The Future of Alzheimer’s
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Introduction
Alzheimer’s disease (AD) is the most common form of dementia but despite its prevalence the disease mechanisms are poorly understood and treatments far from effective. Since more than 1 million people are expected to be affected by 2050 in the UK, this debilitating disease is likely to play a large part in our future careers (Graph 1).

What happens in Alzheimer’s?
Physiological changes in Alzheimer’s
Typically, AD has the following characteristics:
1. Atrophy in the neocortex and hippocampus
2. Decreased matter in the gyri, so enlarged sulci
3. β-Amyloid (Aβ) plaques
4. Neurofibrillary tangles

3 and 4 above are subject to intensive investigation and are discussed in more detail below.

Amyloid plaques
Amyloid plaques form when amyloid precursor protein (APP) is cleaved by a particular pathway (there are two). The enzymes involved in this pathway are (see Fig. 2)1

1. β-secretase
g. γ-secretase

These enzymes produce oligomers of Aβ. If these consist of Aβ-42 tiny fibril-form and aggregate to produce the amyloid plaques.

Neurofibrillary tangles
These originate from a protein called tau, which is important in microtubule assembly. Due to enzyme over-activity, tau is hyperphosphorylated, which is insoluble and aggregates to form tangles (see Fig. 1)2

The genetic cause of Alzheimer’s
Chromosomal anomalies/mutations causing AD have been found on chromosomes 21, 14 and 1.

These errors are primarily in the APP gene (c21) and usually increase Aβ-42 levels, leading to Aβ plaque formation.

However, the majority of AD cases result from old-age dementia rather than chromosomal anomalies/mutations. Several ‘vulnerability genes’ have been identified as risk factors for this type of Alzheimer’s2

The main ‘vulnerability’ gene is the APOE gene. Three common alleles of this gene exist. APOE-ε4 is the allele associated with AD. It is thought to increase the deposition of Aβ, and so result in plaque formation2

Other forms of treatment
Infrared light: Firing infrared light into the brain is thought to stimulate repair of brain cells (see Fig. 5). This therefore slows the progression of Alzheimer’s and is currently undergoing clinical trials.

Leptin: This hormone inhibits hunger and counteracts neuropoietic Y to prevent over-eating. High levels have been shown to reduce extracellular Aβ and tau phosphorylation.

Cognitive stimulation: This aims to stimulate and engage patients, thereby helping restore memory function and sense of identity.

Conclusion
Knowledge of AD is rapidly evolving due to new imaging technology and innovative pharmacological interventions.

Current focus on the amyloid hypothesis needs further research in order to be accepted by the scientific community. The high profile of the infrared ‘helmet’ in the media offers hope for maintaining cognitive skills.

Many avenues are being explored but as yet none have offered the ‘wonder cure’ for AD.

How is Alzheimer’s diagnosed?
Diagnosis of AD is based on:
1. Progressive impairment of memory
2. Decline in one other cognitive domain
3. Changes in personality

Diagnostic stages:
1. Medical history
2. Physical examination
3. Neuropsychological testing
4. Medical Imaging

Current imaging techniques:
SPECT: This measures blood flow in the brain. In patients with Alzheimer’s it shows bilateral hypometabolism1.

PET Scans: Use of FDG (flurodeoxyglucose) PET scan can diagnose presymptomatic AD approximately two years before full manifestation (see Fig. 3)1,6

Future techniques:
Amyloid Imaging: Used for detection of Aβ in AD. A new agent (PIB) is used in conjunction with a PET scan. This binds to Aβ and hence can measure amounts of Aβ (Fig. 4)7

DTI: Diffusion Tensor Imaging: This measures the random motion of water within the brain and detects changes in the white matter of the brain. It has been shown that the health of the brain is better predicted by a DTI scan compared to a traditional MRI scan2

What interventions are available?
The pharmacological approach
Current treatments only address the symptoms rather than causes of AD, demonstrating our poor understanding of the disease. Currently approved drugs include:

1.Donepezil
2. Galantamine
3. Rivastigmine
4. Tacrine
5. Memantine

These are acetyl cholinesterase inhibitors which improve cognitive function within 6-18 months.

A methyl-d-aspartate antagonist - reduces neuronal excitotoxicity.

Systematic reviews and economic evaluation studies highlight the high cost and limited effect of these drugs. As a result NICE guidelines do not recommend memantine for moderate to severe AD patients.

Much hope is being placed on new research addressing the causative mechanisms of the disease.

Targeting β-amyloid protein
New research aimed at the APP pathway tries to inhibit enzymes responsible for plaque formation. The enzymes involved are β- and γ-secretases. Both β inhibitors (e.g. BACE, aspartic acid protease inhibitors) and γ inhibitors (e.g. LY450189 from Eli Lilly) are in phase three clinical trials.

It has also been suggested that antibodies (via passive or active immunity) can be used to clear the Aβ from the CNS, thus reducing plaque formation.

Targeting neurofibrillary tangles
Another area of research is aiming to prevent tau aggregation, thus reducing tangle formation. Methylene blue works in this way and has progressed to phase 3 clinical trials, and has thus far shown promising results.

References
5. 2050
6. 'The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer’s disease’

Figure 1. The current and predicted number of Alzheimer’s patients.

Figure 2. The formation of amyloid plaques. The two enzymes depicted are β-secretase and γ-secretase.

Figure 3. A neurofibrillary tangle.

Figure 4. Comparison of a PET (with PIB) scan of a control (left) and an AD patient (right). This shows there is more Aβ in the AD patient than the control.

Figure 5. The equipment used to fire infrared light into the brain to stimulate brain cell repair.

Table 1. The equipment used to fire infrared light into the brain to stimulate brain cell repair.