OF MICE AND MENTAL ILLNESS

Lars Ittner and his team have stopped Alzheimer's in mice. Next, a cure for humans.

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Most people think of tangles as irritating knots in hair or wires. But when Associate Professor Lars Ittner studies tangles, he is examining microscopic tangles of fibre in the brain cells of mice and men that are a sign of Alzheimer's disease.

The tangles occur when a protein, known as tau, malfunctions and clogs brain cells. The gradual destruction of the brain leads to Alzheimer's, a form of dementia which affects 250,000 Australians and around 35 million older people worldwide. By 2050 it will affect at least double that number, and the treatment of people with Alzheimer's is predicted to eat up three to four per cent of Australia's gross domestic product.

But not if Ittner has his way. The German-born neuroscientist and an international team of researchers at University of Sydney's Brain and Mind Research Institute have developed a vaccine which targets abnormal tau and slows the development of Alzheimer's in mice. The study, reported in the journal *PLos One*, showed that the vaccine halted and cleared "neurofibrillary tangles" in the brain cells of affected mice.

Mice injected with the vaccine put on weight, became fitter and more active, and outlived a control group of mice who were not vaccinated.

The breakthrough has brought new hope of an effective treatment for the millions of people affected by Alzheimer's. Ittner, who heads the Alzheimer's and Parkinson's Disease Laboratory, says: "The vaccine could eventually be used as part of a cocktail of treatments for people suffering from Alzheimer's."

Research in this area is littered with dead ends, so when a promising line of investigation yields results like these, scientists have to temper their excitement with caution. With the increase in life expectancy and explosion in numbers of people suffering from Alzheimer's, Ittner's work has the potential to improve the quality of life of millions of people. Currently, an American pharmaceutical firm is collaborating in the trials to see if the vaccine can be modified for use in humans.

To reach this stage, Ittner spent many long hours at the "mouse house", one of his favourite haunts at the Institute, which accommodates around 4,000 mice, and includes animals being tested in a second trial of the vaccine.

The research team has altered specific mouse genes so that the animals "develop a pathology that is like Alzheimer's. We introduce aspects of the disease to modify their behaviour," says Ittner, who emphasises that the rodents are treated well and spend most of their time in cages where they have lots of objects to chew on, exercise equipment and hiding places.

One floor below, Ittner works with a dozen scientists, including his brother Dr Arne Ittner, a molecular biologist. While Lars, a medical doctor, was headhunted from the University of Zurich in 2005, Arne was recruited from the Swiss Federal Institute of Technology in 2010. "Arne's molecular biology knowledge is phenomenal and his research was critical to this study," says Ittner.

In the laboratory, researchers are busy analysing DNA, culturing neurons or doing microsurgery on mice to find ways to prevent and treat Alzheimer's and related Parkinson's diseases. In one room, monitoring screens show live video footage of mice as they explore an empty

rectangular tray. The mice will be tested to see if they can remember new things introduced into the barren cages.

"We can monitor the brain activity of these mice by reading EEGs (electro encephalograms) from transmitters implanted in their brains," explains Ittner. The restless animals show no sign of being wired up, perhaps giving new meaning to the term "wireless mouse".

The researchers monitor the EEGs for silent seizures, which affect Alzheimer's patients. He says it is a complex disease, with random autopsies of people, who died from other causes, showing the first brain changes may start in teenagers. "It can take 60 to 70 years before it becomes an overt disorder."

Alzheimer's usually first manifests itself in retirees, with one per cent of people over 65 years old affected. The incidence doubles for each five-year increase in age above that. "There are so many processes going on that what we understand is only the tip of the iceberg."

Sufferers progressively lose their memories and have increasing difficulty with thinking, emotional control and behaviour. Eventually, they may not recognise their spouses, children or closest friends, causing enormous distress to themselves and their families. The destructive process has been well documented through the lives of public figures such as former US president Ronald Reagan and in Australia, Hazel Hawke. It is, ultimately, fatal.

Ittner says in 99 per cent of cases, the genetic causes of Alzheimer's are unknown. Inherited genetic faults or familial links to the disease are responsible for less than one per cent of cases.

The symptoms of Alzheimer's are triggered by deposits of two proteins: amyloid beta and abnormal tau. First amyloid beta is deposited as plaque between nerve cells in the brains, stopping messages being relayed. Then abnormal tau blocks up the inside of brain cells.

Scientists at overseas institutions have developed and tested vaccines that target amyloid beta. However, trials of the anti-amyloid vaccines on people were stopped after some patients died from encephalitis, an inflammation of the brain tissues.

By contrast, the vaccine developed by Ittner's team focuses on damaged or abnormal tau. Like scaffolding around a building, normal, healthy tau is essential for maintaining the structure of brain cells. Without it, the neurons would disintegrate and collapse in a jelly-like mass.

However, when part of the tau protein becomes abnormal it creates tangles inside the brain cells. The tangles block up the inside of individual neurons. As neurons are destroyed, the brain atrophies and sections of it die.

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Ittner explains there is a delicate balance in creating an effective, safe Alzheimer's vaccine. In this case, it is critical that the vaccine targets only damaged tau. If the vaccine attacks healthy tau, all the neurons could disintegrate and the brain turn to mush, which would be lethal for anyone vaccinated. "We don't want to go the same way as the amyloid beta therapy which went awry."

Three teams of scientists elsewhere have tested prototype tau vaccines on young mice, with little effect. Instead, Ittner's team vaccinated "older mice", aged between four and 18 months old, that already showed symptoms of Alzheimer's.

The test mice were injected with "pathologically changed" tau protein. They had a "massive reaction" to this, developing antibodies which attacked the abnormal tau. The vaccinated mice recovered their health, while the untreated mice continued to deteriorate and died.

Now a second trial of a "passive form" of the vaccine is showing even more promising results. Ittner says not only is the disease being halted but there are "indications that the memory of mice treated with the vaccine may be improving".

"What we are currently doing is modifying the treatment so it can go straight into humans." He says it will probably be at least five years before the vaccine can be tested in humans, and many years more before it becomes a therapy.

While some people have volunteered to serve as guinea pigs for a trial of the vaccine, Ittner says: "Obviously, I have to reject that. I try to refer them to my colleagues like Sharon Naismith so they can get the best treatment available." [See story below.] "There is still a huge gap between basic research and getting treatment to the bedside." ■

Try this quick quiz...

Using sudoku, crosswords and memory games, Sharon Naismith has devised a regime to help people with early signs of Alzheimer's or memory loss.
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