UCLB Commercialising Technology

AAV Gene Therapy for Wilsons Disease

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Summary

Wilson's disease presents an ideal candidate for somatic gene transfer methodologies owing to its singular genetic root, ATP7B gene. By addressing approximately 30% of hepatocytes, the primary liver cells, this approach holds promise in mitigating Cu storage characteristic of Wilson's disease patients.

Background

Wilson disease is an autosomal-recessive disorder of copper (Cu) metabolism caused by deleterious mutations in the Cu-transporting gene *ATP7B*, responsible of regulating the Cu levels in the body. Wilson disease has a global incidence of 1 in 30,000.

The pathogenesis involves homozygous mutation in the *ATP7B* gene, resulting in impaired biliary secretion of Cu and subsequent Cu accumulation in the liver, cornea, and other tissues leading to cell damage and apoptosis. Although chelation therapy and zinc treatment are commonly used to treat Wilson disease, they are non-curative as they fail to address the underlying metabolic defects in Wilson disease.

Technology

This innovative gene therapy utilized adeno-associated virus (AAV) vectors to deliver stable endogenous expression of the ATP7B gene directly into hepatocytes, with the goal of restoring Cu metabolism in patients with Wilson's disease following a single peripheral vein administration.

To achieve this, the inventors developed a modified ATP7B cDNA, optimised through over 1000 nucleotide changes to the wild-type ATP7B sequence. The resulting unique-codon-optimised cDNA that shares 77% similarity with the wild-type sequence.

In pre-clinical studies employing the AAV vectors encoding the optimized human ATP7B, the researcher observed promising outcomes:

- The vectors led to the expression of transgenic ATP7B protein in homozygous Atp7b-/- rats (LEC rats). The protein levels were approximately 5% of levels observed in control rats.
- The expression of the transgenic human ATP7B in hepatocytes connected to bile canaliculi led to the excretion of bile copper in animals that were administered AAV vectors at levels comparable to those of control animals with the LEA.

Stage of development

The vector is optimised and ready for pre-clinical toxicology studies and then clinical studies

Market

The treatment landscape for Wilson's disease is marked by an unmet clinical need as current options are limited to palliative care, leaving a significant gap for effective therapies:

- With a global incidence estimate ranging from 1 to 4 cases per 100,000 people, there is a substantial number of potential patients.
- The global market for Wilson's Disease Drugs was valuated at approximately USD 527 million in 2022.
- Only two early phase studies using AAV-based therapies for Wilson disease are currently in progress.

Team

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IP

Granted patent in Switzerland, Germany, Spain, France and UK (EP 3390623 A1 20181024)

Further Information

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