Alzheimer's unlocked: New keys to a cure

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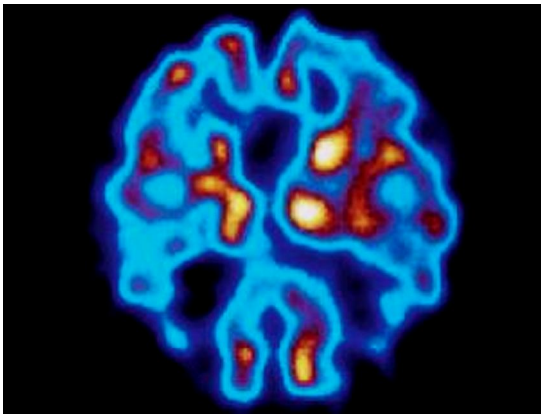
Attempts to treat the world's most common form of dementia may have been attacking its symptoms, not its root cause



PET scans could be used to detect Alzheimer's plaques before symptoms of dementia appear (Image: Tim Beddow/SPL)

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I HAVE lost myself," cried Auguste Deter to her physician. Deter was trying to write her name, scrawling "Mrs" in a spidery script, only to forget the rest every time.

"What are you eating?" the doctor asked Deter on her second day at the hospital for the mentally ill in Frankfurt, Germany, as the confused 51-year-old lunched on cauliflower and pork. "Potatoes," she replied.

That was in 1901. When Deter died five years later, an autopsy revealed that her brain was riddled with strange tangles and plaques of a fibrous material containing the remnants of dead brain cells. She became the first described case of a form of dementia now known by the name of her doctor - one Alois Alzheimer.

Over a century later, research into Alzheimer's disease still revolves around efforts to understand those mysterious plaques and tangles. Despite decades of work, no effective treatment exists, never mind a cure. The world's population is ageing, so that search is becoming more urgent. Alzheimer's disease is now recognised as the most common form of dementia, with over 25 million people living with the disease worldwide, and that number is expected to pass 100 million by 2050 (see diagram). Yet today, even definitively diagnosing the disease can still only be done at autopsy.

The situation is starting to change, however. Thanks to a new imaging technique, the plaques can now be seen in the brains of living people. Not only could this allow early diagnosis, it is helping to overturn the long-standing orthodoxy over the causes of Alzheimer's and paving the way for effective treatments.

For the past two decades, Alzheimer's research has been dominated by the "amyloid cascade hypothesis": the idea that it is the plaques themselves that lead to the cognitive problems of Alzheimer's. They are aggregations of a protein called amyloid beta, which forms naturally in the brain, but whose production somehow goes into overdrive during Alzheimer's disease (see "Brain defence gone wrong?"). The proteins clump together to form plaques, which are toxic to neurons, eventually killing them, or so the theory goes (*Science*, vol 256, p 184).

Drug developers immediately grasped the implication of the theory, that medicines able to block or break up the plaques should slow, or even reverse, the progression of the disease. This idea has guided millions of dollars' worth of drug development effort. Just about every potential Alzheimer's drug in the pipeline targets amyloid and its supposed toxicity.

The excitement has faded fast. So far, at least, none of the treatments derived from the amyloid hypothesis has ever resulted in significant clinical improvement in clinical trials. "It has been a problem for people working on [the amyloid plaque theory] for 20 years - the drugs that have come out of it have all failed at stage II or III of clinical trials," says Susanne Sorensen, head of research at the UK's Alzheimer's Society. Sorensen has never seen a trial that reported people getting better.

Take b-mab, for example. This drug was developed to clear amyloid plaques from the brain, but results released in 2008 showed that it had no significant effect on the rate of cognitive decline (*Neurology*, vol 73, p 2061). That raised a question. Was b-mab failing to clear the plaques, or were the plaques themselves not the problem?

We are now beginning to get answers. A team at the University of Pittsburgh, Pennsylvania, led by William Klunk and Chester Mathis has developed a brain-imaging marker called PiB that selectively sticks to amyloid plaques, lighting them up in PET scans. The marker means plaques can be seen in living people, and changes in plaque size can be monitored.

In February, a Finnish team used PiB to show that when people with mild to moderate Alzheimer's were given b-mab, the plaques did indeed clear - by as much as 25 per cent over 18 months compared with a placebo (*The Lancet Neurology*, vol 9, p 363). Yet people given b-mab experienced the same progression of symptoms as those on the placebo. In other words, the drug was doing what it was supposed to do, but without slowing the disease.

The study seems to confirm what has long been suspected from post-mortem evidence: that plaque size and dementia symptoms don't correlate. That has always been the central objection to the plaque hypothesis, says Dominic Walsh, a neurologist at University College Dublin in Ireland. "Lots of people have Alzheimer's plaques but are not demented."

If the plaques aren't responsible, then what is? Alzheimer saw more than plaques in Deter's brain: there were also the tangles, which form inside neurons themselves.

The tangled material is now known to be made of a protein called tau, which can build up until it almost fills the neuron, which then dies. Crucially, unlike with plaques, the number of tangles in a patient's brain seems to correlate well with their level of dementia.

Recent studies also suggest that stopping tau molecules from clumping together could be an effective drug target. A drug called Rember, made by a Singapore-based start-up called TauRx Pharmaceuticals, has shown promising results in early trials, and the company claims to have an even more effective version that will begin final-stage trials this year.

That might seem to be the end of the amyloid theory. Not quite. A number of studies have investigated what triggers tau to accumulate in neurons in the first place, and they point right back to amyloid beta (*Science*, vol 293, p 1491). So even if tau is the direct cause of dementia, amyloid beta build-up could still be the trigger.

If that is the case, then why don't plaque-targeting drugs seem to work? A growing number of researchers suspect that the problem is that they have been looking at the wrong form of the protein. There is increasing evidence that short chains of amyloid beta molecules known as oligomers are really responsible for the symptoms of Alzheimer's disease. Oligomers - small, soluble precursors to the large, insoluble plaques - appear from cell and animal studies to be damaging to neurons. In fact, many now believe that the plaques may actually be the brain's way of disposing of something toxic.

In April, this theory got a huge boost from a study by Sam Gandy at Mount Sinai School of Medicine, New York, and his colleagues. The team engineered mice to produce oligomers but stop short of developing plaques and found that the animals experienced the same memory and cognitive problems as those that had plaques did (*Annals of Neurology*, DOI: 10.1002/ana.22052). "At least in mice, the oligomer dose did seem to correspond pretty much with the severity of the memory problems," says Gandy.

The real bad boys

The study is a coup de grâce, says Rudolph Tanzi, an Alzheimer's researcher at Harvard Medical School and Massachusetts General Hospital in Boston. "It finally shows exactly what all the previous data were pointing to but never directly showed - we can have a brain with no plaques but still have problems."

Gandy thinks the oligomers may kill brain cells by making them leaky. Like cell membranes, amyloid beta is relatively hydrophobic, which could draw the two together. If the oligomer then punctured the membrane, it would kill the cell. Alternatively, the oligomers may be acting indirectly: other studies have shown that they can cause the precursors of tau tangles to appear (*The Journal of Neuroscience*, vol 30, p 4845). No one knows for sure, though, and to find out researchers first need to know exactly which size of oligomer is the guilty party.

Tanzi suggests dimers - pairs of amyloid molecules linked by strong covalent bonds. "We believe that these are the real bad boys." His team has shown that people with Alzheimer's have equal numbers of antibodies to the amyloid monomer as those without the condition, suggesting that both groups' immune systems are able to mop up any excess of the amyloid monomer that might accumulate as we age. However, the Alzheimer's group had significantly fewer antibodies against the stable dimers, so would be less able to remove this seemingly toxic form of amyloid beta (*The Journal of Biological Chemistry*, vol 280, p 17458).

Whether or not the dimers are the true culprits, or whether larger forms of soluble amyloid beta such as the 12-chained dodecamer are responsible, the oligomer theory is gaining popularity in the field. The theory sounds convincing, says Sorensen.

Dennis Selkoe, a neurologist at Harvard Medical School involved in formulating the original amyloid cascade hypothesis, thinks it's too early to rule out plaques completely, because they don't permanently sequester oligomers. Over time, they can also release them. "I believe there's a limit as to how many oligomers can be efficiently stored within plaques, and when these limits are exceeded, patients begin to experience more and more synaptic dysfunction from free-floating oligomers."

Other researchers are still to be persuaded by the idea. "The major flaw in the oligomer idea is that nobody has really seen these things in either living patients or autopsy brains," says Mark Smith, a neurochemist at Case Western Reserve University in Cleveland, Ohio. They can only be seen after you have isolated them, he points out, so they could just be artefacts of the isolation procedure.

For Gandy, finding a PiB-like marker to show up oligomers in vivo is a priority. Developing PiB took close to a decade, so it might take a while. There might be other ways, though. Not all of the Alzheimer's drugs being tested at the moment are designed to break up amyloid plaques. Some are targeted much earlier in the process, stopping amyloid beta formation at source - so they should stop oligomer formation too.

One group of drugs, called gamma secretase inhibitors, stop amyloid beta formation by blocking the enzyme that makes it. Although one such drug recently failed a clinical trial, another, developed by drug firms Eli Lilly and Elan Pharmaceuticals, is currently in final-stage clinical trials.

Another promising drug prevents amyloid beta from forming oligomers, as well as breaking up plaques. PBT2 has shown cognitive benefits in trials, according to researchers at Prana, an Australian biotech company. They presented their results at the American Aging Association meeting in Portland, Oregon, in June, adding that the drug also frees the zinc and copper trapped in plaques that are needed for the functioning of nerve cells.

Selkoe suspects that for any of these drugs to work, catching the disease early will be key, which could explain why so many have been disappointing. Clinical trials target people with mild to moderate Alzheimer's, and Selkoe argues that attempting to treat the disease when it is already at the moderate stage is too late. Ideally, drugs should be given before symptoms appear, he says. PiB could be very useful here, as the marker might allow pre-symptomatic cases to be identified.

Whichever theory is correct, that Alzheimer's research is branching out can only be a good thing. "Before, it was heresy to question the amyloid hypothesis," says Smith. "I think people are getting a little braver."

Brain defence gone wrong?

Amyloid beta, the protein synonymous with Alzheimer's disease, is continually produced by the body throughout life, but its role in normal brain function has remained a mystery. Robert Moir at Massachusetts General Hospital in Boston recently noticed that the protein closely resembled others key to the non-specific, or "innate", part of our immune system.

The innate immune system differs from the "adaptive" immune system in that it produces generic cells and chemicals to fight infection, while the adaptive side churns out specifically targeted lymphocytes and antibodies. The blood-brain barrier protects the brain from most pathogens, but also blocks adaptive cells, so the brain relies on innate immunity for defence.

Amyloid beta might be part of this. Moir's team tested the protein against 15 important pathogens, and compared its activity to that of an antimicrobial peptide called LL37. Amyloid beta stopped the growth of eight pathogens - in some cases more effectively than LL37. This suggests that Alzheimer's could be the result of the brain's own defences going into overdrive (*PloS One*, DOI: 10.1371/journal.pone.0009505).

Moir, along with colleague Rudolph Tanzi, believes that amyloid beta plays a dual role in the brain. The protein seems to be associated with synapses, the junction between neurons. The researchers suspect that during infection, as well as dealing directly with the pathogen, the protein damps down signal transmission at affected synapses.

"But too much of a good thing and it becomes bad," says Tanzi. Some kind of trauma to the brain, such as chronic infection, a bang to the head or a stroke, could send amyloid production into overdrive, leading to Alzheimer's.

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