Is Alzheimer's research missing a piece of the puzzle?

After two major failed drugs trials, it may be time for scientists to rethink the way they approach dementia, says *Victoria Lambert*

When scientists at Merck announced last week that they were putting an end to late-stage trials of their latest Alzheimer's drug, it wasn't just patients and families who were devastated. With verubecestat, a once-promising therapy, declared as having no positive effect, its failure set alarm bells ringing across the entire drug research community.

This was the second Alzheimer's treatment trial to be cancelled in short order. In November, solanezumab, an injectable therapy from US pharma giant Eli Lilly – also aimed at mild to moderate forms of Alzheimer's – had been halted in late-stage trials.

Bart De Strooper, director of the new £250 million Dementia Research Institute at University College London, has warned that researchers must change the way they think about the disease in response to the lack of progress.

"Researchers have had too simplistic an approach to dementia," he said. "What is emerging is that these brain diseases are highly complex, with many processes, not just one. We need to make our research more nuanced."

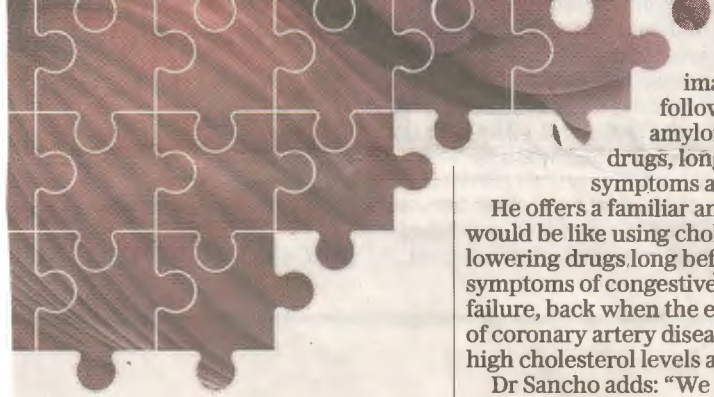
Solanezumab and verubecestat both affect the build-up of amyloid proteins, which turn into sticky clumps of plaque found in the brains of people with Alzheimer's disease. Verubecestat belongs to a class of drugs called BACE inhibitors, which interfere with the production of Beta-secretase 1, an enzyme known as BACE1, while solanezumab is a monoclonal antibody designed to clear away amyloid.

For years, these proteins have been the focus of researchers desperate to find a way to stop the progression of the illness. Indeed, there is still an ongoing trial into a drug called AZD3293, a collaboration between AstraZeneca and Eli Lilly, not due to end until May 2019.

But do these public failures mean that scientists have been looking in the wrong place all along? Are we at crisis point for research into Alzheimer's?

The news about US drug giant Merck's failed therapy is certainly disappointing, says Dr Rosa Sancho, head of research at Alzheimer's Research UK – especially, she points out, for those affected by dementia involved in the trial itself. "We're waiting to hear from Merck once they have analysed their data fully to see what we can learn from this setback."

But she insists the situation is not without its positives, the principal lesson from the trials being that



amyloid plaques are building up many years before the symptoms of dementia start to show. "Probably what has happened is that by the time patients got the Merck drug, it was already too late," she says.

Rudolph Tanzi, vice-chair of neurology and director of the Genetics

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and Aging Research Unit at Massachusetts General Hospital in the United States agrees. "The failure of the BACE inhibitor at Merck is further proof that targeting amyloid plaques after clinical symptoms arise is too late," he says.

"Amyloid plaques trigger the disease a decade or so before symptoms. Successfully treating this disease will require early detection of plaque in the brain by imaging, followed by amyloid-lowering drugs, long before symptoms arise."

He offers a familiar analogy: "It would be like using cholesterol-lowering drugs long before symptoms of congestive heart failure, back when the earliest signs of coronary artery disease or even high cholesterol levels are detected."

Dr Sancho adds: "We have to change our thinking – we have to start treatment earlier." She points out that verubecestat may yet be useful. Another trial is under way on people without dementia but who are experiencing memory loss and thinking problems. "There is a chance those people will benefit more."

Consultant neuroradiologist Dr Emer MacSweeney, chief executive and medical director at Re:Cognition Health, a consultancy, isn't writing off BACE inhibitors just yet, either.

"For the Merck study, patients were not pre-screened for amyloid positivity before entering the trial.

"Positive amyloid status can be demonstrated using a new brain-imaging technique or spinal fluid analysis and is now the recognised hallmark for Alzheimer's disease. New clinical trials for similar medications have been able to use the new diagnostic test for amyloid protein and select only those individuals proved to be amyloid positive. These studies are ongoing and there is cautious optimism, although results are not available yet."

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New thinking on Alzheimer's

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Of course, Alzheimer's is not the first or only disease to have been so difficult to treat. Professor Jackie Hunter, chief executive of BenevolentBio, the bioscience division of pharmaceutical company BenevolentAI, points to work on multiple sclerosis (MS): "A couple of decades ago, therapies were limited and many new interventions failed. However, they enabled new research and better understanding of the disease, which in turn led to new and more effective therapies for MS.

"Oncology has the highest rate of failure in terms of new therapy trials, but no one says we should stop work on trying to find a cure for cancers."

Already, there are other promising drugs coming through, including agents that target inflammation and other changes in the brain. Dr McSweeney says: "There is no reason to believe we are in a crisis. More time, energy and funding are being directed into new drug development for Alzheimer's than ever before.

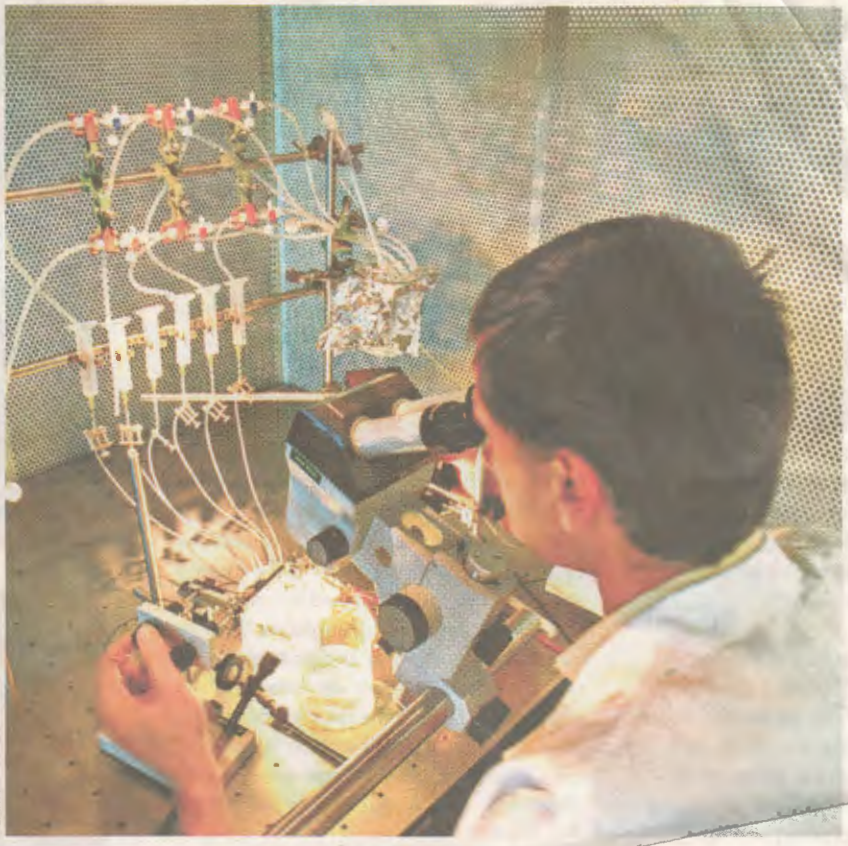
"These medications are not just designed to slow progression of symptoms (disease-modifying drugs), but also to boost memory and other cognitive function (symptomatic drugs). Symptomatic drugs help the dying brain cells to work more effectively, whereas disease-modifying drugs are aimed at stopping, or significantly slowing, the death of brain cells in the first instance."

One last but significant positive to emerge from Eli Lilly's trial is attitudinal – and could be influential.

Not only was the company open about its test failures, but representatives agreed to speak at a symposium called by Alzheimer's Research UK, where they showed all their data and allowed discussion about the next steps. Dr Sancho hopes other drug developers will follow Eli Lilly's lead, and share results with the dementia research community.

"We're seeing more discussion around what happened and hope this will continue," she says. "Dementia is a such a pressing challenge in society. It makes sense to take and share as much as we can from the data."

For more information on reducing your risk, go to alzheimers.org.uk



ALAMY

A researcher studies Alzheimer's disease: there are promising drugs coming through that target changes in the brain

'It makes sense to take and share as much as we can from the data'

DEMENTIA WITHOUT DRUGS
FIVE WAYS TO REDUCE YOUR RISK

• Get moving
Physical activity has been associated with reduced risk for dementia. You need to be active enough to raise your heart rate and get a bit out of breath for at least 30 minutes, five times a week. Walk, cycle, swim or join an exercise or dance group.

• Stop smoking
By smoking, you put yourself at a greater risk of developing dementia as well as harming your lungs, heart and circulation.

• Eat a healthy, balanced diet
This means a high proportion of oily fish, fruit, vegetables, unrefined cereals and olive oil, and low levels of red meat and sugar. Try to cut down on saturated fat (eg, cakes, biscuits and most cheeses) and limit sugary treats.

• Keep your alcohol within recommended limits
These changed in 2016: they are now a maximum of 14 units each week for men and women, spread over three or more days. This is the same as four or five large glasses of wine, or seven pints of beer or lager with a lower alcohol content. Regularly exceeding these weekly limits increases your dementia risk.

• Give your brain a daily workout
Reading, doing puzzles, word searches or crosswords, playing cards or learning something new – maybe another language – all help. There is a bit less evidence, but keeping socially engaged and having a good network of friends may also reduce your dementia risk.

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