THERAPEUTIC GENOME EDITING FOR CHARCOT-MARIE-TOOTH DISEASE TYPE 1A

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Charcot-Marie-Tooth 1A (CMT1A) is the most common inherited neuropathy without a known therapy, which is caused by a 1.4 Mb duplication on human chromosome 17, which includes the gene encoding the peripheral myelin protein of 22 kDa (PMP22). Overexpressed PMP22 protein from its gene duplication is thought to cause demyelination and subsequently axonal degeneration in the peripheral nervous system (PNS). Here, we targeted regulatory region of human PMP22 to normalize overexpressed PMP22 level in C22 mice, a mouse model of CMT1A harboring multi copies of human PMP22. Direct local intraneural delivery of CRISPR/Cas9 designed to target TATA-box of PMP22 before the onset of disease, downregulates gene expression of PMP22 and preserves both myelin and axons. Notably, the same approach was effective in partial rescue of demyelination even after the onset of disease. Collectively, our data present a potential therapeutic efficacy of CRISPR/Cas9-mediated targeting of regulatory region of PMP22 to treat CMT1A.

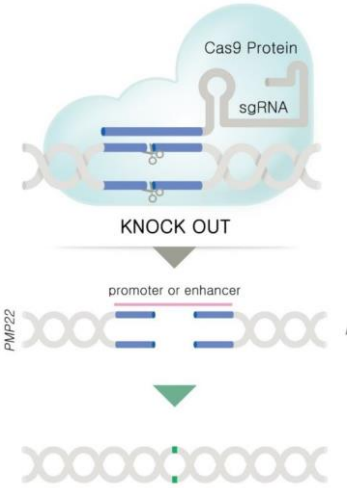

Figure 1 – Schematic diagram describing gene editing strategy for CMT1A