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PERIPHERAL NEUROPATHIES

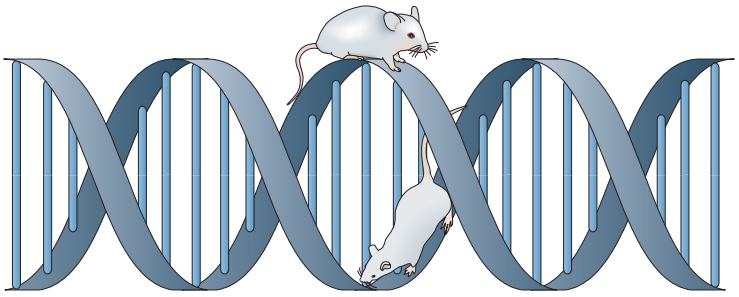
Antisense therapy for Charcot–Marie–Tooth disease?

Antisense oligonucleotides (ASOs) could be used to treat Charcot–Marie–Tooth disease (CMT), according to a new study. Research in mouse and rat models of CMT found that ASO therapy could halt disease progress and even reverse the symptoms of neuropathy.

CMT encompasses a group of inherited peripheral neuropathies that are characterized by progressive muscle weakness and numbness of sensation. No effective therapies are currently available for these conditions. The most common form of CMT — CMT1A — is caused by a duplication of *PMP22*, which encodes peripheral myelin protein 22, a major component of myelin.

In rodent models of CMT1A, overexpression of *PMP22* is sufficient to cause demyelination. Subsequent reduction of this overexpression results in remyelination, suggesting that lowering the expression levels of *PMP22* is a viable therapeutic strategy in patients with CMT1A.

"It seemed to us that antisense technology was the perfect solution for treating CMT1A," explains Hien Tran Zhao, the corresponding author of the new study. "Antisense drugs can be designed to selectively lower PMP22 to normal levels, which has the potential to halt or reverse this disease."



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The team designed an ASO that bound to the 3′-untranslated region of *PMP22*, and they tested its effects in a mouse model of CMT1A that overexpressed a human *PMP22* transgene (C22 mice). C22 mice that received weekly subcutaneous injections of the ASO showed a 50% reduction of *PMP22* mRNA after 9 weeks, compared with C22 controls that were given saline solution. ASO treatment also reversed the decline in grip strength and rotarod performance that is seen in C22 animals, as well as restoring motor neuron conduction velocity and increasing the number of myelinated axons.

RNA sequencing in untreated C22 mice revealed a number of transcriptional changes compared with wild-type mice, including a reduction in transcripts associated with lipid biosynthesis and an increase in transcripts associated with inhibition of myelination. ASO therapy reversed many of these disease-associated changes.

Finally, the team showed that ASO treatment could suppress *PMP22* transcription and ameliorate symptoms of neuropathy in a rat model of CMT1A. A reduction in *PMP22* RNA could be detected in skin biopsies from these animals, offering a potential biomarker for target engagement in future clinical trials.

"Taken together, these results support the use of ASOs as a potential treatment for CMT1A," explains Zhao. "We are now working to identify compounds suitable for clinical development."

Charlotte Ridler

> "these results support the use of ASOs as a potential treatment for CMT1A"

ORIGINAL ARTICLE Zhao, H. T. *et al.* PMP22 antisense oligonucleotides reverse Charcot–Marie–Tooth disease type 1A features in rodent models. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI96499 (2017)