

Randall Bateman is leading a team that has just come up with a blood test to screen people at risk of developing Alzheimer's disease, years before the symptoms appear.

BLOOD TEST FOR ALZHEIMER'S

There is still no cure for Alzheimer's disease, but there is cause for optimism. In recent years, significant progress to understand the underlying mechanisms of the illness and to diagnose it faster has been made.

Researchers from Washington University School of Medicine in St. Louis have just reported the use of a blood test that can measure levels of the amyloid beta protein and predict their accumulation in the brain. Aggregates of amyloid beta in the brain are a hallmark of Alzheimer's disease and start building up 15 to 20 years before patients get the first symptoms.

Led by Dr Randall Bateman, the team hopes that the test will become widely used to identify people who are likely to

develop Alzheimer's before clinical manifestations arise, earlier and more accurately than with the current gold standard method – the PET brain scan.

Alzheimer's path of physiology

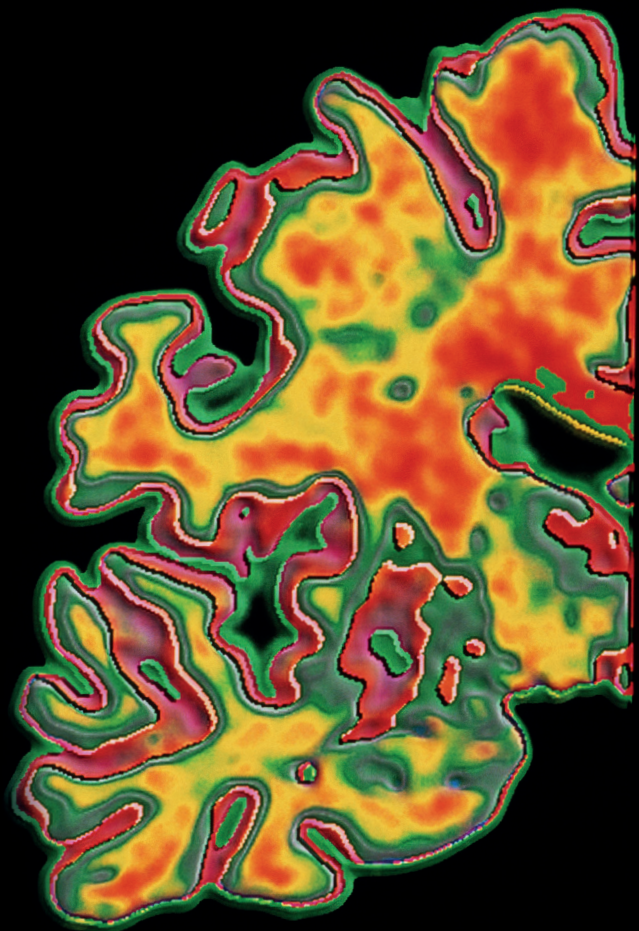
Since childhood, Bateman had been fascinated by the ageing process and interested in untangling the mysteries of how the human brain functions. His interest in Alzheimer's grew during his residency, where he was able to see firsthand the impact of the disease on patients.

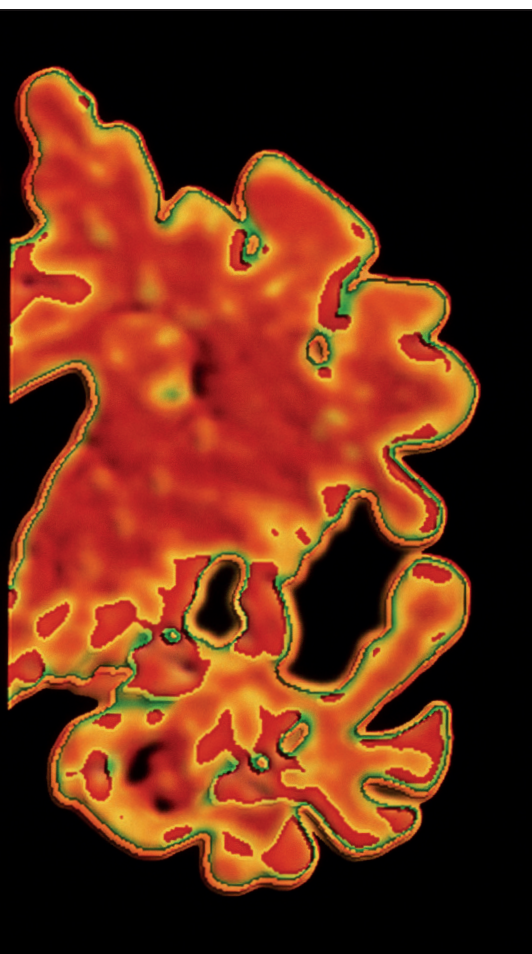
In his lab in St-Louis, the focus is on building up an understanding of the mechanisms that lead to the development of Alzheimer's. The team studies the pathophysiology of the disease, and explores the processes that lead to clinical symptoms of memory loss, cognitive impairments, dementia, and eventually

death. "We are trying to focus on some of the fundamental questions – why people get Alzheimer's disease, why Alzheimer's is such an age-related disease and what brings about the various changes that occur in Alzheimer's. Being able to disentangle and decipher what actually leads to the disease process is quite important," Bateman explains.

Their recent work around the blood test, published in the journal *Neurology*, is the result of more than a decade of research into why people develop an increased amount of aggregated amyloid beta proteins in the brain. In 2004, the scientific community discovered that it was possible to track the amount of these amyloid plaques with PET scans. Bateman and his team went on to develop a method to measure amyloid beta clearance rates and established that as people get older, their ability to clear the proteins decrease by about four-fold. A specific form of the protein – amyloid beta 42 – seemed particularly problematic.

In their latest research, they have looked at blood samples from 158 people





aged 50 years old and over. These participants had also done PET scans. The scientists worked to determine the degree to which amyloid beta changes in their blood were associated with changes in the brain, and in what order these changes came about.

The team used mass spectrometry to precisely measure the amounts of amyloid beta 42 in the blood, as well as the amount of amyloid beta 40. The ratio of these two proteins in the blood goes down as they aggregate in the brain. Bateman and his colleagues classified each blood sample and PET scan as amyloid positive or negative, and discovered that the blood tests were concordant with the scans 88% of the time.

The researchers also found out that it was possible to identify these changes in the blood before the changes in the brain, meaning that people who could go to develop clinical symptoms of Alzheimer's could now potentially be identified earlier. "Our most significant finding is that when you identified a change in levels of blood amyloid beta, it looks like this change

could be spotted about five to six years before these changes were noted on PET scans, on average," Bateman explains.

Prevention trials

The clinical implications may be far-reaching, and one of the most interesting ideas that has arisen is to use the blood test as a screening tool to identify people at risk of Alzheimer's before symptoms appear, and to get them quicker into prevention trials. "There are likely to be two uses to this test – identifying who is likely to get the disease in the future and for people who already have symptoms, to confirm or refute that their symptoms are due to Alzheimer's," Bateman says.

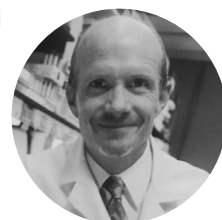
For years now, the scientific community has sought to conduct clinical trials of preventive drug treatments. However, the challenges of identifying participants with brain changes, but no cognitive problems, has slowed them down. "It is imperative to test a treatment targeting the amyloid plaques as they are developing, not when they are fully established and the symptoms of the disease starts. But it's difficult because the disease progresses inevitably but slowly, and because it's a disease of the brain it's difficult to track overtime, unlike a tumor, for example. What it means is that you need much larger and longer trials, which makes it expensive, and you lose time finding the right participants," Bateman adds.

Using the test to screen thousands of people a month, enrolling them and finding treatments faster, could, in the long term, mean lower economic costs of treating a disease which affects 5.8 millions people in the US and nearly a




DR RANDALL BATEMAN

- ✓ Current Charles F. and Joanne Knight Distinguished Professor of Neurology, Director of the Dominantly Inherited Alzheimer Network (DIAN), and Director of the DIAN Trials Unit.



- ✓ Recipient of a number of awards, including the Beeson Award for Ageing Research, Alzheimer's Association Zenith Award.
- ✓ Co-founder of biotechnology company C2N Diagnostics.

million in the UK, as well as reducing the human suffering associated with Alzheimer's. The test will not be available for a few years, but its commercialisation is already underway.

Bateman and his team are now screening a little over a thousand people in St. Louis to demonstrate the feasibility of their approach. "There have been struggles in the field of Alzheimer's research, and it's true we do not have yet a trial that has demonstrated a clear benefit of treatment of the disease but we are honing in on what is likely to benefit patients and we have great progress from a diagnostic standpoint, with PET scans and now this blood test. We should not lose sight of all the advances that have been made, for the sake of patients and their loved-ones", the scientist concludes. 

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