Although a highly effective drug has not yet been approved for the treatment of Alzheimer’s disease, pivotal advances were made in 2014, leading to substantial knowledge about therapeutic targets and early stages of disease.

Two phase 3 trials of anti-amyloid-β monoclonal antibodies\(^1\,^2\) did not show significant benefits in cognitive or functional primary outcomes; however, they revealed insights into the disease course and suggested improvements in trial methodology. Bapineuzumab had no effect on cognition, while showing minimal effects on biomarkers, including a slight decrease in accumulation of fibrillar amyloid only in individuals who carried the APOE4 allele and a slight lowering of CSF phospho-tau.\(^1\) Solanezumab bound significant amounts of soluble amyloid-β, its biomarker of target engagement, but did not show significant benefits in the primary cognitive outcome.\(^2\) However, there were benefits in secondary outcome measures of cognition only in patients with mild dementia, but not in those with moderate dementia, suggesting that earlier stages of disease are more amenable to therapeutic benefits. Similarly, in a phase 2 study of crenezumab,\(^3\) an antibody which also targets soluble amyloid β in addition to aggregated forms, cognitive benefit was detected only in patients with mild Alzheimer’s disease and at the highest doses of crenezumab used in the study.

Several monoclonal antibodies, including solanezumab, gantenerumab, and crenezumab, are in late-stage clinical development in trials of populations at early disease stages. Another disease-modifying approach involves β-secretase inhibitors, designed to block the production of amyloid β, which are now being tested in phase 2 and phase 3 clinical trials.\(^4\) These studies are bolstered by target engagements of more than 80% lowering of amyloid β production.\(^4\) Together, these clinical trials suggest that the magnitude of target engagement and stage of disease are crucial, and provide tantalising evidence that these disease-modifying approaches could be nearing confirmation.

Several prevention trials have launched to test prevention in dominantly inherited Alzheimer’s disease and in people thought to be at high risk of Alzheimer’s disease due to the presence of fibrillar amyloid deposits in the brain. The Alzheimer’s Prevention Initiative (API) Colombian trial and the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease trial (A4 trial) launched in the past year,\(^7\) and the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) prevention trial continued from the year before. In 2014, three new prevention efforts were announced. The API announced a future prevention trial in APOE4 homozygous participants. The DIAN-TU trial platform announced the next stage to prevent cognitive decline in a platform prevention trial of the DIAN-TU Adaptive Prevention Trial (DIAN-TU APT),\(^8\) and the European Innovative Medicines Initiative (IMI) announced the European Prevention of Alzheimer’s Disease study, a cohort study to initiate adaptive prevention trials.

In support of these novel approaches to treat or prevent Alzheimer’s disease, there has been rapid development of trial methodology, biomarkers, and cognitive measurements. The specialty continues to move into the investigation of early disease stages, aiming to treat before symptoms manifest. On the basis of trial results showing that one in four trial participants did not have cerebral amyloidosis,\(^4\,^5\) biomarkers are playing an ever more important part in the selection of participants, through screening for the presence of cerebral amyloid by PET scan and CSF measures.

Approaches to accelerate drug development are underway, bolstered by international efforts initiated for the API Colombian trial see http://www.clinicaltrials.gov/ct2/show/NCT01998841
For the A4 Study see http://www.clinicaltrials.gov/ct2/show/NCT02008357
For the DIAN-TU trial see http://www.clinicaltrials.gov/ct2/show/NCT01750005
For more on the APOE4 trial from API see http://www.banneralz.org/research-plus-discovery/alzheimers-prevention-initiative.aspx
For DIAN-TU platform see http://www.DIAN-TU.org
For the European Prevention of Alzheimer’s Disease study see http://www.imi.europa.eu
at the G8 dementia summit, and establishment of the World Dementia Council. Rapid development of tau PET imaging measures has shown strong correlations of tau deposits with gold standard clinical and cognitive measures.10–11 Tau PET imaging is being added to trials, in addition to amyloid imaging. CSF biomarkers, and MRI, to provide insight into the in-vivo actions of the drug candidates, and to develop surrogate biomarkers to accelerate future trials. Cognitive tests continue to evolve with the development of sensitive measures of cognitive decline associated with amyloid pathology, several novel cognitive composites, and frequent longitudinal assessments promising better metrics to judge drug effects.6

The range of clinical targets for Alzheimer’s disease treatment has expanded, with novel tau-directed and apolipoprotein-E-directed therapies. Unifying hypotheses in neurodegenerative diseases suggest that protein misfolding and prion-like spreading mechanisms might be common to most of these diseases. Disease-modifying treatments that target α-synuclein in Parkinson’s disease,12 tau in frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration,13 and C9orf72 in amyotrophic lateral sclerosis and frontotemporal dementia continue to develop based on advancements in basic science studies. Basic science developments have also provided other insights, including the development of amyloid pathology in a dish,14 and the findings that young blood restores old brain function,15 suggesting that age-related changes are reversible. Novel genetic risks for Alzheimer’s disease continue to be identified (eg, in the gene coding for phospholipase D316) and findings that Alzheimer’s disease continues to be identified (eg, in the gene coding for phospholipase D316) and findings that young blood dramatically lowers CSF beta-amyloid in patients with mild-to-moderate Alzheimer’s disease.17

Increased governmental support is essential to address the burden of Alzheimer’s disease; however, the future of research funding is uncertain. There is a wealth of basic science knowledge, hypotheses, and targets whose translation into clinical therapies is constrained by limited fiscal resources. In support of the efforts to develop effective treatments and prevention strategies, public-private partnerships such as the NIH Advanced Medicines Program have accelerated implementation of tau PET imaging and RNA analysis in trials. In addition to the multi-national Alzheimer’s Disease Neuroimaging Initiative (ADNI) and the global DIAN, several observational cohorts are also being established, with networks to better understand frontotemporal dementia and dementia in Down’s syndrome. The European IMI has initiated several Alzheimer’s disease programmes to understand and accelerate therapeutics development. The global coordination of these efforts will be instrumental to address the global burden of Alzheimer’s disease.

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8 Preclinical trials in autosomal dominant AD: implementation of the DIAN-TU trial. Rev Neurol 2013; 169: 737–43.
Headache research in 2014: advancing migraine therapy

Acute migraine attacks can be distressing and disabling. The problem is increased if pain killers, and even triptans, are ineffective or can’t be given because of contraindications, as is the case for 10–15% of patients. Headache researchers have been looking for new alternatives to the available treatments for decades. These alternatives should ideally not have vasoconstrictive properties, which are one of the main drawbacks of the triptans. For nearly three decades, calcitonin gene-related peptide (CGRP) has been known to play a crucial part in the pathophysiology of various primary headache disorders. Over the past 3–5 years, pharmacological targeting of structures involved in CGRP signalling has become a promising approach in pharmacological migraine therapy. In 2013, CGRP-receptor antagonists were shown to be effective for prevention of migraines, but possibly unsafe because of hepatotoxicity concerns. In 2014, two large, randomised, controlled, double-blind phase 2 trials showed that two CGRP-antibodies, ALD403 and LY2951742, significantly reduced the number of migraine days per month compared with placebo (saline in both studies) treatment. In the ALD403 trial, 174 patients with migraine were randomised and assigned to either ALD403 or placebo treatment. Migraine frequency, measured as migraine days per 28 day period, was reduced by 5·6 days in the ALD403 group compared with 4·6 days in the saline group (p=0·0306) in weeks 5–8. In the LY2951742 trial, 217 patients randomly received either a single dose of LY2951742 or placebo. LY2951742 reduced the number of migraine headache days per 28 days by 4·2 (62·5%) days, compared with 3·0 (42·3%) days in the saline group (p=0·0030) after 12 weeks. In both trials, no safety concerns with respect to administration of CGRP-antibodies or severe drug-specific adverse effects were reported. About 16% of patients in both trials were completely headache-free after administration of medication, and this effect lasted for several months for most patients. Since all these patients were refractory to most medications when they entered the study, these results are remarkable. The substantial placebo response in both studies is puzzling, however, and warrants further investigation. Nevertheless, these new antibodies represent a promising therapeutic approach for migraine prevention, and seem to be well tolerated and short of side effects.

Another pivotal study last year focused on the pituitary adenylate cyclase activating polypeptide-38 (PACAP) pathway. PACAP has been shown to induce migraine-like attacks in patients with migraine, whereas the structurally related vasoactive intestinal polypeptide (VIP) probably does not. Researchers from Copenhagen compared the attack-inducing properties of PACAP with those of VIP in patients with migraine and reported a significantly higher attack-inducing potential for PACAP. Since the affinity of PACAP for the pronociceptive PAC1 receptor is much greater than that of VIP, it seems that...