First clinical trial involving in vivo CRISPR human gene editing

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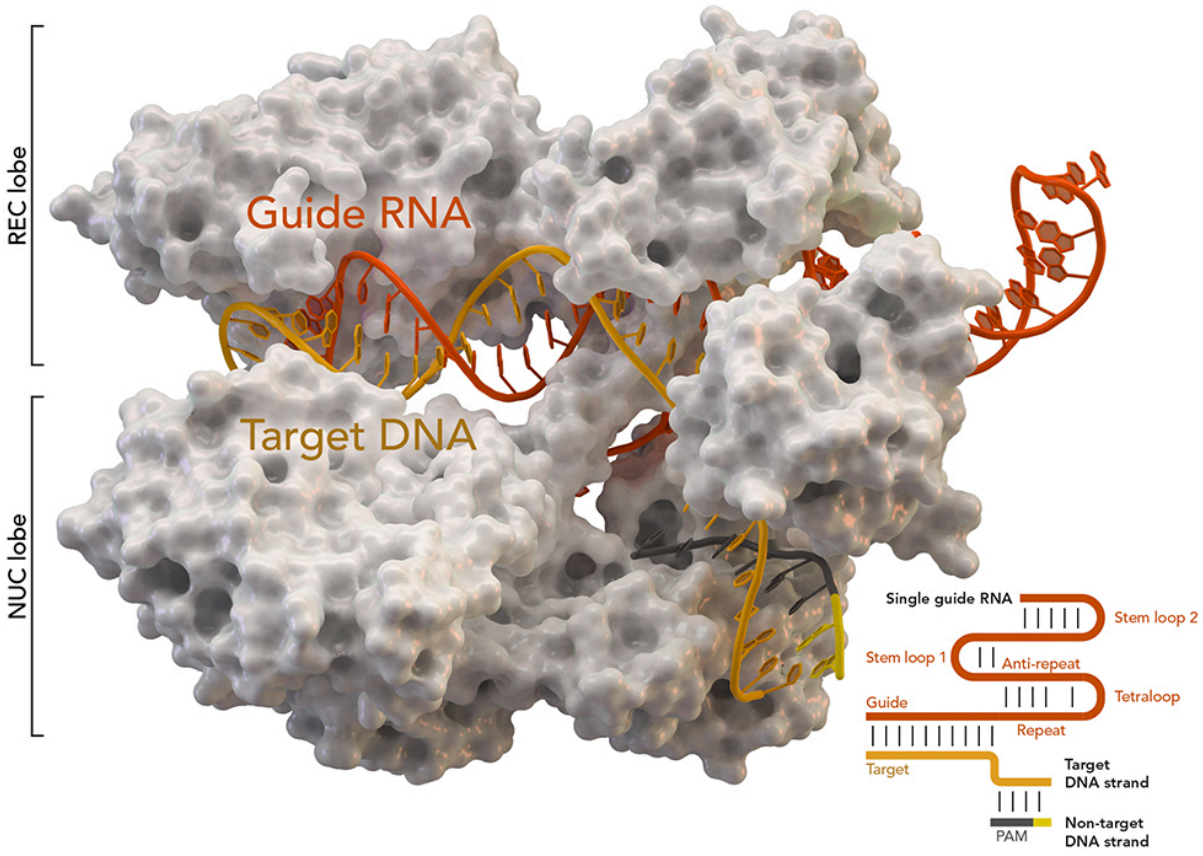

CRISPR-associated protein Cas9 (white) from Staphylococcus aureus based on Protein Database ID 5AXW. Credit: Thomas Splettstoesser (Wikipedia, CC BY-SA 4.0)

A team of researchers from Intellia Therapeutics, Inc. and Regeneron Pharmaceuticals has conducted the first clinical trial involving in vivo CRISPR human gene editing. In their paper published in *The New England Journal of Medicine*, the group describes developing a CRISPR technique for treating transthyretin amyloidosis (ATTR amyloidosis) patients and administering a therapy called NTLA-2001 to six patients as part of a Phase 1 clinical trial.

Transthyretin amyloidosis (ATTR amyloidosis) is an inherited genetic disorder that involves TTR misfolded proteins—patients with it experience painful protein build-up around nerve cells—in most cases, it is progressive and fatal. In this new effort, the researchers sought to treat such patients by editing the TTR genes in ways that made them mimic patients that do not have the disorder.

The therapy consisted of lipid nanoparticles carrying the genome editor to the liver. The first part of the process involved guidance to the genes to be edited while the second part involved using RNA messaging to conduct the gene edits. In the trial, the patients were divided into groups, with each receiving a different dose of the NTLA-2001 therapy. Testing of the patients afterward showed that those who received 0.1 mg of the therapy saw reductions in TTR protein levels of 52%. Those who received a 0.3 mg dose saw an average decrease of 87%.

The researchers note that the results for the patients receiving the higher dose outperformed patients who receive a drug called patisiran to treat their symptoms—such patients on average see an 80% reduction in TTR protein levels; not enough to prevent the progression of the disease. They also note that their approach requires one dose, while patisiran must be given regularly. The researchers also found that none of the patients in the clinical trial reported any adverse reactions to the NTLA-2001 therapy.

The researchers suggest that their therapy approach merits further testing—the next step will be to give patients higher doses of NTLA-2001 to see if it will reduce protein levels to the point that it stops the progression of the disease. If these tests are successful, the group plans to test the therapy on larger numbers of patients.

More information: Julian D. Gillmore et al, CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis, *New England Journal of Medicine* (2021). DOI: 10.1056/NEJMoa2107454