Molecular Therapy
Nucleic Acids
Commentary

Accessory oligos for neuronal delivery of therapeutic siRNAs for ALS

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Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease that usually affects individuals in the prime of their lives. ALS is mostly associated with mutations in the superoxide dismutase (SOD1) gene, resulting in misfolded proteins that accumulate in neuronal tissue and cause loss of motor neuron function and eventual patient death.[1] RNA interference (RNAi) via antisense oligonucleotides (ASOs) could provide a viable treatment option for ALS because ASOs can directly target polymorphisms and specific mutations in SOD1, triggering precise degradation of mutant transcripts. One such treatment, QALSODY (tofersen), an ASO treatment that triggers degradation of SOD1 mRNA, just received accelerated approval from the US Food and Drug Administration.[2,3] However, the delivery of small interfering RNAs (siRNAs) and ASOs to the CNS is challenging due to their inability to cross the blood-brain barrier, necessitating more invasive routes of administration. Fortunately, a recent publication by Place, Li, and colleagues proposes an elegant solution for this barrier.[4] These investigators developed a panel of SOD1 siRNAs that can degrade most SOD1 isoforms. They first tested these siRNAS *in vitro*, where they identified the top 5 performing siRNAs with potency in the low picomolar range. Next, the authors conjugated the siRNAs to a 14-nt accessory oligonucleotide (ACO) to exploit the self-delivery property of ACOs to deliver the siRNAs *in vivo* to the brains of mice hemizygous for the $SOD1^{G93A}$ transgene, a common mouse model of ALS. The ACO was designed such that it was inert and lacked homology to any known transcripts. By attaching the ACO to the 5′ end of the siRNA passenger strand, the authors successfully delivered the siRNA-ACOs to the brain in SOD^{G93A} mice, accomplishing knockdown of mutant SOD1 transcripts. The *in vivo* application of this novel delivery scheme resulted in delayed disease progression, prolonged survival, and preserved motor function in SOD^{G93A} mice. The major drawback to this approach is that the ACOs need to be administered intrathecally to reach the CNS, which carries the risk of lumbar-puncture-associated adverse events.[2] Nonetheless, the siRNA-ACOs functionally associated with the RNAi machinery *in vivo* to exert therapeutic effects. This novel siRNA delivery mechanism has the potential for use in treating other neurodegenerative diseases, such as Huntington's disease and frontotemporal dementia. Keep an eye out for further applications of this ACO approach in the future.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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