These results by Dr Decourt suggest that lenalidomide has the potential to lower Alzheimer’s disease brain pathology and to do so over a long period of time.

Dr Boris Decourt of Arizona State University is looking to the anti-cancer drug lenalidomide as a possible treatment for Alzheimer’s disease. This FDA-approved compound alters the actions of the inflammatory molecule, tumour necrosis factor alpha (TNF-α), tackling many physiological aspects and vicious pathological cycles of the devastating neurodegenerative disorder when given at an early stage of the disease.

Breaking the vicious cycle: new potential therapy for Alzheimer’s disease

The World Health Organization estimates that a new case of dementia is diagnosed every four seconds. Alzheimer’s disease (AD) is the most prevalent form of dementia, affecting approximately 47 million individuals worldwide, and imposing an estimated cost of $605 billion annuually. These numbers are expected to triple by 2050 as the global population lives longer than ever before. Furthermore, it is thought that only 25% of people suffering AD actually receive a diagnosis. These figures emphasise the urgent need to discover a cure for AD, and the importance of scientific research for age-related neurodegenerative disorders.

NEUROPATHOLOGICAL HALLMARKS OF ALZHEIMER’S DISEASE

AD is characterised by two major pathological features in the brain (used during autopsy to confirm the diagnosis of AD after death): firstly, the aggregation of small proteins named amyloid beta (Aβ) into senile (or amyloid) plaques outside of the cells; and secondly, the accumulation of an abnormal form of the tau protein into fibrillar tangles inside neurons.

Aβ fragments are formed when the amyloid precursor protein (APP) is broken down by two enzymes called β-secretase and γ-secretase. The latter process is exaggerated in AD, which results in an excess of Aβ, which then aggregates into plaques (Figure 1). Both plaques and tangles impede cellular functions such as neuronal signalling and connectivity, which, over several years, leads to the death of neurons in brain areas associated with learning and memory.

While inflammatory events were initially thought to be secondary to neurodegeneration, more recent studies have revealed that inflammatory mediators may be released at early stages of AD and exacerbate Aβ production – for example by increasing the levels of β- and γ-secretases (Figure 2). The vicious cycle created by these factors is pivotal to the progression of AD, and highlights the multifaceted and unrelenting nature of AD, as well as the challenges associated with the search for potential therapeutics.

TARGETING TUMOUR NECROSIS FACTOR ALPHA FOR ALZHEIMER’S DISEASE

Cytokines are molecules produced and released by immune cells to communicate with each other and other cells. TNF-α is one of the first molecules released during inflammation, thus its levels and the location and duration of its release often dictate how long the immune reaction will last. Importantly for AD, the levels of both TNF-α and its cellular receptor TNFR1 were found to be elevated in the brains of AD patients, as well as in ageing individuals and sufferers of mild cognitive impairment (MCI), an early form of AD. Furthermore, in vitro experiments, the addition of Aβ to cells results in the robust release of TNF-α. Additional investigations have shown that TNF-α stimulates the expression of APP, β- and γ-secretases, thus aggravating the release of Aβ. These results strengthen the connection between the presence of
In a Tg mouse model of AD that develops Aβ plaques, just four weeks of lenalidomide treatment robustly reduced TNF-α and β-secretase gene expression ... and lowered the brain Aβ loads.

4 weeks - APP23

12 weeks - APP23

Looking at facts and statistics, the need for research into AD and treatment possibilities is clear. What was it that led you to study inflammation in AD in particular?

During the first year I was working in Arizona for the NIH study, I read the scientific papers about Alzheimer’s disease and noticed that inflammation was present at all stages of the disease.

Why, in your opinion, do we not yet have a comprehensive treatment for AD?

This is a very difficult question for which the brightest minds on the planet have no answer yet. I believe it’s a combination of very complex mechanisms at play that are difficult to decipher, plus some lack of understanding of the natural function of some proteins involved in AD (e.g., Aβ) is present in the blood and body of everybody, but we do not know what it does naturally, and a lack of good disease study models (Tg mice are created by genetic engineering using human mutations) or monkey study is available at this time – we know for a fact that human and mouse models are different, just four weeks of lenalidomide to reduce AD-associated inflammation.

Do your lenalidomide studies show promise for the use of other compounds targeting the inflammatory processes of AD?

Several anti-inflammatory drugs have been tested in AD-like mice. While most work in mice, they don’t work in humans to treat AD. This is why we are using the strongest anti-inflammatory class of molecules for our studies. We first want to test whether they work in several AD-like mice. If they do, we’ll test the drugs in humans, and if they are efficient in humans we will investigate the molecular processes targeted by the drugs to find less toxic alternatives (even though it is lower than thalidomide, lenalidomide shows some toxicity in humans).

Use of lenalidomide as AD treatment is particularly appealing due to its FDA-approval status. Could studies into multiple uses of FDA-approved compounds prove an effective approach to rapid treatment discovery for AD and other diseases?

Given the success of the tri-therapy for AIDS, this approach of using multiple therapies is currently under investigation by other scientists. However, at this point it is difficult to decide which therapies are the most promising as none of them have proven effective individually in clinical trials.

If your hypotheses are proven in the current study, what are the next steps leading to prescription of lenalidomide to treat AD and their timeline?

Our current project is expected to provide the answers we need for a human clinical trial by 2023. That’s why we are using the strongest anti-inflammatory class of molecules for our studies. We first want to test whether they work in several AD-like mice. If they do, we’ll test the drugs in humans, and if they are efficient in humans we will investigate the molecular processes targeted by the drugs to find less toxic alternatives (even though it is lower than thalidomide, lenalidomide shows some toxicity in humans).

Arguably most importantly, however, the team hopes to find the optimal regimen of lenalidomide to reduce AD-associated symptoms and brain pathologies. This will entail varying the ages of animals receiving treatment, treatment course duration and dosages to determine the efficacy of lenalidomide as AD treatment. Biological markers such as TNF-α and other inflammatory markers, Aβ levels, amyloid plaques, and tau tangles, will be interrogated alongside assessments of cognitive measures such as working and spatial memories. This is particularly significant as, dependent on data collected from these studies, lenalidomide may continue into clinical testing as a very hopeful therapeutic to treat the enigma that is Alzheimer’s disease.