Alzheimer’s disease (AD) is the most common form of dementia. AD is a terminal, progressive disease with no effective treatments that slow or stop its progression. Alzheimer’s disease is diagnosed with neurophsycological testing, of which there are several types (Karttunen et al., 2011; Harrison 2013). The first symptoms of AD are usually mild-cognitive impairments such as language difficulties, attention deficits and memory impairments especially regarding the formation of new memories (Price et al., 1993; Arnaiz and Almkvist, 2003). However, recent studies suggest that the mild-cognitive deficits in early or preclinical AD may be more widespread in nature (Salmon, 2012) and also associated with behavioural symptoms (Karttunen et al., 2011). In addition, not all people that present with mild-cognitive impairments will progress to a diagnosis of AD (Arnaiz and Almkvist, 2003; Robert et al., 2006; Klekociuk and Summers; 2012). Ongoing research at the Wicking Dementia Research and Education Centre is currently investigating whether we can better predict which patients with mild-cognitive impairment will progress to a diagnosis of AD. As AD progresses cognitive impairments increase; language skills (including speech, reading and writing) and executive function (planning/judgement) deteriorate, yet long-term memory (the oldest memories) remains intact until the very end-stages of disease (Carlesime and Oscar-Berman, 1992; Price et al., 1993). Eventually in the late stages of AD long-term memories will also be lost, motor skills are impaired, communication becomes difficult and other behavioural symptoms occur, most commonly agitation, anxiety and irritability (Price et al., 1993; Mega et al., 1996; Karttunen et al., 2011). AD patients will become less independent as the disease progresses over time requiring increasing care, the end stages of AD commonly spent bedridden and incontinence and dysphagia (difficulty swallowing) are common.

The pathological hallmarks of AD include β-amyloid (Aβ) plaques, neurofibrillary tangles (NFTs), dystrophic neurites and neuropil threads. All of these pathological hallmarks involve abnormal insoluble protein aggregates that have the capacity to disturb normal cellular functioning (Woodhouse et al., 2006). Plaques are comprised of Aβ protein, which forms insoluble fibrils that aggregate masses in the extracellular space. Neurofibrillary tangles are principally comprised of altered tau proteins that occur in the cell body of specific subsets of neurons in the cortex and hippocampus. Similarly, neuropil threads are also accumulations of abnormal tau proteins that principally occur in the cellular processes (dendrites) of NFT-bearing nerve cells (Braak et al., 1996). Dystrophic neurites are aberrantly shaped neuronal processes, which are specifically associated with Aβ plaques that contain aberrant accumulations of cytoskeletal proteins (that make up the skeleton of the cell) and cytoskeletal-associated proteins. However, there is disagreement within the AD literature as to whether it is Aβ plaques, soluble Aβ or NFTs that are the primary causative agent of AD. AD-associated pathology appears first in the limbic and basal frontal, temporal and occipital cortices and subsequently spreads to the remaining areas of the cerebral cortex (Braak and Braak, 1991). This burden of pathology increases as AD progresses, eventually resulting in substantial brain atrophy, which is at least partially due to overt neuronal degeneration and death. The clinical symptoms of AD are most likely due to the loss of connections (synapses) between neurons and neuronal death.
There are presently no effective drug treatments to halt or slow the progression of AD or to efficiently decrease the symptoms of AD (Parnetti et al., 1997). The therapeutic agents most commonly used for AD are cholinesterase inhibitors, which enhance cholinergic neurotransmission (Brion, 1996; Brodaty et al., 2001) and N-methyl-D-aspartate (NMDA) glutamate receptor antagonists (Livingston and Katona, 2004). However, both of these therapeutics only decrease the clinical symptoms of AD in subset of patients, and then this is usually only temporary, as these therapeutics do not affect disease progression (Parnetti et al., 1997). Thus, there is dire need for effective therapeutic interventions that either slow or stop the progression of AD. To develop new efficient therapeutic agents for AD we need to better understand what causes AD and how the disease progresses, thus, basic research on the mechanisms involved in AD are highly important. There are a range of strategies being investigated for the development of new AD therapeutics that include but aren’t limited to: anti-inflammatory drugs, dietary supplements and antioxidants, cytoskeletal stabilising drugs, drugs that modify the production of Aβ, Aβ aggregation inhibitors, increasing Aβ clearance from the brain, drugs that alter the regulation of genes, the connections between nerve cells and the activity of nerve cells. As the number of promising therapeutics in animal models of AD that have translated into successful clinical trials are very few, there is an increasing focus on developing combination therapies that incorporate multiple drugs acting via different pathways for the treatment of AD (http://www.alzforum.org/new/detail.asp?id=3517),

It should also be noted that another hurdle in finding an effective therapeutic for AD is the accurate diagnosis of AD early in disease. It is unlikely that therapeutics will be very effective if they are applied late in AD, after many neurons have already died. The successful application of therapeutics in clinical settings would likely need to occur early in the disease process before substantial neuronal degeneration and death has occurred. The accurate diagnosis of preclinical or early AD cases prior to the clinical diagnosis of AD utilising a combined biomarker/imaging approach may soon be possible (Borroni et al., 2007; de Leon et al., 2007; Bateman et al., 2012) and this represents another important area of ongoing AD research.

If you would like to learn more about dementia and Alzheimer’s disease, including symptoms, risk factors, pathology, disease progression, dementia care and management, and future research pathways, you can access the Wicking Dementia and Research Education Centre’s free Massive Open Online Course (MOOC) at http://www.utas.edu.au/wicking/wca/mooc.
References


