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Researchers develop a promising gene-editing strategy for spinal muscular atrophy

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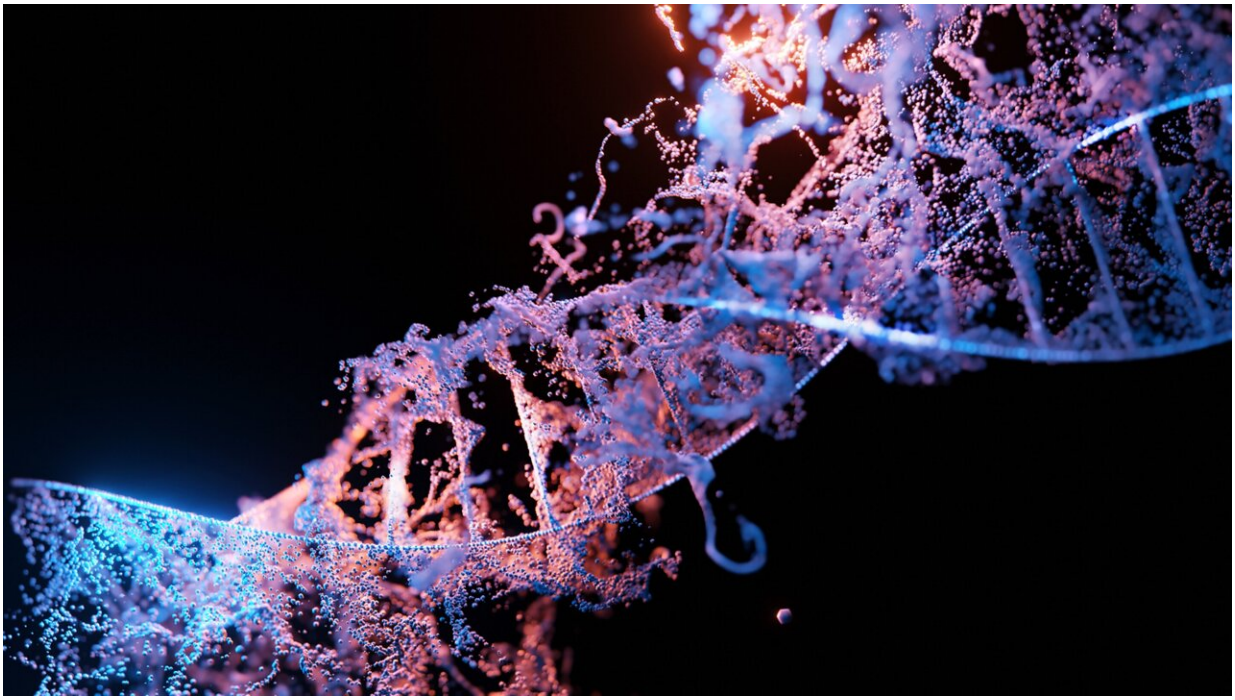

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Spinal muscular atrophy (SMA) is a devastating pediatric neuromuscular disorder caused by loss-of-function mutations in the SMN1 gene, which prevents the body from producing enough of the survival motor neuron (SMN) protein that is important for development and neuronal function.

Motor neurons affected by SMA include those that control movement in

the arms, legs, face, chest, throat and tongue, as well as those used in speaking, walking, swallowing and breathing.

While there are effective gene and molecular therapies that have led to remarkable improvements patients with SMA, there is still no definitive genetic cure that treats the root cause of this disease, and concerns about the longevity and efficacy of the current approaches remain.

Serendipitously, humans also encode gene called SMN2 that is similar to SMN1.

In a study published in Nature Biomedical Engineering, a research team led by Christiano Alves, Ph.D., and Benjamin Kleinstiver, Ph.D., developed a customized CRISPR base editor that "activates" SMN2 to restore SMN protein expression to normal levels irrespective of a patient's SMN1 mutation.

The team validated the safety and efficacy of their approach in cell lines before delivering the treatment via an AAV viral vector into a mouse model of SMA.

They found that the treatment resulted in precise SMN2 editing in vivo, restoring the production of the SMN protein and improving disease symptoms.

"By developing a single genome editing strategy to correct SMN2 to enable high levels of SMN protein expression, our approach could avoid the need to correct different types of mutations in the SMN1 gene," explains Kleinstiver, an Assistant Investigator at the Center for Genomic Medicine at Mass General, an Assistant Professor at Harvard Medical School, and Kayden-Lambert MGH Research Scholar 2023–2028.

"Although our results are the initial steps towards a longer-term goal, the

optimization of a single editing approach to treat all patients could eventually streamline progress into the clinic."

"Our approach to treat SMA by editing SMN2 followed the blueprint of approved SMA drugs. Continued development of our base editing approach should provide a long-lasting genetic treatment for SMA, where a durable one-time edit offers major advantages compared to existing therapies," says Alves, the lead and co-corresponding author of the study. Alves is an Assistant Investigator at the Center for Genomic Medicine and an Instructor in Neurology at HMS.

There are several steps ahead to continue the development of these strategies towards a once-and-done therapy for SMA, including:

- Testing the impact of a combinatorial therapy with other drugs approved for SMA treatment, to maximize efficacy.
- Developing alternative delivery methods for these base editors which would require lower AAV doses, or non-viral delivery methods that could obviate concerns about the use of AAV.

The team notes that their results are complementary to another recent study from Arbab et al, where they undertook a similar approach to permanently edit SMN2 using base editors towards treating SMA.

More information: Christiano R. R. Alves et al, Optimization of base editors for the functional correction of SMN2 as a treatment for spinal muscular atrophy, *Nature Biomedical Engineering* (2023). DOI: 10.1038/s41551-023-01132-z

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