Aberdeen University's Professor Claude Wischik

**Long journey to lift curse of ‘awful’ disease**

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In July 2008, at a conference in Chicago, a paper was delivered which ignited a spark of hope for people with dementia, their families and loved ones. Professor Claude Wischik, Professor of Old Age Psychiatry at the University of Aberdeen, as well as being the Executive Chairman of TauRx Therapeutics, led the research which suggested that, for the first time, Alzheimer’s disease could be stopped in its tracks.

This devastating illness, which affects millions worldwide, already has a huge social, personal and economic cost, both for those directly affected by it, and for the countries they live in.

Conservative estimates suggest there are between five and six million people in America living with Alzheimer’s, where it is the seventh-leading cause of death. In reality, because of under-diagnosis and other factors, this number is likely to be far higher.

According to the US-based Alzheimer’s Association, the direct and indirect costs of Alzheimer’s and other dementias to Medicare, Medicaid [US healthcare insurance schemes) and businesses amount to more than $148 billion each year.

This bill is set to rocket, however, as the population ages. Between 2015 and 2050 it is expected that the numbers of people with the disease will grow to such an extent that the costs could bankrupt the US economy, let alone the insurance schemes.

And that’s not mentioning the human cost. “You don’t need me to tell you how awful this disease is,” says Prof Wischik. “It’s a highly destructive disease process which destroys individuals and families. For the husband or wife of someone with Alzheimer’s it’s awful – they see the person they love being eaten away in a ghastly, protracted way.”

Prof Wischik has been made aware of many such stories in the months since his research findings were announced. Even now, he receives one or two emails or letters per week, usually from the family of someone with Alzheimer’s, desperate to know when the treatment might be available. Some want to know where the next trials will be held, and are offering to travel or do whatever is required to gain access to the drug for their loved one.

He has had thousands of such emails and, although he cannot help but be touched by the stories, Prof Wischik knows in his heart that the process of getting a drug to market cannot be hurried. “Someone wrote to me recently asking why I couldn’t make the drug available to a small number of people – they asked what the ‘downside’ could be. My answer is that there are only downsides – if the treatment worked, I wouldn’t be able to cite the data [to prove it works]; if there were apparent adverse events, how could you know whether the drug was responsible or not?

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“That’s precisely why we need to run a double-blind control trial, so that we can compare the drug to placebo – we need to know both what the side-effects are and to confirm the efficacy signal that we saw in our earlier study.”

Prof Wischik is more aware than most that his results need to be watertight to convince the rest of the scientific community. For many years now, the majority of research into Alzheimer’s has concentrated, not on the “tangles” of tau protein which are the target of his drug, but on another tack altogether. Known as the amyloid theory, this is based on the fact that plaques of a substance called beta amyloid are known to develop and build up in the brains of people with Alzheimer’s. This has been the target for therapies including vaccines and attracts most funding into the disease. But although there have been several large-scale trials, none has proved successful, leading some to ask whether the amyloid theory is dead.

The build up of amyloid plaques, which does occur in Alzheimer’s, can also take place without dementia developing in the course of normal aging, says Prof Wischik. Recent brain scan data using novel tracers for beta amyloid have simply confirmed what we already know from our post-mortem studies in the 1990s, that amyloid build-up does not appear to be the factor that drives mental deterioration, he says. Even where treatments have been shown to clear beta amyloid, there has not been a corresponding improvement in cognitive abilities, and the build-up of tau protein aggregates has continued unabated. Conversely, if someone has a build up of tau tangles, then he or she will have dementia. Tau, he believes, is the crucial factor.

As well as providing targets for treatment, the tau tangles are also critical for early diagnosis, he says. It is possible to stage, or to diagnose dementia by looking at the level of tau aggregation and the spread of the tangle pathology throughout the brain. This is done on the Braak scale. At Braak stage 2, tau tangles have accumulated to such an extent that some neurons will die, but there may be no evidence of cognitive impairment. By the age of 65, almost one in five of us will be at Braak stage 2. It takes around 10 years to move from Braak stage 2 to 3, where there will be signs of memory impairment. Around 45 per cent of 80-year-olds will have reached this stage. Even so, only around 10 per cent will have been diagnosed with dementia. By stage 4, the tau tangles will have caused significant cognitive and memory impairment, while by stage 5, 80 per cent of patients will have a diagnosis of moderate to severe dementia.

As things stand, once a person has reached stage 2 on the Braak scale, the journey to dementia is inexorable. Even the best current treatments might only delay progress by a few months, while thoughts of a cure are way out of reach.

The new drug, however (which will probably have an entirely new name), not only appears to “dissolve” the bundles or tangles of tau, but has an impact on people’s cognitive function.

In the Phase 2 clinical trial, involving 321 patients with mild and moderate disease in the UK and Singapore, the people who were on the drug did not have significantly different cognitive scores at the beginning and the end of the first year of the trial – in other words, the decline seen in the control arm of the trial appeared to have been halted.

What is more, repeated brain scans showed that the treatment had the greatest effect in brain regions critical to memory where the density of the tangles was greatest. In contrast, the control group (which was not taking the drug) showed a significant decline in cognitive function and on brain scans over the period of the trial.

Disappointingly, the highest dose of the original remberTM did not perform well in the Phase 2 trial, leading the scientists to change the formula so that it could be better taken up by the body, without prohibitive side-effects. This is particularly exciting because, if Prof Wischik is right, then high doses might even reverse the cognitive decline associated with Alzheimer’s disease, at least in the early stages, and possibly other forms of dementia as well.

Although he is obviously enthusiastic about the treatment and delighted that it will shortly go into Phase 3 clinical trials, Prof Wischik cautions against over-optimism. “The positive results we saw in our Phase 2 trial need to be repeated. This will take time – these things always take time,” he says.

The regulators, including the US FDA, have been very helpful, he says, and have recognised that the team is breaking new ground, not just in the form of the treatment but in the analysis methods they will be deploying to show that the treatment is disease-modifying. Indeed, he says, TauRx has significantly upped its game in the last year, taking on a new chief medical officer who has previously taken a leading drug through phase 3 trials to market, and beefing up its capacity generally.

Prof Wischik is optimistic that the outstanding required funding will be forthcoming – and says that the latest fundraising round appears to be on track with a high level of interest from potential investors.
The investors could see a several-fold return for their money, but Prof Wischik is aware of the responsibility that working with other people's money brings.

'I personally don’t think it’s risky in light of our Phase 2 data," he says. 'But I suppose I’ve gambled with my professional life, while they are gambling with their money. For patients there is no gamble, only the grim certainty that the disease will progress. The duty of care with respect to both patients and investors is a heavy burden to carry, but it needs to be carried if we are to make any real progress with this awful disease.'

Millions of people with dementia and their families, now and in the future, will be hoping that Prof Wischik's life work proves a winner for all concerned.

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