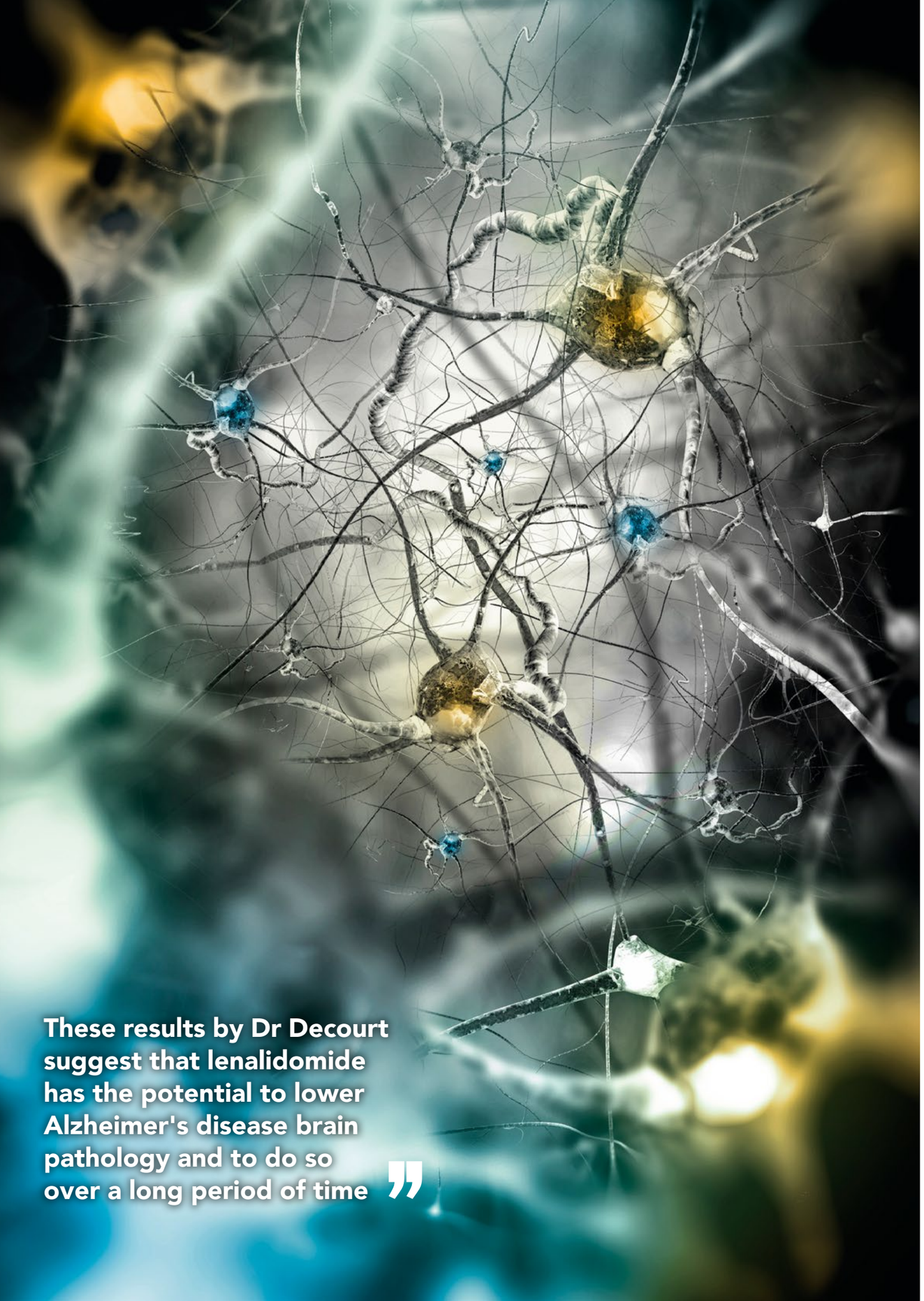


These results by Dr Decourt suggest that lenalidomide has the potential to lower Alzheimer's disease brain pathology and to do so over a long period of time”

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

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.

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 annually. 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 fibrillary 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.

INFLAMMATION IN ALZHEIMER’S

Dr Decourt and his team are studying the role of inflammation in AD, and are testing different methods to modulate brain inflammation. This is because many age-related disorders, including neurodegenerative diseases, are associated with chronic inflammation. Inflammation is a natural reaction of the body to defend itself against foreign entities (e.g., microbes), abnormal cells (e.g., cancer cells), and protein aggregates. In the case of AD, it has been shown that Aβ and amyloid plaques damage the structure and function of cells. This stimulates the immune cells located in the brain to develop an inflammatory reaction in an attempt to eliminate the cause of cell injury (Aβ and amyloid plaques) and the wounded cells and tissues. Moreover, the immune and other support cells are activated in the process and release an array of inflammatory molecules (called cytokines and chemokines), which may contribute to further cell dysfunction and neuronal death.

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

The processes regulating inflammation are complex in nature, involving a combination of cells (e.g., white blood cells such as neutrophils and macrophages) and a plethora of molecules. A key factor in this inflammation is the cytokine tumour necrosis factor-α (TNF-α).

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 for 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 *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

Figure 1

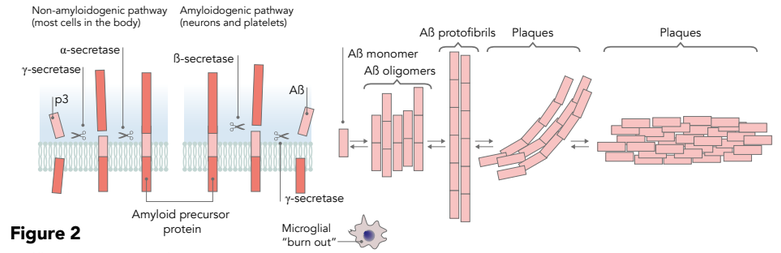
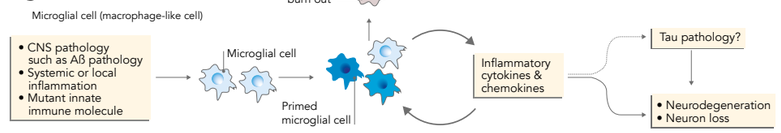
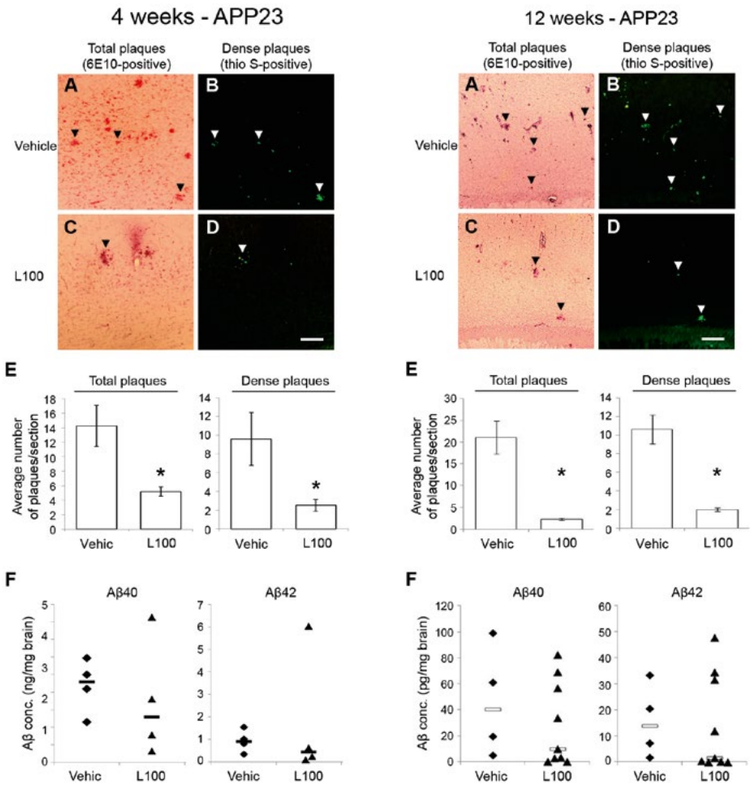


Figure 2



Aβ and TNF-α abnormalities. In relation to tangle formation, much less is known about TNF-α involvement, though recent data has suggested a connection. Consequently, some scientists have proposed to modulate TNF-α as a therapeutic intervention to slow down the progression of AD.

Further evidence of TNF-α involvement in AD comes from studies on transgenic (Tg) mice – mice genetically engineered to develop AD-like symptoms and brain pathology (i.e., plaques and tangles). More than 30 Tg AD-like mouse strains have been created to date, and most express elevated levels of TNF-α in their brain compared to healthy animals. Different methods have been tested to reduce TNF-α activity in Tg mice, which include inactivating the *TNF-α* and *TNFR1* genes, and using a large number of drugs of higher or lower TNF-α-inhibiting strength (e.g., aspirin). Most of these methods alleviated Aβ, inflammation and tau pathologies within the brains of Tg mice, and also led to improved working memory and cognition. However, to date none of the drugs has proven efficient at improving AD symptoms and pathology when tested in humans.



ANTI-CANCER DRUGS

Given the lack of efficacy of common anti-inflammatory drugs to treat AD, Dr Decourt and his team have decided to test some of the strongest TNF-α inhibitors commercially available, called immunomodulators. The first compound they investigated was thalidomide. Preclinical data showed that thalidomide reduces Aβ loads and AD-like symptoms in Tg mouse models of AD. These data seeded the development of an NIH-supported clinical trial that tested thalidomide in AD patients. However, the high rate of adverse events recorded during the trial indicated that thalidomide is not a suitable treatment for AD given the frailty of these patients.

Because of the toxicity recorded with thalidomide, Dr Decourt is now examining the therapeutic potential of the thalidomide analogue lenalidomide. This compound is also FDA-approved for blood cancer treatment and is better tolerated by cancer patients than thalidomide. 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 to levels comparable to non-transgenic mice, and lowered the brain Aβ loads. Similar results were observed following a 12-week treatment period. Interestingly, the reduction of the β-secretase protein levels was not observed until the 12-week treatment period. These results from Dr Decourt suggest that lenalidomide has the potential to lower AD brain pathology over a long period of time, by normalising the activity of enzymes responsible for the production of Aβ to non-pathological levels.

FUTURE PROMISE

These very encouraging results helped Dr Decourt and his group secure an NIH grant to take the investigations into lenalidomide further. First, the team are asking whether lenalidomide directly reduces β-secretase levels witnessed in the experiments outlined above, or whether this is mediated via a modulation of TNF-α activity in immune cells. Second, the effects of the drug are being assessed on tau pathology: there is assumed to be a link between TNF-α and tau abnormalities because tangles form in chronic inflammatory environments, but no study has assessed the potential of lenalidomide on tau tangles yet. Researchers will look at tau pathology alongside and independently of Aβ plaques in order to fully comprehend the mechanisms at play, using a combination of cell culture experiments and AD-like mice.

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

Q&A

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 Banner Health, I read a lot of 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?

That's 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 information, but only 5% of the AD cases in humans are due to genetic mutations; and, compared to cancer for example, no dog or monkey study is available at this time – we know for a fact that human and mouse metabolisms are different, particularly when it comes to drug treatment).

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 yet. 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-approved 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 timescale?

Our current project is expected to provide the answers we need for a human trial in 2019. Thus, the first tests in humans will likely not start before 2019 or 2020 and last for two to five years. Then, we need to make sure the drug works for AD by measuring AD-specific biomarkers. Thus, in the best case scenario the drug will likely not be prescribed on a large scale before 2025. Another issue is the price of the drug. Currently in the USA, the pharmaceutical company Celgene sells a 10mg pill for $500. Conducting a thorough clinical trial with this price would require $2–5M, which very few sponsors are willing to invest at this point.

Arguably most importantly, however, the team hope 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.

Detail

RESEARCH OBJECTIVES

Dr Decourt's current work focuses on understanding the underlying pathology of Alzheimer's disease and exploring possible new therapies.

FUNDING

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COLLABORATORS

- Gary D'Souza, PhD, Arizona State University-Banner Health Neurodegenerative Diseases Research Center
- Marwan N Sabbagh, MD, Director of the Alzheimer's and Memory Disorders Division at the Barrow Neurological Institute

BIO

Dr Boris Decourt is a neuroscientist focusing his translational research efforts on discovering neurological disorders' biological mechanisms and possible therapeutic interventions via the regulation of inflammatory processes. His current research targets Alzheimer's disease and associated brain pathologies. His ultimate goal is to translate his discoveries from bench to bedside.

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