IN BRIEF

GENETICS

Gene editing shows promise in LCA10

New preclinical data support the development of a gene-editing strategy for restoring vision loss in patients with Leber congenital amaurosis type 10 (LCA10), an autosomal recessive condition caused by biallelic loss-of-function mutations in the *CEP290* gene. Maeder and colleagues have developed EDIT-101, an experimental genome-editing medicine designed to remove the abnormal splice donor site caused by the IVS26 mutation in *CEP290* (which most commonly causes LCA10), and thereby restore normal *CEP290* expression. In their study, the researchers showed that subretinal delivery of EDIT-101 in a human CEP290 IVS26 knock-in mouse model resulted in fast and sustained *CEP290* gene editing. They also demonstrated productive gene editing in a comparable surrogate nonhuman primate vector at levels meeting the target therapeutic threshold.

ORIGINAL ARTICLE Maeder, M. L. et al. Development of a gene-editing approach to restore vision loss in Leber congenital amaurosis type 10. *Nat. Med.* https://doi.org/10.1038/s41591-018-0327-9 (2019)

MULTIPLE SCLEROSIS

Prolonging the integrated stress response could be beneficial in multiple sclerosis

Enhancement of the integrated stress response (ISR), an innate cellular protective signalling pathway, might be useful in the treatment of multiple sclerosis, according to a new study published in *Brain*. Chen et al. showed that Sephin1, which inhibits the dephosphorylation of the ISR target eIF2α, prolonged eIF2α phosphorylation in stressed primary oligodendrocytes, thereby prolonging the protective response. The researchers showed that Sephin1 delayed the onset of clinical symptoms in mice with experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, and that Sephin1 in combination with interferon-β provided additional benefits in slowing disease progression. Consistent with the idea that Sephin1 inhibits PPP1R15A (a subunit of the protein complex that dephosphorylates eIF2α), mice with mutant *PPP1R15A* showed delayed onset of EAE similar to the Sephin1-treated mice.

ORIGINAL ARTICLE Chen, Y. et al. Sephin1, which prolongs the integrated stress response, is a promising therapeutic for multiple sclerosis. *Brain* https://doi.org/10.1093/brain/awy322 (2019)

PARKINSON DISEASE

Lifestyle factors and progression of PD

A number of lifestyle factors affect progression of Parkinson disease (PD), according to researchers in the USA. Paul and co-workers analysed data on smoking, physical activity and consumption of coffee, caffeinated tea and alcohol in a cohort of 360 patients who had received a PD diagnosis in the past 3 years. All patients were included in survival analyses and 252 patients were assessed for signs of progression in terms of motor function and cognition in 2–4 visits over an average of 5.3 years. Coffee was found to be protective against motor function decline, cognitive decline and mortality. Moderate alcohol consumption (versus no alcohol consumption and versus heavy alcohol consumption) was protective against motor function decline. A history of participation in competitive sports was protective against cognitive decline and decline in motor function, whereas current cigarette smoking was associated with faster cognitive decline.

ORIGINAL ARTICLE Paul, K. C. et al. The association between lifestyle factors and Parkinson's disease progression and mortality. *Mov. Disord.* **34**, 58–66 (2019)

ALZHEIMER DISEASE

Decreased NREM sleep linked with tauopathy

Decreased non-rapid eye movement (NREM) sleep is associated with tauopathy in early Alzheimer disease (AD), according to a new study published in *Science Translational Medicine*.

"Sleep and AD are currently hypothesized to have a two-way or bidirectional relationship, with sleep disturbances potentially increasing the risk of developing AD and changes in sleep–wake activity potentially serving as a marker for AD pathology," explains Brendan Lucey, the first author on the new paper. "Our paper focused on sleep as a marker for AD pathology."

The study included 119 individuals aged >60 years who were enrolled in longitudinal studies of ageing. Lucey et al. monitored sleep at home for up to six nights, using a device that recorded single-channel EEG on the forehead, as well as actigraphy and sleep logs. In addition to sleep monitoring, the participants underwent standardized cognitive assessments, lumbar punctures to collect cerebrospinal fluid (CSF) for measurement of AD biomarkers (amyloid-β_{42} ($A\beta_{42}$), total tau and phosphorylated tau), brain imaging with tau tracers and apolipoprotein E genotyping.

The researchers found an inverse relationship between NREM slow-wave activity (SWA) and tau levels on PET scans. This relationship was maximal at the slowest frequencies, 1–2 Hz. Lucey et al. then looked for associations between NREM SWA and CSF AD biomarkers. They found no significant association between NREM SWA and CSF $A\beta_{42}$ (a marker for amyloid deposition), but they did find an inverse relationship between NREM SWA and the CSF tau:$A\beta_{42}$ ratio (a predictor of conversion to symptomatic AD).

ALZHEIMER DISEASE

Stroke trial drug is effective in Alzheimer disease mouse model

A drug that has been successful in a phase II trial in patients with stroke prevents development of amyloid-β (Aβ) pathology in a mouse model of Alzheimer disease (AD), according to a recent study. The work identifies a new candidate drug for testing in early AD in humans.

The drug — called 3K3A-activated protein C (APC) — is a recombinant variant of endogenous APC, a protease with anticoagulant, cytoprotective, vasculoprotective and anti-inflammatory properties. 3K3A-APC has been engineered to retain the protective effects of APC but minimize the associated risk of bleeding. Previous work has demonstrated that 3K3A-APC protects neurons in animal models of stroke, traumatic brain injury, amyotrophic lateral sclerosis and multiple sclerosis. A phase IIa trial has shown that the drug is safe, well tolerated and beneficial in patients with ischaemic stroke.

"We thought 3K3A-APC would be good to try in AD mice for direct protection of neurons from Aβ toxicity, improving brain circulation and blood–brain barrier integrity, and reducing inflammation," explains Berislav Zlokovic, lead author of the new study.

To test their hypothesis, Zlokovic and colleagues treated 5XFAD mice, which express five mutations in the genes that encode amyloid precursor protein and presenilin 1, with 3K3A-APC for 4 months. The mice were treated before the peak of Aβ accumulation to investigate whether disease onset could be delayed. As the researchers hoped, treatment improved blood–brain barrier integrity and the treated mice exhibited behavioural improvements, but unexpected effects also occurred.