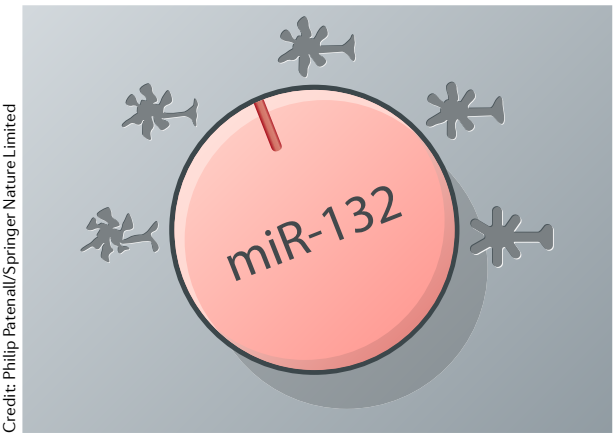

Credit: Philip Patenall/Springer Nature Limited

health and indicate that miR-132 supplementation could be of therapeutic value for the treatment of tau-associated neurodegenerative disorders," concludes Krichevsky. "Our work is now focusing on further dissection of miR-132 signalling and development of therapeutic approaches for miR-132 supplementation or induction in the brain."

Heather Wood

> "miR-132 reduced the formation of pathological forms of the tau protein"

ORIGINAL ARTICLE El Fatimy, R. et al. MicroRNA-132 provides neuroprotection for tauopathies via multiple signalling pathways. *Acta Neuropathol.* https://doi.org/10.1007/s00401-018-1880-5 (2018)

also worsened the cognitive defects associated with Aβ deposition in *APP*-mutant mice, and was associated with increased mortality.

These findings suggest that genes on chromosome 21 other than *APP* promote the deposition of Aβ. The team are now conducting experiments to pinpoint the individual genes that are responsible for this effect. These genes could represent therapeutic targets to counter AD in individuals with Down syndrome.

"I hope that our basic research paves the way for the development of an effective treatment for this really important and often overlooked group of patients with AD," comments Wiseman. The researchers are currently working closely with clinical research teams as a part of the LonDownS consortium with a view to develop treatments for AD in individuals with Down syndrome.

Charlotte Ridler

> "expression of the partial extra copy of chromosome 21 substantially increased the deposition of Aβ"

ORIGINAL ARTICLE Wiseman, F. K. et al. Trisomy of human chromosome 21 enhances amyloid-β deposition independently of an extra copy of APP. *Brain* https://doi.org/10.1093/brain/awy159 (2018)

PERIPHERAL NEUROPATHIES

Treatment success in hereditary transthyretin amyloidosis

Blocking production of transthyretin (TTR) improves the polyneuropathy caused by hereditary TTR amyloidosis (hATTR), two new phase III trials have shown. The two drugs, patisiran and inotersen, also improved quality of life for patients.

hATTR is caused by mutations in the *TTR* gene, which lead to misfolding and systemic deposition of the TTR protein. Polyneuropathy is a major manifestation of the disease.

"Neuropathic changes result in profound sensorimotor disturbances, with deterioration in activities of daily living and ambulation, diarrhoea, hypotension, impotence and bladder disturbances," explains David Adams, who led one trial and was involved in the other.

TTR is primarily synthesized in the liver, and both of the trialled therapeutic strategies are designed to stop its production. Patisiran is an RNA interference therapeutic that is specifically targeted to hepatic cells by lipid nanoparticles, and inotersen is an antisense oligonucleotide. Both of the agents target *TTR* mRNA.

The trial of patisiran included 225 patients with hATTR stages 1 or 2. Patients were randomly assigned to receive intravenous patisiran or a placebo. The drug was administered once every 3 weeks for 18 months.

After 18 months of treatment, mean scores on the modified Neuropathy Impairment Score + 7 (mNIS + 7) were significantly lower among patients who received patisiran than among those who received placebo. Scores decreased from baseline in 56% of patients who received patisiran and in just 4% of patients who received placebo. Furthermore, quality of life (assessed with the Norfolk Quality of Life–Diabetic Neuropathy (QOL–DN) questionnaire) at 18 months was better than baseline among patients who received patisiran. Mild or moderate adverse events were common with patisiran, but the rate of serious adverse events was no higher than with placebo.

"Patisiran reversed the disease and efficacy was observed regardless of the stage of the disease," says Adams. "Until now, only a few patients have had access to liver transplantation or TTR stabilizers, which slow progression only in stage 1 disease. We think that most patients can benefit from patisiran."

In the trial of inotersen, led by Teresa Coelho, 172 patients with stage 1 or 2 hATTR were randomly assigned to receive weekly injections of inotersen or a placebo for 15 months. Reductions in mNIS + 7 scores and Norfolk QOL–DN scores were greater with inotersen than with placebo. "The efficacy against both co-primary end points was remarkable," says Coelho. "Not only did patients do better, but many experienced improvements in their disease."

Safety was a greater concern with inotersen than with patisiran. One person died from an intracranial haemorrhage associated with thrombocytopenia, an adverse effect seen in 54% of patients who received inotersen. Three patients who received inotersen developed glomerulonephritis.

Nevertheless, the results of both trials suggest that RNA-based therapies could transform treatment of hATTR. "We look forward to the potential approval of inotersen so we can begin getting this important drug to patients," says Coelho.

The success of these drugs could be just the beginning. "Ionis is developing a drug similar to inotersen that is even more potent and convenient to use, so I am looking forward to participating in clinical trials of 'next-generation' antisense drugs," concludes Coelho.

Ian Fyfe

ORIGINAL ARTICLES Adams, D. et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N. Engl. J. Med.* **379**, 11–21 (2018) | Benson, M. D. et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N. Engl. J. Med.* **379**, 22–31 (2018)