 km<sup>2</sup> of forest was cleared over the same period. But Gill, a joint director of the FSI, is openly critical of the FSI's assessment.

"We have to accept the grave reality that the current figure of forest cover in India is way over the top and based on facile assumptions," Gill argues. To bring these allegations to light,