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AAV-based gene therapy for Non-Ketotic Hyperglycinaemia

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Summary

A novel AAV-based gene therapy approach for Non-Ketotic Hyperglycinaemia (NKH).

Background

NKH, or glycine encephalopathy, is a rare, life-limiting inherited metabolic disease characterised by accumulation of excess glycine in the body. With an incidence of 1/60,000 worldwide, it affects newborns with respiratory distress, muscle hypotonia and seizures. Babies who survive the neonatal period suffer profound developmental delay, complex epilepsy, and premature lethality (median age of death is 8 years). NKH is an autosomal recessive condition caused by mutations in genes encoding enzymes active in the Glycine Cleavage System (GCS) localised to the mitochondria and resulting in accumulation of glycine in the body fluids and tissues. 80% of cases are caused by mutations in *GLDC*.

There is no cure; the current treatment for NKH is based on use of sodium benzoate, to lower glycine levels in the body, and management of epilepsy. A limitation of this approach is that benzoate causes severe gastrointestinal distress and vomiting, may lead to carnitine deficiency and can be toxic. Furthermore, while benzoate can lower systemic glycine, this does not overcome the suppression of one-carbon folate metabolism that results from loss of glycine cleavage system activity.

Technology

The approach described in this invention is to provide gene therapy using adeno-associated virus (AAV) vectors focussing on delivering a correct copy of *GLDC*. The development and testing of AAV vectors have been made use of a *Gldc*-deficient mouse model of NKH developed and extensively characterised in the Greene lab.

Development Stage

The inventors successfully have achieved expression of mouse Gldc (mGldc) in brain and liver, demonstrated activity of vector-expressed mGldc, developed a vector to express human GLDC in brain and liver, normalisation of folate one-carbon metabolism (FOCM) in brain tissue of AAV-treated mice. normalisation of glycine abundance in brain tissue of Gldc-deficient mice treated with AAV vectors, medium-term effects of treatment and Long-term safety testing (non-GLP).

Market

NKH has an estimated incidence of 1 in 76,000, making it the second most common disorder of amino acid metabolism, after phenylketonuria.

Inventors

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IP

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Further Information

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References

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