Battle against fatal neurodegenerative disease advances on two fronts

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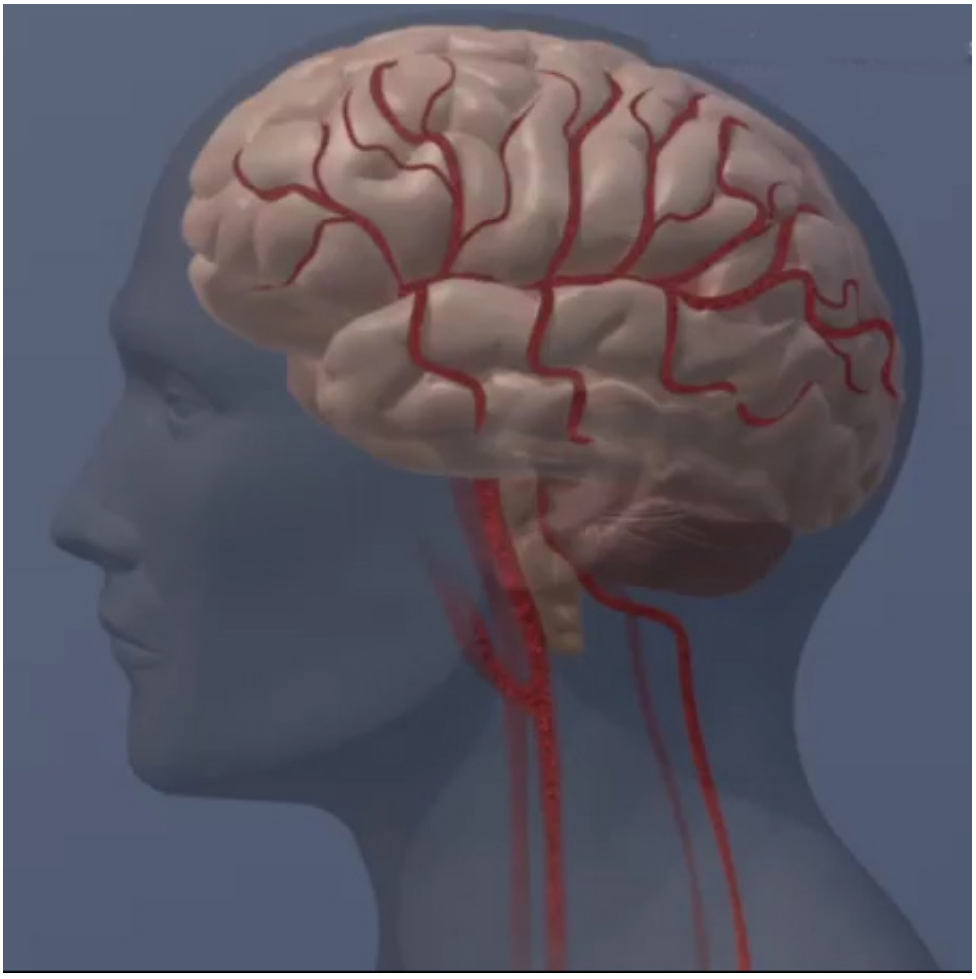

Credit: copyright American Heart Association

European researchers are pioneering a vaccine and treatment for

amyotrophic lateral sclerosis.

In 2005, an American triathlete named Jon Blais was diagnosed with an incurable neurodegenerative disease known as amyotrophic lateral sclerosis, or ALS. He was 33 years old.

Given no more than five years to live, Blais set about ticking off his final bucket-list challenge: the annual "Ironman World Championship" in the US state of Hawaii. In October 2005, six months after his diagnosis, he became the only person with ALS ever to cross the finish line.

German-Dutch duo

At the following year's event, Blais was wheelchair-bound. By the time of the 2007 contest, he was dead.

"It shows how ALS can hit anybody at any age," said Professor Dieter Edbauer, a specialist in the cell biological mechanisms of neurodegeneration at the German Center for Neurodegenerative Diseases, or DZNE. "Current drugs can extend life only by a few months."

Edbauer leads a research project that received EU funding to develop a vaccine against the most common genetic variant of ALS. Called GA-VAX, the project began in 2022 and is due to run into 2025.

In addition to the DZNE, GA-VAX includes a Dutch vaccine development and manufacturing company named Intravacc.

Based in a science park near Utrecht, Intravacc acts as a partner to organizations worldwide seeking to turn vaccine ideas into preventive and therapeutic breakthroughs.

Fast killer

First identified in 1869, ALS is characterized by the progressive degeneration of nerve cells in the spinal cord and brain.

It often begins with spasms, twitching or a weakness in an arm or leg before quickly affecting all muscles. Most commonly, ALS hits people aged between 40 and 70 and about two people per every 100 000 worldwide are newly diagnosed with the disease annually.

"No one has ever been cured of ALS and life expectancy is typically just two to five years, which is far worse than most cancers," said Edbauer.

Eureka moment

He began his research career as a medical student working on cancer vaccines and later focused on the biology of Alzheimer's and Fragile X Syndrome—a genetic condition that causes intellectual disability.

Then, more than a decade ago, Edbauer turned his attention to ALS as a result of a Eureka moment tied to a discovery by scientists in the US of a rare gene mutation.

In 2011, these researchers found a mutation in a gene called C9orf72 that acts as a trigger for a form of ALS now known as C9-ALS.

The mutation occurs when a small part of the DNA for the C9orf72 gene is repeated hundreds of extra times. Edbauer discovered that this "repeat expansion" leads to the production of toxic proteins that contribute to neuron degeneration.

"It was a crazy idea really, but we knew that ALS patients had a unique

pathology," he said. "My hypothesis was that the C9orf72 repeat expansion could be translated into aggregating proteins, although this region of the gene is normally not translated at all."

Edbauer said that he and his colleagues made antibodies against these repeat proteins and were 'stunned' when labeling all the mysterious aggregates uniquely present in the brain and spinal cord of C9-ALS patients.

He found that his antibodies could block toxicity of the repeat proteins in cell culture and realized his early work on cancer vaccines might be applicable to ALS.

Vaccine hope

Fast-forward to today and, through GA-VAX, Edbauer is developing a vaccine that would prompt the immune system to produce antibodies against the most abundant of the harmful repeat proteins, called poly-GA.

The planned vaccine has the potential to slow or even prevent the progression of ALS in C9-ALS patients, who account for between 5% and 10% of all cases of the disease.

Previous results from a prototype vaccine in mice have been promising, according to Edbauer.

"We have shown that the prototype vaccine reduces the aggregation of harmful proteins and inflammation in the brain, ultimately preserving neuron function," he said.

Working with Intravacc has helped Edbauer improve the prototype vaccine used in mice for eventual use in humans. Before then, several

steps are still needed.

These include tests to refine the vaccine formulation and dose. With safety and efficacy data, the team can apply to conduct clinical trials on patients genetically tested for C9-ALS.

That could happen as soon as 2026, with an actual vaccine possible less than a decade later, according to Edbauer.

"Maybe within five to 10 years it will become a more manageable disease," he said.

Brain barrier

Farther north in Europe, a regenerative-drugs expert named Merja Voutilainen also has ALS in her sights.

An associate professor of regenerative pharmacology at the University of Helsinki in Finland, Voutilainen led an EU-funded project that involved groundbreaking work into a treatment for the disease.

The treatment involves proteins that can increase neuron survival, growth and repair and protect against toxins. These proteins are so-called neurotrophic factors.

Voutilainen's project was called FutureTrophicFactors and wrapped up in January 2024 after five years. It focused on a way to deliver proteins with neurotrophic-factor properties to the brain.

Traditionally, these proteins are too big to cross the blood brain barrier—a protective filter in the brain that allows only certain substances to pass through. The barrier is basically the brain's natural defense against foreign invaders.

As a result, for such proteins to be effective, they require the tricky task of being injected directly into the brain.

"Brain injections are not easy to perform and not many doctors can do them," said Voutilainen.

Protein pathway

In FutureTrophicFactors, Voutilainen and colleagues discovered smaller versions of proteins with neurotrophic-factor properties.

Her team showed that these versions, called "fragments," are small enough to penetrate the blood brain barrier while retaining their effectiveness.

"These fragments can cross the blood brain barrier, which is a breakthrough meaning they can be injected under the skin, like insulin, then go straight to the brain and the spinal cord," Voutilainen said. "They can be used for the treatment of neurodegenerative diseases such as ALS and Parkinson's."

Pre-clinical trials in mice have shown that this treatment works, protecting and restoring motor neurons.

In the wake of FutureTrophicFactors, the research team is preparing further preclinical trials on transgenic mice and rats to collect more data.

Clinical testing on ALS patients could start during the next five years and the actual treatment might become available in five to 10 years, according to Voutilainen.

She regards earlier, easier treatment as key to increasing the survival of neurons for people with ALS.

"I really hope through this work we can both slow down the disease and, at least partially, cure it," said Voutilainen. "I'm optimistic."

More information:

- GA-VAX
- FutureTrophicFactors

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