

# Towards a gene therapy approach to treat inherited demyelinating neuropathies

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## Summary

Inherited demyelinating neuropathies are genetically heterogeneous but all result from mutations affecting myelin-related genes expressed in Schwann cells. X-linked Charcot-Marie-Tooth disease (CMT1X) is one of the commonest types and is associated with mostly loss-of-function mutations in the *GJB1* gene encoding the gap junction protein Cx32. In order to develop a gene replacement therapy for this disease, we cloned a novel lentiviral vector in which the *GJB1* gene is placed under the control of the Schwann cell-specific rat *Mpz/P0* promoter. This LV.Mpz-*GJB1* vector was delivered by a single intraneural injection into adult mouse sciatic nerves distal to the sciatic notch or, to achieve a more widespread expression, by a single lumbar intrathecal injection. EGFP reporter gene expression was detected throughout the length of the injected nerve in up to 50% of Schwann cells starting two weeks after intraneural injection and remaining stable for up to 16 weeks. By comparison, lumbar intrathecal vector delivery led to widespread expression in various components of the peripheral nervous system, including the spinal roots, dorsal root ganglia and along the sciatic and femoral nerves, remaining stable for up to 16 weeks, with similar expression rates ranging from 35%-55% of Schwann cells. Using the Cx32 knockout mouse, an authentic mouse model of CMT1X, we demonstrated that intraneural gene delivery restores Cx32 expression and improves the pathology of the injected nerve. Furthermore, intrathecal gene delivery in the same model resulted in widespread pathology rescue as well as in significant improvement of behavioral motor and electrophysiological parameters of peripheral nerve function. Our studies provide a proof of principle that gene therapy may be feasible for CMT1X and other inherited neuropathies that share similar cellular mechanisms.

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