Vaccsheet

Avacc® 31: A peptide-based conjugate vaccine targeting a neurotoxic dipeptide repeat protein found in patients with C9orf72 amyotrophic lateral sclerosis (C9-ALS)

At a glance

Technology
Peptide-based conjugate vaccine built on Con-Vacc Technology.

Status
Finishing pre-clinical phase.

Unmet need
The prevalence of ALS is 5–12:100,000. 5–10% of cases are due to an HRE in C9orf72.

10%
C9orf72 ALS

Target
Aggregating poly-Glycine-Alanine resulting from a hexanucleotide repeat expansion (HRE) in C9orf72.

Route of administration & schedule
Subcutaneous injection; life-long repeated boosters.

Vaccsheet

Disease: C9orf72 amyotrophic lateral sclerosis (C9-ALS)

Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motor neuron disease. Although rare, this orphan disease has extensive socioeconomic impact and is predicted to increase with the aging global population.[1] The progressive paralysis of ALS is incurable, leading to death within 2–5 years of diagnosis. Currently available therapies only alleviate symptoms and extend life by a few months.

ALS has a global prevalence of 5–12:100,000,[2] with a lifetime risk of development of about 1:400.[3] ALS has a significant genetic component. In the Western Hemisphere, the C9orf72 hexanucleotide repeat expansion (HRE) is found in 5–10% of all patients and is thus, the most common known cause.[2] Patients carrying the C9orf72 HRE are equally likely to develop ALS, frontotemporal dementia (FTD), or a mixed disease.

Therapeutic concept: A conjugate vaccine targeting poly-GA repeats

The research group of Prof. Dr. Dieter Edbauer at the German Center for Neurodegenerative Diseases (DZNE: Deutsches Zentrum für Neurodegenerative Erkrankungen) demonstrated that in ALS patients with C9orf72 mutations, a massively expanded $(G_4C_2)_n$ repeat sequence is translated into neurotoxic long aggregating repeat proteins, most abundantly poly-Glycine-Alanine (poly-GA).[4] In cell and mouse models, poly-GA molecules trigger ALS-related downstream pathology, culminating in motor neuron death.

An experimental therapeutic vaccine developed by the DZNE team stimulates the production of antibodies against poly-GA, which has shown pre-clinical efficacy in a mouse model (see “Status: Development of the therapeutic vaccine targeting C9-ALS”).

Technology: A clinically proven platform

A commercial version of the experimental vaccine builds on Intravacc’s time-tested Con-Vacc platform. The platform offers a unique set of capabilities and services to produce an optimized antigen bound to a protein carrier antigen, including high-quality antigen design, effective conjugation methods with different carriers, and expertise in characterizing these constructs. The platform has generated several successful vaccines, including a shigellosis vaccine in phase II clinical trials and a Hib vaccine that has been on the market for several years.

Status: Development of the therapeutic vaccine targeting C9-ALS

The DZNE and Intravacc have joined forces to develop this C9-ALS therapeutic vaccine candidate for a First-in-Human (FiH) phase Ib/IIa clinical trial. A 2.5 million EUR grant from the European Union (EIC Transition Grant) funds the pre-clinical development by the consortium to advance the project to the clinical stage.[5]

In a C9orf72 mouse model,[6] the experimental vaccine reduces poly-GA aggregates and inflammation, while largely preventing motor deficits (Figure 1). Vaccinating either before or after symptom presentation was effective in reducing neuronal damage (Figure 2).

Monthly vaccinations to boost anti-GA antibodies prevents motor deficits in a C9orf72 mouse model

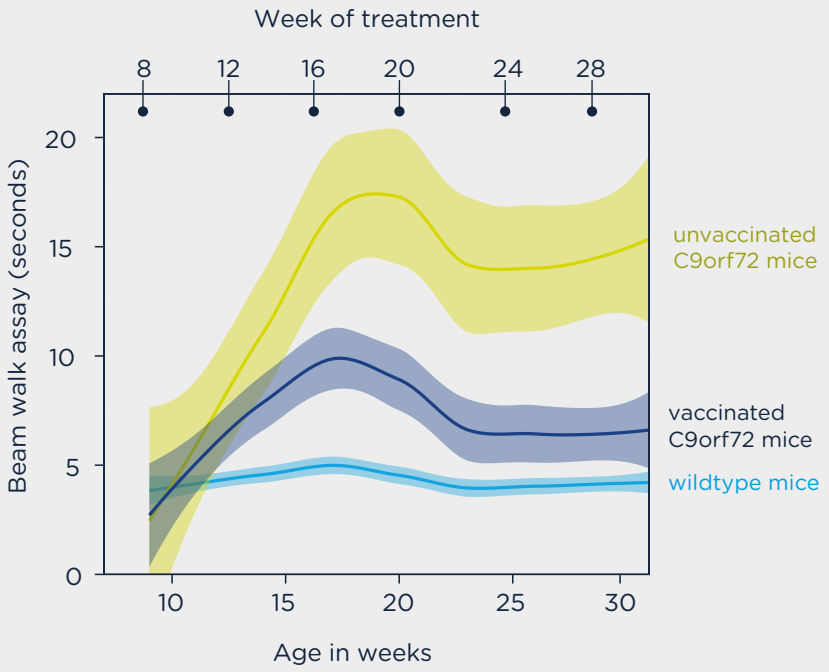

Figure 1. Motor performance was significantly better in vaccinated versus unvaccinated C9orf72 mice. Wildtype and C9orf72 mice received a series of phosphate buffer saline (PBS) injections or an experimental vaccine every four weeks. The time to complete a beam walk was recorded from week 9 onward. By week 29, the vaccinated C9orf72 mice took half the time to cross the beam compared to unvaccinated C9orf72 mice (6.9 vs. 14.8 s, averaged over weeks 29–31). Data adapted from Zhou et al. 2020 to create a smoothened time series.[7]

Vaccination before or after symptom presentation reduced neuronal damage in a C9orf72 mouse model

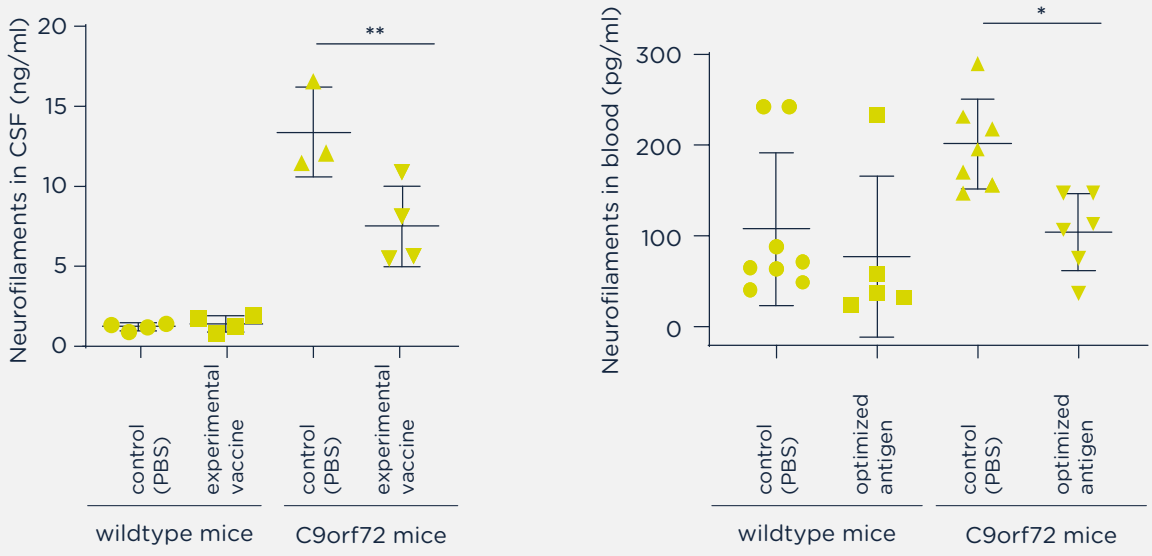

Figure 2. High levels of neurofilament light chain in cerebrospinal fluid (CSF) or blood are a marker associated with progressive neurodegeneration in ALS and other diseases. Levels decreased in vaccinated C9orf72 mice, both when the vaccination regimen began before (week 8; left) or after (week 22; right) symptom onset. Error bars represent standard deviation Data adapted from Zhou et al. 2020.[7]

The next development steps are planned across workflow areas to successfully reach initial clinical stages:

Manufacturing

Optimize the manufacturing properties of the vaccine to establish a streamlined production and quality control that is scalable to GMP.

Characterization

Conduct immunogenicity, toxicology, and safety pharmacology studies, and determine dose range, formulation, and administration route. Perform efficacy studies of the optimized antigen in a poly-GA mouse model.

Regulatory affairs

Prepare a draft Clinical Trial Application (CTA) for a phase Ib/IIa study of the optimized vaccine in diagnosed C9orf72 ALS patients.

Other supportive data and structures for partnership or licensing are available and can be presented in a confidential follow-up meeting.

GA-VAX

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[3] Ryan *et al*. 2019. JAMA Neurol. doi: 10.1001/jamaneurol.2019.2044

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Intravacc. Innovating vaccines

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