Alzheimer’s Disease and Tau as a New Therapeutic Target

01 | What is Alzheimer’s disease?

47.5 million people worldwide live with dementia. Alzheimer’s disease is the most common cause, contributing to 60–70% of cases.

- Alzheimer’s disease (AD) damages and destroys neurons, cells that enable the flow of information and thoughts in parts of the brain involved in cognitive function.
- This causes loss of memory and reduction in reasoning.
- As AD spreads to other areas of the brain, it also affects spatial awareness and eventually basic bodily functions.

02 | Defining features of Alzheimer’s disease

Two defining features of AD are the build-up of tangles of tau protein inside neurons and amyloid plaques outside them.

Amyloid

- Amyloid plaques are one of the hallmarks of AD and believed to interfere with communication between neurons, contributing to cell death.
- They are made up of aggregated fragments of a protein called beta-amyloid, which is released following the breakdown of a larger protein (amyloid precursor protein).
- Historically, most AD research and development has focused on targeting the prevention or removal of amyloid plaques.

Development of amyloid plaques:

<table>
<thead>
<tr>
<th>APP</th>
<th>Cell membrane</th>
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<tbody>
<tr>
<td>BETA-SECRETASE</td>
<td>Cell Surface</td>
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<tr>
<td>GAMMA-SECRETASE</td>
<td>Inside Cell</td>
</tr>
<tr>
<td>FIBRILS</td>
<td>Oligomers</td>
</tr>
<tr>
<td>Oligomers</td>
<td>Amyloid Plaque</td>
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</tbody>
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Tau

- In AD, tau proteins abnormally aggregate inside neurons in the brain, leading to the formation of tau tangles.
- The increase in tau tangles eventually overpowers the normal functioning of the affected neuron and results in its death.

Development of tau tangles:

<table>
<thead>
<tr>
<th>Cell membrane</th>
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<tbody>
<tr>
<td>TAU TANGLE</td>
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<tr>
<td>TAU MOLECULES STABILISING MICROTUBULE</td>
</tr>
<tr>
<td>WITHOUT TAU, MICROTUBULE DISINTEGRATES</td>
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**The tau tangle pathway**

A growing body of evidence supports the tau tangle pathway as one of the main drivers of AD. A healthy neuron is supported internally by a ‘skeleton’ of microtubules that transport nutrients and help maintain the axons (lengthy projections of neurons) that are crucial for communication across the brain. Tau proteins contribute to the stability of these microtubules. In a neuron affected by AD, tau proteins are unable to fulfil this function and steadily accumulate within the neuron, forming tangles. The microtubules also begin to disintegrate interfering with neuron to neuron communication. Once initiated, the process spreads into previously healthy neurons, first in the area of the brain critical for memory, and then to other areas.

**Inhibition of tau tangle pathway as a potential therapy**

The inhibition and reduction of tau tangles in the brain is a potential focus for AD therapies. Tau tangles first appear some 20 years before AD symptoms are apparent. Highly specialized brain imaging is now being used to show tau tangles in the brain. There are well-established correlations between the spread of tau pathology, resulting progressive destruction of neurons and extent of the clinical symptoms of AD in terms of the severity of cognitive impairment. An AD treatment that can effectively halt or delay the progression of the disease is urgently needed. Tau-based treatments for AD have thus become of increasing interest as this new target offers a different therapeutic approach, providing hope for the future.

**References**