Inflammation in Alzheimer's disease

Friend or foe?

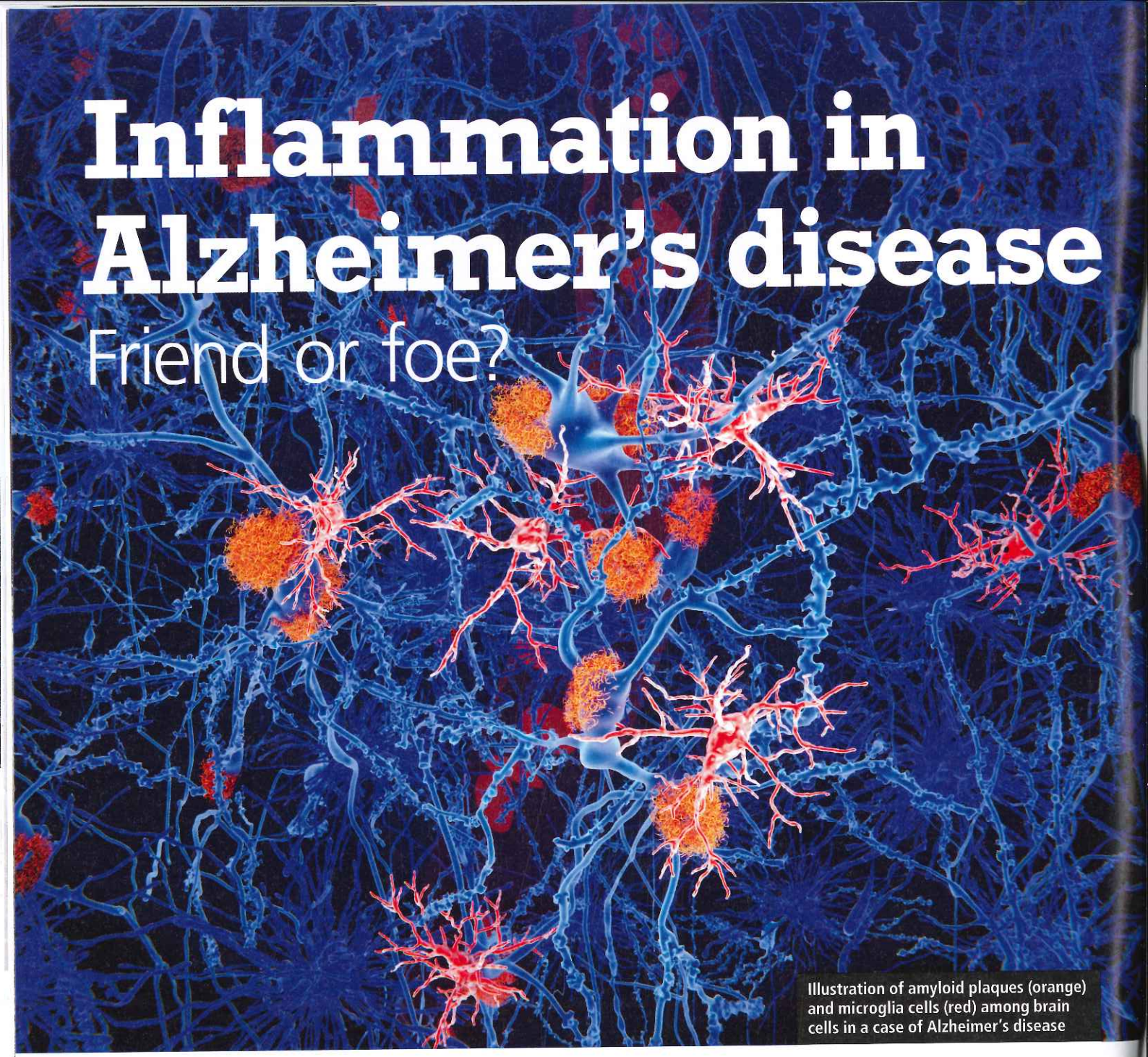


Illustration of amyloid plaques (orange) and microglia cells (red) among brain cells in a case of Alzheimer's disease

Tessa Swanton

Inflammation is an important immune response that protects us from the consequences of infection and tissue injury. How do our bodies initiate inflammatory responses, and what happens when inflammation gets out of control in brain diseases such as Alzheimer's? Neuroscience and immunology researcher Tessa Swanton explains

Exam links

AQA Cell recognition and the immune system; Nerve impulses
Edexcel A Plasma cells and macrophages; Nerve impulse transmission; The human brain
Edexcel B Response to infection; Mammalian nervous system
OCR A The primary non-specific defences against pathogens in animals
OCR B The immune system; The symptoms and possible causes of Alzheimer's disease
WJEC Eduqas The nervous system; The immune response; The brain

The brain is the most complex organ in the body. It is made up of approximately 90 billion nerve cells that form connections at junctions called **synapses**. Nerve cells communicate with each other across synapses through the transmission of electrical and chemical signals. This allows us to process both internal and external stimuli and respond to our environment. In doing so, we are able to coordinate movement,

speech, and the ability to think, make decisions, feel emotion and form memories. So when the brain is affected by disease, it can have devastating effects.

What is Alzheimer's disease?

Alzheimer's is a brain disease that is characterised by the loss of nerve cells and synapses in areas of the brain that are important for memory, such as the hippocampus. As the disease progresses, areas of the brain that are associated with thinking, language, movement and behaviour also become affected. As a result, the brain loses its ability to function properly. Patients with Alzheimer's disease develop severe memory loss, which is later accompanied by changes in mood and behaviour, and problems with decision-making, language and movement.

The term used to describe this set of symptoms is **dementia**. The severity of dementia in patients worsens with disease progression. Patients eventually become unable to carry out everyday tasks and ultimately have to rely on full-time care. Alzheimer's disease is particularly distressing for the family and friends of those affected, as patients lose their ability to recognise loved ones and remember the memories they have shared.

Terms explained

Amyloid plaques A hallmark feature of Alzheimer's disease, composed of clumps of amyloid beta protein that are deposited outside nerve cells and disrupt communication between nerve cells.

Dementia The umbrella term used to describe the common symptoms associated with Alzheimer's disease, including memory loss, mood and behavioural changes, and problems with speech and movement.

Interleukin-1 A pro-inflammatory cytokine that plays an important role in the immune response.

Neurodegeneration The progressive loss of the structure and function of nerve cells, and a defining feature of Alzheimer's disease.

Neurofibrillary tangles Aggregates of tau protein in nerve cells that accumulate in the brain of people with Alzheimer's disease and disrupt nerve cell function.

Pathogen A microorganism that can cause disease.

Sterile inflammation Inflammation that occurs in the absence of a pathogen, usually triggered by physical, chemical or metabolic stimuli.

Synapse The junction where two nerve cells meet, across which chemical and electrical signals are transmitted.

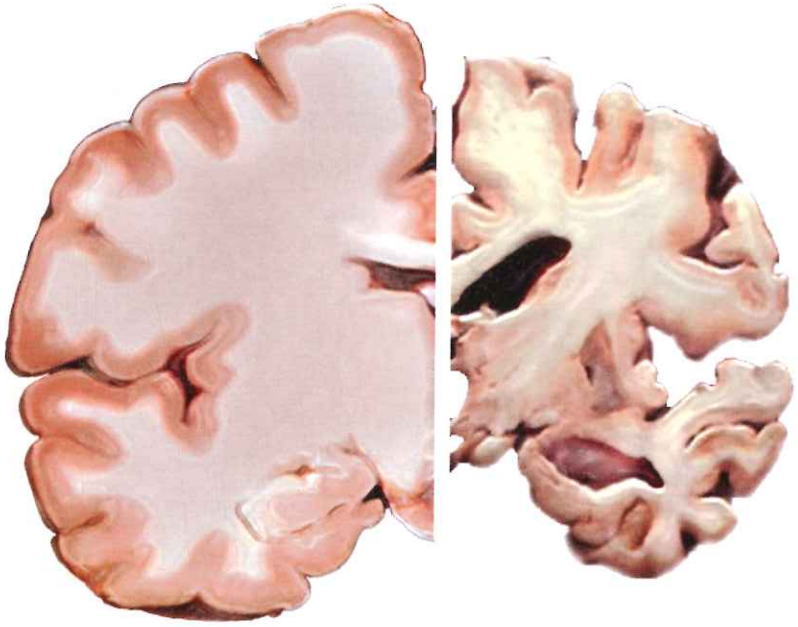


Figure 1 Section of post-mortem healthy brain **(left)** compared with a typical brain of a patient with Alzheimer's disease **(right)** at the same magnification

Alzheimer's impact

In the UK, around 500 000 people are currently diagnosed with Alzheimer's disease, with those over the age of 65 being predominantly affected. This makes Alzheimer's disease the most common cause of dementia, and this figure is expected to double over the next 25 years. Not only does Alzheimer's disease have a devastating impact on its patients and their carers, it also places a huge financial burden on health services. In the UK, one in four hospital beds are occupied by dementia patients aged over 65.

To date there is no cure for Alzheimer's disease. Current drugs treat the symptoms of the disease rather than its causes and fail to prevent its progression.

Shared activities — physical, mental, social or creative — can help patients with dementia and their carers to enjoy their time together

Box 1
The role of amyloid beta and tau in Alzheimer's disease

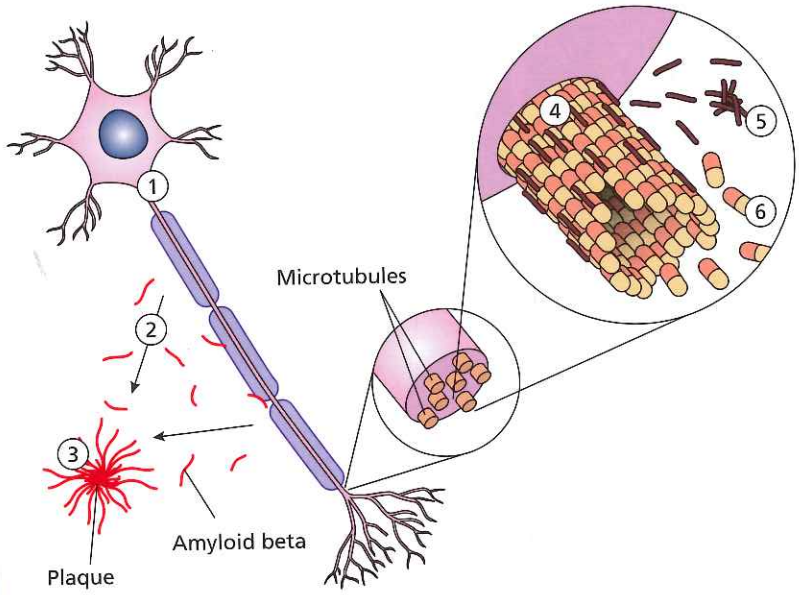


Figure 1.1

1 Amyloid beta is a fragment of a larger protein called APP that is found in healthy nerve cells.

2 In Alzheimer's disease, amyloid beta peptides are released from nerve cells and clump together into sticky plaques that are deposited outside nerve cells.

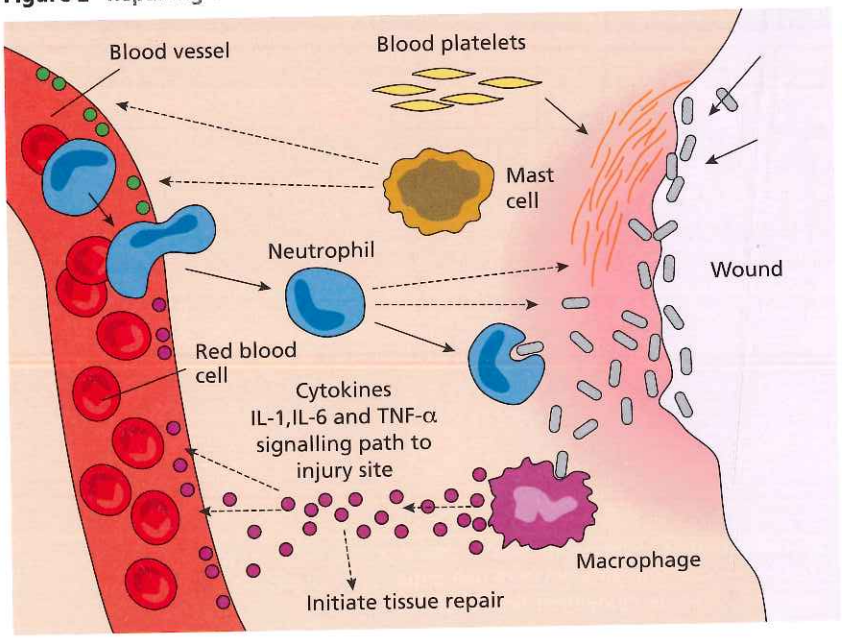
3 Amyloid beta plaques are toxic to nerve cells and synapses, promoting neurodegeneration.

4 Another protein called tau helps to maintain the structure and stability of microtubules in nerve cells. Microtubules are important for the transportation of cargo around nerve cells and maintaining cell structure.

5 In Alzheimer's disease, tau dissociates from microtubules and clumps together to form neurofibrillary tangles in nerve cells, affecting their function.

6 The microtubules also break down. Without a means of transporting matter around the cell, nerve cells eventually die.

Figure 2 Repairing a wound



This is why there is a great deal of research being undertaken to understand exactly what causes the disease, so that new disease-modifying treatments can be developed.

Key proteins

During Alzheimer's disease, nerve cells become damaged and eventually die, a process called **neurodegeneration**. Figure 1 shows a comparison between a healthy brain and a typical Alzheimer's disease brain, which weighs approximately 140 grams (10%) lighter. Scientists are not sure exactly how or why this happens, but the build-up of two key proteins — amyloid beta and tau — in the brain plays a major role.

Amyloid beta and tau have important functions in the healthy brain. However, in Alzheimer's disease, their shape changes and they clump together, forming deposits (termed **amyloid plaques** and **neurofibrillary tangles**, respectively) inside and around nerve cells. This affects the function of nerve cells and their ability to communicate (see Box 1).

The build-up of amyloid beta plaques and neurofibrillary tangles in the brain has long been considered the sole driving force for Alzheimer's disease progression. However, recent research suggests that inflammation in the brain also plays a major role. Both amyloid beta and tau can activate inflammatory processes that promote nerve cell death. The reciprocal relationship can also occur, whereby inflammatory pathways can enhance the production of amyloid beta and tau deposits in the brain. Therefore, studying brain inflammation may provide further insight into the mechanisms involved in disease progression. Such research may reveal new drug targets and allow better treatment of Alzheimer's disease.

What is inflammation?

Imagine you have cut your foot on a dirty nail. Harmful **pathogens** enter your body and your foot becomes swollen, red, warm and painful. These are 'the four pillars of inflammation', first described by the Roman Cornelius Celsus (30–38 BCE), and signs that your immune system is working properly. But why is inflammation important and how does it start?

White blood cell recruitment and phagocytosis

Immune cells have specific receptors on their surface that allow them to distinguish between self (our own cells and proteins) and non-self (foreign molecules expressed by pathogens called antigens). In the presence of a pathogen, a type of white blood cell — a mast cell — is activated. Mast cells contain granules. These granules contain inflammatory

molecules including histamine, which are released from the cell when it becomes activated. Histamine acts on specific receptors on smooth muscle cells within arterioles, causing arterioles to expand. This vasodilation increases the flow of blood to the site of injury, causing redness, heat, swelling and pain around the affected area. Increased blood flow also brings platelets and proteins including fibrin to the injured area, which interact with each other to form a clot. This creates a barrier to further pathogen entry and helps to initiate tissue repair (see Figure 2).

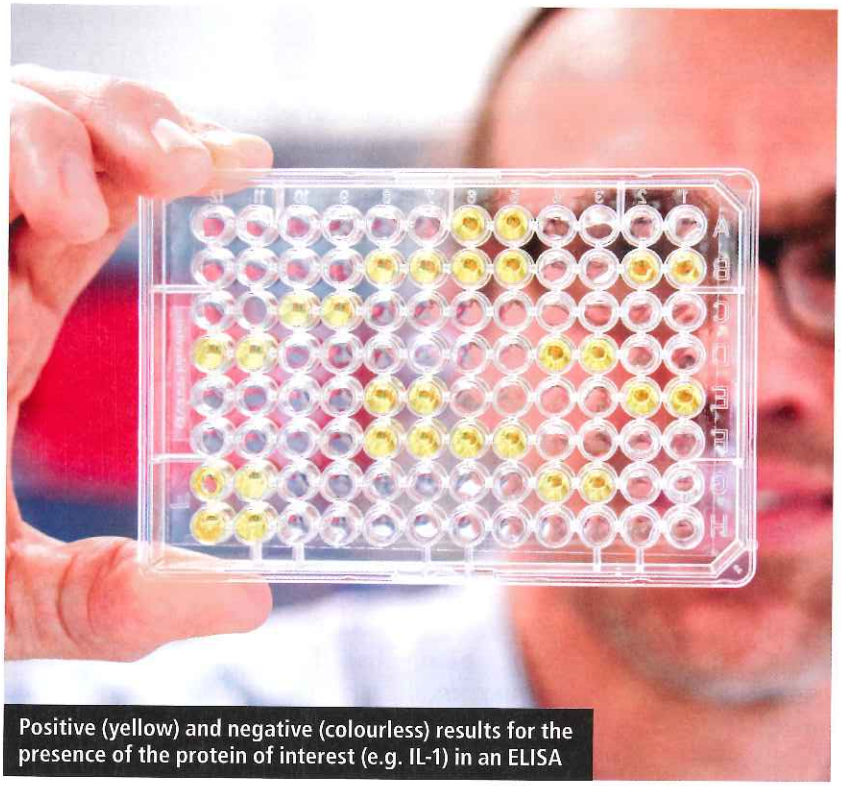
A special type of white blood cell called macrophages, which are present at the affected site, recognise the pathogen and engulf it via a process called phagocytosis. On doing so, macrophages also release inflammatory proteins called cytokines, which serve as signals for the recruitment of other immune cells, such as neutrophils, to the site of damage. The key cytokines involved in this acute inflammatory response include **interleukin-1** (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α). These pro-inflammatory cytokines orchestrate pathogen destruction and tissue repair in a number of ways. First, they enhance the expression of specific adhesion molecules, such as E-selectin, vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) on blood vessel walls. As their name suggests, adhesion molecules allow circulating neutrophils to attach to capillary walls and be recruited to the site of injury via a process called diapedesis (see Figure 2). Once at the site of infection, neutrophils phagocytose the pathogen and release toxic factors, allowing efficient destruction of the pathogen.

To summarise, inflammation is an essential part of our immune response to infection and tissue damage as it:

- creates an inhospitable environment for pathogen growth, minimising the spread of infection
- promotes the recruitment of immune cells to the site of infection that attack and destroy the pathogen
- promotes healing and tissue repair

Sterile inflammation

However, inflammation can also happen in the absence of any pathogen — **sterile inflammation**. In the same way that immune cells have receptors that recognise foreign pathogens, these receptors can also sense and react to damage-associated stimuli including asbestos, silica, and even amyloid beta. Similarly to pathogen-associated inflammation, sterile inflammation is characterised by the production of the inflammatory cytokines IL-1, IL-6 and TNF-α, and the recruitment of neutrophils and macrophages to the site of damage. If left unresolved, sterile inflammation can be highly damaging to host tissue and can contribute to the development of various diseases, including Alzheimer's.



Positive (yellow) and negative (colourless) results for the presence of the protein of interest (e.g. IL-1) in an ELISA

Inflammation in the brain

Until relatively recently, the brain was considered an immune-privileged organ. Inflammation was only thought to occur in the brain after disruption of the blood–brain barrier and the subsequent infiltration of immune cells. However, it is now clear that the brain has its own immune cells, called microglia, which can activate inflammatory pathways in the brain in response to specific pathogenic or sterile stimuli.

Microglia are the resident macrophages of the brain and play an important role in maintaining brain homeostasis. Microglia phagocytose cellular debris and produce matter that supports nerve cell growth. In Alzheimer's disease, microglia surround amyloid plaques and are thought to play a beneficial role in the early stages of the disease, phagocytosing amyloid plaques and clearing them from the brain. However, as the disease progresses, the number of amyloid plaques in the brain increases and microglia lose their ability to remove the plaques efficiently.

Continued exposure of amyloid plaques to microglia causes microglia to become more inflammatory than phagocytic. Amyloid beta promotes the production of various pro-inflammatory cytokines, including IL-1, IL-6 and TNF-α, in microglia. These cytokines damage nerve cells and cause them to die, promoting neurodegeneration and the progression of Alzheimer's disease.

Anti-inflammatory drugs: a treatment option for Alzheimer's disease?

Several epidemiological studies have identified an association between the long-term use of anti-inflammatory drugs and a reduced risk of developing Alzheimer's disease. Genetic studies have also identified mutations in inflammatory genes that are associated with an increased risk of developing Alzheimer's disease. Given the detrimental role of brain inflammation in the progression of Alzheimer's disease, could anti-inflammatory drugs be used to treat it?

Box 2 The enzyme-linked immunosorbent assay (ELISA)

ELISA is a laboratory technique that allows scientists to detect specific proteins within a sample taken, in this case, from immune cells treated with drug X.

We want to see how well drug X inhibits the production of IL-1 by these cells. If the level of IL-1 in the sample is low, this suggests that drug X is effective, and is a potential drug candidate for the treatment of Alzheimer's disease.

ELISA uses antibodies that recognise the specific protein of interest and specific enzymes that catalyse a reaction that produces a fluorescent signal in the presence of a particular substrate. The level of fluorescence after substrate addition is directly proportional to the amount of protein, in this case IL-1, in that particular sample.

1 A well in an ELISA plate is coated with capture antibody specific for the protein of interest (IL-1) overnight. The capture antibody sticks to the bottom of the plate.

2 In the morning, the remaining space on the plate is blocked with an unrelated protein to minimise binding of the antibody to other proteins when our sample is added (non-specific binding).

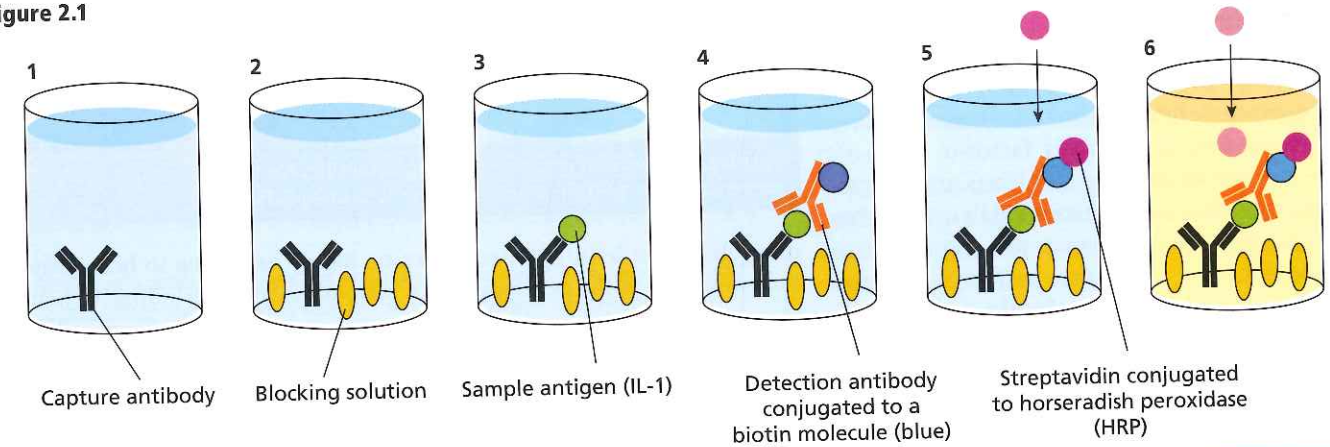
3 The sample to be tested is then added to the plate, and the capture antibody will bind to the protein of interest (IL-1) in the sample.

4 A detection antibody, also specific for the protein of interest, conjugated to a biotin molecule is then added.

5 Streptavidin-horseradish peroxidase is then added. Streptavidin binds tightly to biotin on the detection antibody and is also conjugated to the enzyme horseradish peroxidase (HRP).

6 When a specific substrate is added (pink in Figure 3.1), HRP breaks down the substrate into a fluorescent product. The level of fluorescence emitted is directly proportional to the concentration of the protein of interest in the sample.

Figure 2.1



Our research team has recently shown that a specific group of anti-inflammatory drugs, called fenamate NSAIDs (non-steroidal anti-inflammatory drugs), prevent IL-1 production in immune cells. Fenamate NSAIDs had a beneficial effect when given to mice genetically engineered to exhibit symptoms of Alzheimer's disease. The drugs improved memory and learning, and reduced brain inflammation in these mice.

Our research team is now working on developing new drugs that inhibit IL-1 production, with even better activity than fenamate NSAIDs. Mouse microglia are exposed to inflammatory stimuli known to cause IL-1 production, along with the drug of interest. One way we can see whether or not drugs are effective at inhibiting IL-1 production in immune cells is through a technique called an enzyme-linked immunosorbent assay (ELISA). This technique helps researchers determine the concentration of a specific protein, in this case IL-1, in a cell or tissue sample (see Box 2).

ELISA is useful for drug discovery research projects like ours as it helps to identify drug candidates for further preclinical (cell and animal) and clinical (human) studies. Large, high-throughput drug screens can assess hundreds of drugs for their ability to reduce the production of IL-1 in immune cells. The most effective can then be optimised further, before their therapeutic effect is later assessed in animal models of Alzheimer's disease. If drugs prove to be beneficial in animal models, their ability to stop or delay disease progression in patients with Alzheimer's disease can then be evaluated in clinical trials.

It is the mission of Alzheimer's Research UK to bring about the first life-changing treatment for dementia by 2025. Alzheimer's is a complex disease, but through research projects like ours, hopefully we will be able to tackle the disease and provide better treatment for dementia patients.

Things to do

- Become an Alzheimer's Society volunteer: **www.alzheimers.org.uk/get-involved/volunteering**
- Become a dementia friend: **www.dementiafriends.org.uk**

Tessa Swanton is a neuroscience and immunology researcher at The University of Manchester.

Key points

- Inflammation is an essential immune response that protects us from infection and tissue damage.
- If left unchecked, inflammation can actually be damaging and can contribute to diseases such as Alzheimer's disease.
- Treatment options for Alzheimer's disease are currently limited and fail to halt progression of the disease.
- Given the role of inflammation in Alzheimer's disease, treating patients with anti-inflammatory drugs could be beneficial.