affected cortical regions of patients with FTLD types 1, 2 and 3, in two families with chromosome-17-associated frontotemporal dementia with parkinsonism, and also in patients with ALS, a disease with similar clinical and pathological characteristics to FTLD. A signature pattern of TDP-43 fragments was found in samples from affected individuals, whereas only intact protein was found in unaffected brains and those with Alzheimer's disease. Although normally a nuclear protein, TDP-43 was absent from the nuclei of affected neurons; TDP-43-positive ubiquitinated inclusion bodies were found only in the cytoplasm.

The identification of TDP-43 fragments as the major components of the inclusion bodies found in ALS and both sporadic and familial frontotemporal dementia might indicate a common disease mechanism for these disorders. The authors state that understanding the molecular basis of these diseases will help the development of better therapies for affected individuals.

Original article Neumann M *et al.* (2006) Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* **314:** 130–133

Fingolimod shows therapeutic potential for relapsing multiple sclerosis

Multiple sclerosis is considered an autoimmune disease in which autoreactive T cells and macrophages attack myelin sheaths, leading to progressive focal demyelination and neurological disability. In a small trial involving patients with relapsing multiple sclerosis, Kappos *et al.* have demonstrated the therapeutic effect of fingolimod, a new oral immunomodulating agent.

In total, 281 patients were randomized to receive either 1.25 mg or 5.0 mg of fingolimod or placebo once daily. In a 6-month extension to the trial (months 7–12), those patients receiving placebo were randomized to one of the fingolimod doses (patients and researchers remained unaware of dose assignments).

At the end of the core study, the proportion of patients with gadolinium-enhanced lesions as evidenced by MRI was lower in both fingolimod groups than in the placebo group ($P<0.001$ for both). In addition, the annualized relapse rate was lower for individuals in both fingolimod groups (0.35/year in those receiving 1.25 mg and 0.36/year in those receiving 5.0 mg) than in those randomized to placebo (0.77/year). Adverse events associated with fingolimod included nasopharyngitis, dyspnea, and headache. During the extension phase, the number of gadolinium-enhanced lesions and relapse rates remained low in those patients who received continuous fingolimod, and at month 12 over 80% of these patients were free of gadolinium-enhanced lesions. Notably, the number of gadolinium-enhanced lesions decreased markedly among those patients who switched from placebo to fingolimod, as did the annualized relapse rate. On the basis of these results, the authors conclude that larger, longer-term studies of fingolimod are warranted.

Original article Kappos L *et al.* (2006) Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med* **355:** 1124–1140

Sleep-related breathing disorder increases the risk of developing depression

Sleep-related breathing disorder (SRBD) is a relatively common condition associated with impaired daytime functioning and considerable morbidity. Clinical studies have linked the condition with depression, and in a longitudinal population-based study Peppard and colleagues investigated whether SRBD is a longitudinal predictor of depression.

Data were gathered for 1,408 participants with SRBD (788 male, 620 female) from the Wisconsin Sleep Cohort Study, and analysis of cross-sectional and longitudinal associations between SRBD and depression was undertaken. Participants underwent polysomnography sleep studies and clinical assessments at 4-year intervals, and were questioned about their medical history, sleep problems and lifestyle. Depression was assessed using the Zung Self-Rating Depression Scale, and participants with a score of 50 or higher, or those taking antidepressant medications, were considered to be depressed. SRBD was categorized according to the apnea-hypopnea index (events per hour).

There was a strong longitudinal association between increased SRBD and the development of depression in those depression-free at baseline. An increase of one SRBD category over a 4-year period—for example from minimal to mild—was associated with a 1.8-fold increase