Gene editing offers hope for people with hereditary disorder

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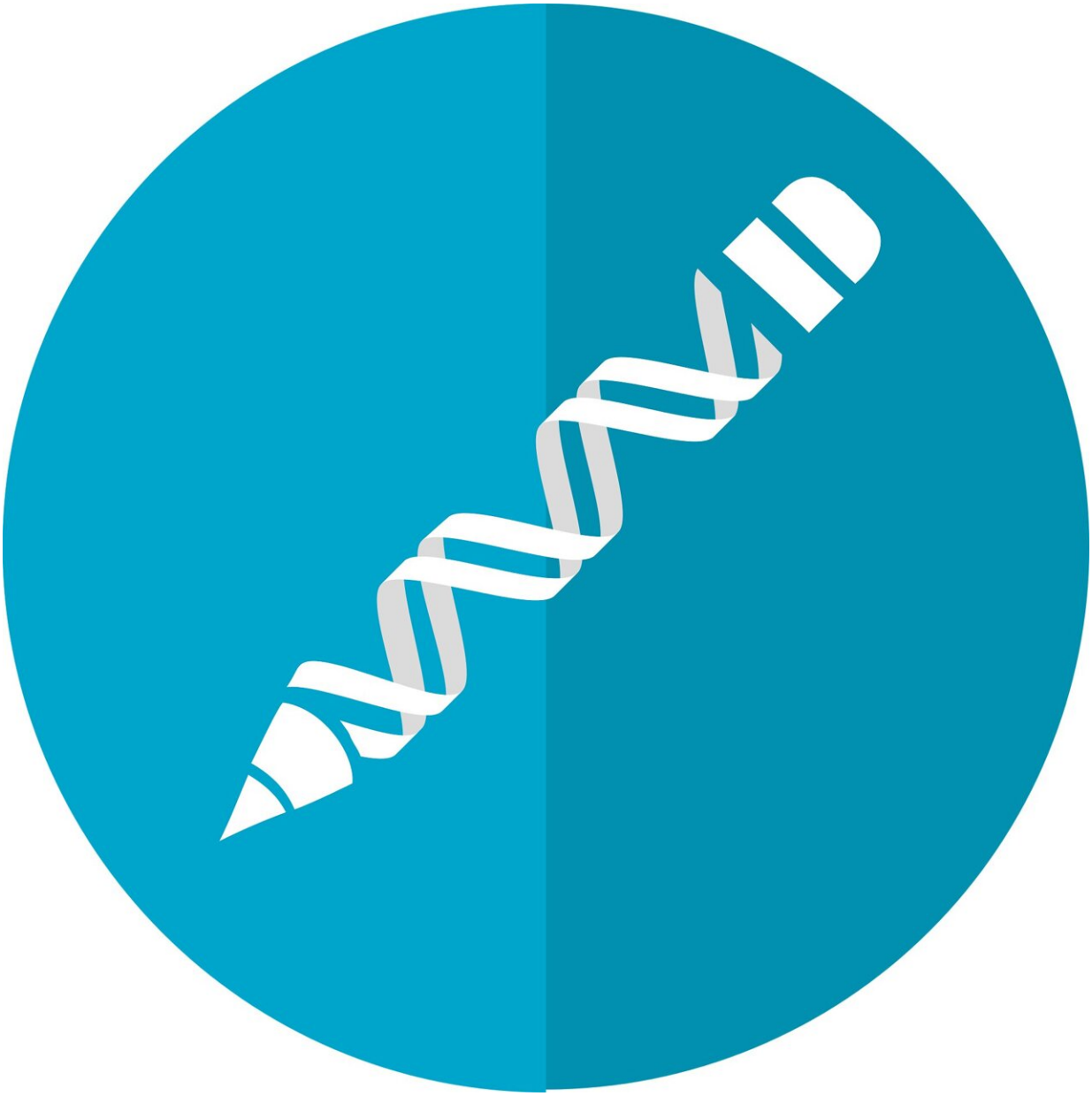

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A group of patients with a hereditary disorder have had their lives transformed by a single treatment of a breakthrough gene-editing therapy, according to the lead researcher of a trial published in the New England Journal of Medicine.

The patients from New Zealand, the Netherlands and the UK have hereditary angioedema, a genetic disorder characterized by severe, painful and unpredictable swelling attacks. These interfere with daily life and can affect airways and prove fatal.

Now researchers from the University of Auckland, Amsterdam University Medical Center and Cambridge University Hospitals have successfully treated more than 10 patients with the CRISPR/Cas9 therapy, with interim results
just published.

"It looks as if the single-dose treatment will provide a permanent cure for my hereditary angioedema patients' very disabling symptoms," says principal investigator Dr. Hilary Longhurst, who is both a clinical immunologist at Auckland Hospital Te Toku Tumai and an honorary associate professor at the University of Auckland.

"Plus, of course, there is huge potential for development of similar CRISPR/Cas9 treatments for other genetic disorders." Globally, it is estimated one in 50,000 people have hereditary angioedema, however, because it is rare, it is often not correctly diagnosed.

In the Phase I study, there were no serious or lasting side effects from the single infusion, which took place over two to four hours under

clinical supervision from late 2021 and onwards.

The investigational therapy, called NTLA-2002, utilizes in vivo CRISPR/Cas9 technology to target the KLKB1 gene, which is responsible for producing plasma prekallikrein.By editing this gene, the therapy reduces the levels of total plasma kallikrein, effectively preventing angioedema (swelling) attacks.

The trial demonstrated dose-dependent reduction in total plasma kallikrein protein with reductions of up to 95% achieved. A mean reduction of 95% in angioedema attacks was observed across all patients through to the latest follow-up.

The patients from the initial study will be followed up for a further 15 years to continue to assess long-term safety and efficacy. A larger and more robust, double-blinded, placebo-controlled Phase II trial is underway and a Phase III trial is planned to start in the second half of 2024.

Dr. Danny Cohn, from the Department of Vascular Medicine at the Amsterdam University Medical Center says these promising results are a step forward for this group of patients.

"We've never been closer to the ultimate treatment goal of normalizing hereditary angioedema patients' lives and offering total control of the disease," says Dr. Cohn.

Dr. Padmalal Gurugama, consultant in clinical immunology and allergy at Cambridge University Hospitals, UK says the gene editing therapy has the potential to significantly improve patients' lives.

"Hereditary angioedema can cause patients severe swellings and intense pain which can be life-threatening as well as restricting normal activities,

such as going to work or school.

"Because it is often misdiagnosed, many patients undergo unnecessary treatments and invasive procedures."

The therapy affects only the patient and is not passed on to their children, who still have an even chance of inheriting the disorder.

So far, the only approved CRISPR therapy, CASGEVY, is for sickle cell disease and beta thalassemia. However, CASGEVY is an ex vivo CRISPR therapy, where the cells are taken from the patient and edited outside of the body and then reinfused, whereas NTLA-2002 is an in vivo CRISPR therapy, where the targeted gene editing occurs directly within the body.

CRISPR technologies are being used to develop treatments for a wide range of diseases, such as genetic disease, cardiovascular disease, cancer and autoimmune diseases.

More information: Hilary J. Longhurst et al, CRISPR-Cas9 In Vivo Gene Editing of KLKB1 for Hereditary Angioedema, *New England Journal of Medicine* (2024). DOI: 10.1056/NEJMoa2309149

Provided by University of Auckland

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