



## Tau FAQs

### What is tau?

Tau protein is a critical protein for the normal function of your brain cells. It has a very important role in stabilising the structure of the brain cell, and it also plays a role in energy and transport and how your cells talk to one another in the brain.

### What role does tau play in Alzheimer's disease?

As we age, our cells produce normal waste products which are usually cleared by the cell, but less quickly as we grow older. These waste products, such as lipofuscin, can capture normal free tau proteins, causing them to misfold and bind to the waste products. This misfolding and change in their shape initiates a cascade response, where more and more free tau proteins are attracted to them in the same misfolded structure. The misfolded tau aggregates and forms a large insoluble stack which can no longer be cleared by the cell. At some point this process rapidly accelerates and these insoluble tau stacks pass between cells and clump to form tangles. A build up of tangles causes the cell to swell and burst. Once the brain cell is gone, there is no repairing or regaining it.

### What are tau tangles or neurofibrillary tangles?

Tau tangles are formed when aggregated and misfolded tau stacks clump together. They ultimately cause the irreversible cell damage in the brain associated with clinical dementia.

### Why is tau a target for drug development?

We understand that tau has a central role in Alzheimer's disease pathology. In 1991, Professor Heiko Braak of Germany reported a tool that directly measured the development of Alzheimer's related pathology in patients. Braak graded the presence, distribution, and density of tau tangles in the brain and defined six distinct stages of Alzheimer's progression (Braak stages). Studies have since confirmed that this spread of tau pathology correlates strongly with the severity of disease and its progression. Therefore, by targeting this process, it is hoped the damage caused to brain cells can be avoided. Tau pathology begins decades before any symptoms of dementia are seen. We estimate that approximately 50% of the over 45 population may have some form of tau pathology in the brain. Given the prevalence of Alzheimer's disease and the large unmet medical need, tau is an important target for drug development.



### **How can tau pathology be measured in people?**

It is currently quite difficult to accurately measure tau pathology in people, but specialist brain PET scans enable this. In future, it is hoped that the development of new blood-based biomarkers will allow physicians to measure tau pathology quickly and accurately using a simple blood test.

### **When were tau tangles first identified and by whom?**

The first published description of 'neurofibrillary tangles' was in 1906 by Dr Alois Alzheimer, a German neurologist. He presented the case of a female patient with mysterious tangles in the brain at a scientific meeting of psychiatrists in München. Alzheimer considered this 'presenile dementia' to be a new type of psychiatric disorder characterized by the presence of neurofibrillary tangles. It is this disease which would later be named Alzheimer's disease as the same tangles came to be identified in older cases with dementia as well.

### **When was it discovered that the tangles were made of tau protein?**

In 1985, PhD student Claude Wischik, while at the University of Cambridge, set out to identify the structure of the paired helical filaments (PHFs) which make up the tangles associated with Alzheimer's disease. In 1988, he published his discovery that the PHFs are composed of tau protein. Until then, a number of proteins had been identified as bound up in tangle structures within neurons, but it had not been possible to determine which were part of the core structure of the PHF. The body of work published in 1988 defined for the first time the core structure of the PHF and showed that a short fragment from the microtubule-binding domain of tau was a structural building-block of the PHF. Later work showed that this fragment of tau accounted for at least 90% of the protein mass of the PHF.