age groups are provided, such measurements might be used for individual patient monitoring.

Overall, the findings from multiple sclerosis research in 2018 hold great promise for the treatment of progressive multiple sclerosis and for the availability of new biomarkers to monitor disease progression.

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New therapies for neuromuscular diseases in 2018

Advances in treatments for neuromuscular diseases, particularly those with a genetic basis, have been a key story this year, illustrated by treatment of the rare condition hereditary transthyretin amyloidosis. This progressive, multisystemic, autosomal dominant disorder leads to death on average within 3–15 years of symptom onset and is caused by mutations in the *TTR* gene that trigger deposition of misfolded transthyretin protein throughout the body. Sensory, motor, and autonomic polyneuropathy is a major feature of the disease and a substantial determinant of disability and quality of life. Two successful double-blind, randomised, placebo-controlled phase 3 trials, APOLLO[1] and NEURO-TTR,[2] used different gene therapy approaches to block the production of transthyretin in the liver, which is the predominant source of this protein, and illustrate different paradigms for the treatment of genetic disease. Patisiran, administered intravenously in APOLLO, is a double-stranded siRNA that targets *TTR* mRNA for cleavage and reduces the levels of both mutant and wild-type transthyretin; the drug, encapsulated in a lipid nanoparticle, precisely targets *TTR* mRNA in hepatocytes. Inotersen, delivered subcutaneously in NEURO-TTR, is a 2′-O-methoxyethyl-modified antisense oligonucleotide that inhibits the hepatic production of transthyretin protein by binding to *TTR* mRNA. Both treatments resulted in significant improvements in neuropathy, as measured by the modified Neuropathy Impairment Score+7 (difference of −34·0 points for patisiran [95% CI −39·9 to −28·1; p<0·001]; −19·7 points for inotersen [−26·4 to −13·0; p<0·001]) and quality of life scores (difference of −21·1 points for patisiran [95% CI, −27·2 to −15·0; p<0·001]; −11·7 points for inotersen [−18·3 to −5·1; p<0·001]) compared with placebo.[1,2] On the basis of these results, disease progression was considered to be halted or reversed. Mild-to-moderate adverse events were frequent with patisiran, but inotersen caused more frequent serious adverse effects, including thrombocytopenia in more than 50% of patients (with one resultant death from an intracranial haemorrhage in NEURO-TTR) and glomerulonephritis in 3% of patients; treatment with inotersen will therefore require enhanced monitoring. It remains to be seen whether these drugs will be efficacious for cardiomyopathy associated with hereditary transthyretin amyloidosis, and long-term follow-up is needed. Patisiran is now the first RNA-interfering therapy to be approved by the US Food and Drug Administration.

Conceptually, it would seem most appealing to edit the patient's genome itself to treat genetic disorders. An exciting development in the laboratory, which offers hope for the future treatment of many genetic neuromuscular and neurodegenerative diseases, is somatic cell mutagenesis using enzymatic clustered regularly spaced short palindromic repeats (CRISPR)-Cas9 gene editing, a type of so-called magic bullet that can precisely edit

DNA. In this system, the Cas9 endonuclease is guided by a single guide RNA to its complementary DNA sequence, where it induces a double-strand break, allowing editing. One major advantage of CRISPR-Cas9 over antisense oligonucleotides is that treatment with this sort of paradigm should require only one dose. However, a single-dose treatment also runs the risk that side-effects might be lifelong. A study[3] of a transgenic mouse model of amyotrophic lateral sclerosis that carried human mutant *SOD1* used adeno-associated virus 9 to deliver CRISPR-Cas9 and a single guide RNA designed to disrupt *SOD1*. Treated mice had reduced concentrations of mutant SOD1 protein, a delay in onset of symptoms of amyotrophic lateral sclerosis, and 25% longer survival, compared with untreated mutant mice. A similar approach is being investigated in animal models of Duchenne muscular dystrophy: building on earlier murine work, CRISPR-Cas9 components targeted to dystrophin in a canine model of Duchenne muscular dystrophy substantially increased concentrations of dystrophin.[4] Treated dogs also showed improved muscle histology. There is a long way to go before this therapy can be used in humans, and there are important hurdles to be overcome, including safety concerns, but these early studies are very promising.

Many of these exciting treatments for neuromuscular disorders are costly and raise concerns about the affordability of health care going forward, so it was a relief to see a successful trial of a comparatively inexpensive treatment for chronic inflammatory demyelinating polyneuropathy. In the PATH study[5]—a randomised, placebo-controlled, double-blind trial of subcutaneous immunoglobulin for chronic inflammatory demyelinating polyneuropathy—172 patients whose neuropathy was responsive to intravenous immunoglobulin were randomly allocated to placebo, low-dose subcutaneous immunoglobulin, or high-dose subcutaneous immunoglobulin. Relapse or withdrawal rates were significantly higher in the placebo group (n=36; 63% [95% CI 50–74]) than in the high-dose subcutaneous immunoglobulin group (n=19; 33% [22–46]) or low-dose subcutaneous immunoglobulin group (n=22; 39% [27–52]), and the treatment was well tolerated at both doses. Subcutaneous immunoglobulin offers a more convenient option for patients hitherto dependent on intravenous immunoglobulin, and can be administered at home, which improves quality of life and reduces costs associated with infusion-based treatments.

Overall, 2018 has seen innovation in the application and delivery of new therapies. Now that the ice is broken, the practical use of gene therapy in neuromuscular disease is a new area that should see huge strides in the next few years.

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Pain research in 2018: the year of translational studies

For decades, the traditional bottom-up approach in chronic pain research has consisted of investigation into mechanisms of pain in animal models, then attempted translation of the data obtained to the clinic.[1,2] However, because it is difficult to predict mechanistic conservation between animals and humans, several treatments developed on the basis of the mechanisms identified in animals have subsequently failed in humans.[2] A translational top-down approach to research has also been tried, consisting of stratifying patients on the basis of their sensory phenotypes (ie, specific combinations of signs and symptoms), with the hypothesis that