DEMENTIA IN DETAIL:
Amyloid, tau and Alzheimer's disease
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GLOSSARY

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<tr>
<td>Alzheimer’s disease</td>
<td>A physical disease that causes symptoms such as memory loss and confusion. The leading cause of dementia.</td>
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<td>Amyloid beta</td>
<td>A type of protein that sticks together to form sticky clumps, or plaques, in Alzheimer’s disease which damage our brain cells.</td>
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<td>Amyloid cascade hypothesis</td>
<td>The theory that amyloid beta build-up in the brain triggers changes that lead to the symptoms of Alzheimer’s.</td>
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<td>Amyloid precursor protein</td>
<td>A long protein, which is cut up into smaller segments to be used by the body. One of these is amyloid beta.</td>
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<td>DNA</td>
<td>Our cell’s instructions for making proteins.</td>
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<td>Enzyme</td>
<td>A special protein that helps processes happen in our body.</td>
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<td>Fibril</td>
<td>A long thread of a protein, such as amyloid beta.</td>
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<tr>
<td>Nerve cell</td>
<td>Cells that send signals throughout our brain and body.</td>
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<tr>
<td>Oligomer</td>
<td>A small clump of a protein, such as amyloid beta.</td>
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<tr>
<td>Protofibril</td>
<td>A short thread of a protein, such as amyloid beta.</td>
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<tr>
<td>Tau</td>
<td>A protein that provides support for our cells. In Alzheimer’s, these can detach from our cell’s scaffolding and form toxic tangles.</td>
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Research suggests that Alzheimer’s disease is linked to the build-up of two proteins in the brain, called amyloid and tau. These proteins are associated with damage to the cells in our brains, including nerve cells. Nerve cells send messages throughout the body.

Amyloid forms plaques between all types of brain cells, and tau forms tangles inside nerve cells. In Alzheimer’s disease, damage spreads throughout the brain, affecting regions involved in important functions such as memory, thinking, and movement.

Alzheimer’s symptoms depend on where in the brain our nerve cells are damaged. As damage spreads to different regions of the brain, more complex symptoms can develop, and people are less able to do things like eat and move around.

Although we currently don’t have a full picture of what causes the proteins to build up, we know that this can start to occur decades before symptoms like memory problems appear.
WHAT IS A PROTEIN?

Proteins are molecules that form the building blocks of life. There are thousands of different types in your body, and these have a variety of roles, including transporting things around the body, providing structural support within cells and maintaining our tissues and organs. Your DNA is an instruction manual for all the proteins that your body builds.

Proteins are made up of long chains of smaller units called amino acids. There are 20 different amino acids. The combination and order of amino acids determines the 3D shape a protein will fold into - this shape determines how it behaves and what role it plays in our body.

The proteins we eat are broken down in our guts into amino acids, which then get made back into different proteins by our cells. So, the protein in our diet is not the same as the amyloid and tau in our brains.
WHAT CAN GO WRONG WITH PROTEINS?

Proteins sometimes misfold into an abnormal shape. This affects how they work and is commonly found in the brains of people with degenerative diseases like Alzheimer’s, Huntington’s and Parkinson’s.

Proteins can misfold because of:

- **A DNA mutation** that causes a change in a protein’s amino acid sequence.
- **A missing enzyme** required for the protein to fold correctly. An enzyme is a type of protein that helps processes take place.
- **A build-up of damage** to the healthy protein that causes it to change shape.

This misfolding can result in a number of issues, including:

- The protein stops working properly.
- The protein becomes ‘sticky’, and builds up, disrupting the cells and blood vessels nearby.

Image credit: Prof Tara Spires-Jones
**WHAT IS AMYLOID?**

Amyloid precursor protein (APP) is a protein that is found in healthy bodies and brains. It is thought to play a role in the normal development of nerve cells.

A misfolded version of amyloid called amyloid-beta (Aβ) is found in the brains of people with Alzheimer’s disease. Aβ is formed when APP is chopped into smaller, sticky proteins that clump together and form plaques. These are not related to the plaque that can build up on teeth. Plaques build up between nerve cells in the brain and are a hallmark feature of Alzheimer’s disease. In healthy brains, the smaller proteins that APP is chopped into are not sticky.

**Stages of amyloid plaque formation**

1. **Amyloid precursor protein (APP)**
2. **Enzyme cuts APP into smaller pieces**
3. **Misfolded amyloid-beta proteins**
4. **A few proteins clump together to form a toxic oligomer**
5. **As the protofibril continues to grow, it forms an amyloid fibril**
6. **As proteins keep joining the oligomer, it becomes a toxic protofibril**
7. **Fibrils join together to form an amyloid plaque**

*Image credit: Prof Tammaryn Lashley*
HOW DOES AMYLOID AFFECT CELLS IN ALZHEIMER’S DISEASE?

It is not currently fully understood how amyloid-beta affects cells. Researchers are working hard to find out more but some theories suggest:

• **Aβ plaques are directly toxic to nerve cells.** They damage the cell membranes, disrupting their ability to transmit messages and maintain normal function.

• **Aβ plaques lead to problems with the tau protein in what’s known as the amyloid cascade hypothesis.** Read more [here](#).

• Smaller clumps of Aβ called **oligomers** damage the membrane surrounding nerve cells. The cell membrane is a vital part of a nerve cell, and damage to it can affect how the cells conduct signals.

The precise link between Aβ plaques and Alzheimer’s disease is unclear. Not everyone with high levels of Aβ plaques has Alzheimer’s symptoms, and some people with symptoms have low levels of Aβ.

Image credit: Prof Nigel Hooper
WHAT IS TAU?

All our cells contain an internal scaffolding made of many specialist proteins. **Tau is an important protein that adds structural support inside our brain cells.**

Changes in the way tau behaves have been found in many brain diseases, including Alzheimer’s disease, frontotemporal dementia, and corticobasal degeneration.

In Alzheimer’s disease, too many molecules stick to tau, which changes its shape and causes it to detach from the nerve cell’s scaffolding and no longer provide structural support. This detached tau is more likely to misfold and stick together to form tau tangles.

Without tau’s support, the cell’s scaffolding disintegrates, which interferes with the nerve cell’s ability to function properly. So, tau tangles are considered toxic.

In contrast with Aβ plaques, the link between tau tangles and problems with thinking and memory is much clearer and stronger.

Image credit: Dr Grace Hallinan
In Alzheimer's, tau proteins disconnect from nerve cell scaffolding, which supports the cell’s structure. This happens because damaged cells often have more molecules, such as phosphate, floating around. These molecules interact with tau, changing its shape and making it no longer fit into the scaffolding.

- Tau detaches from cell scaffolding
- Too many phosphate molecules bind to tau and change its shape
- Tau builds up and forms toxic tangles
- Cell scaffolding becomes less stable
- Scaffolding does not work properly
- Cell death
AMYLOID AND TAU: A DANGEROUS PAIR?

The first successful treatments to target the underlying causes of Alzheimer’s, lecanemab and donanemab, slow the disease by removing amyloid from the brain. These aim to delay the onset of dementia symptoms, allowing people to live independently for longer. They also provide support for theories suggesting that amyloid build-up contributes to Alzheimer’s.

If a disease can be slowed, then it can be stopped. There is now more hope than ever that a cure will become a reality for future generations.

However, current treatments don’t stop the disease in its tracks; symptoms will still get worse over time. This suggests that there may be something other than just the presence of Aβ plaques or tau tangles responsible for ongoing damage to the brain.

Research suggests that interactions between amyloid and tau may hold the key to their toxicity. So, future treatments that target these interactions may prove more effective.

Find out more about lecanemab [here](#) and donanemab [here](#).
Evidence suggests:

- **Amyloid-beta build-up** may occur very early in the **disease process**, triggering downstream effects, including tau changes described earlier, in the **amyloid cascade hypothesis**.

- **Smaller forms of amyloid-beta and tau** may work together to damage the connections between nerve cells (synapses), independent of plaques and tangles.

- **Amyloid-beta and tau** may work together to damage **mitochondria**, which provide cells with energy to complete essential functions.

- **Amyloid-beta and tau** may interact with glial cells, including **astrocytes**, which provide the brain with structural support, and **microglia**, which act as a specialised immune system to protect the brain from damage.
WHY IS UNDERSTANDING AMYLOID AND TAU IMPORTANT?

Methods to detect amyloid and tau in people will allow for earlier and more accurate diagnosis of Alzheimer’s.

Spinal fluid (CSF) tests and brain imaging methods such as PET scans are now established methods of imaging amyloid, and show promise in imaging tau, too. Blood tests also show promise in detecting the presence of these proteins at an early stage. And offer a quicker, less invasive way of diagnosing dementia.

Understanding how these proteins lead to the symptoms of Alzheimer’s disease will also help us to develop more effective treatments.
Alzheimer’s Research UK has funded crucial research that helps researchers understand amyloid and tau. This includes funding Prof Sir John Hardy (pictured) after he first suggested the highly influential **amyloid cascade hypothesis**. This was the first theory explaining how amyloid triggers Alzheimer’s disease and led many pharmaceutical (drug) companies to develop drugs that attempt to clear amyloid from the brain.

Recently, we awarded a Research Fellowship to Dr Amy Pooler, who discovered vital clues about how tau spreads from cell to cell. This work has had widespread impact throughout the scientific community and is bringing researchers closer to developing treatments to stop the protein's abnormal behaviour, keeping nerve cells healthier for longer.

Find out more about dementia, including treatments and reducing your risk on our website or by contacting the Dementia Research Infoline:

- **infoline@alzheimersresearchuk.org**
- **0300 111 5 111**

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