AAV9-Based Gene Therapy in Monogenic Neurologic Diseases

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A key challenge faced by both science and medicine has been to address the source of disease-causing mutations in multiple somatic cells and then to scale and adapt that technology to treat disease.

At AveXis, a Novartis company, we have built on 30 years of science to deliver on this challenge by demonstrating the long-term curative potential of gene therapy and its capacity to make an impact on the daily lives of those suffering rare and devastating genetic diseases.

We believe, and have now demonstrated, that gene therapy is a rational approach for the treatment of rare monogenic diseases in particular—one that allows for the efficient delivery of a therapeutic vector construct with the potential to address a disease's root cause.

Our initial focus is on a devastating rare disease called spinal muscular atrophy (SMA). SMA is caused by deletions and/or mutations of the survival motor neuron 1 (*SMN1*) gene[1,2]. In the most severe forms, SMA results in the rapid and irreversible loss of motor neurons, affecting muscle functions, including breathing, swallowing, and basic movement[1]. Clinically, this translates to progressive muscle weakness, paralysis, and—when left untreated in its most common form—permanent ventilation or death[2].

The AveXis approach to SMA is to replace the *SMN1* gene in the motor neurons of the central nervous system. We have seen success in this endeavor both scientifically and clinically.

INNOVATION AND COMMITMENT CAN TRANSFORM THE LIVES OF PATIENTS WITH RARE GENETIC DISEASE

Building on this success, today we are applying this exciting and pioneering therapeutic approach to other monogenic neurologic and muscle diseases with a scalable platform based on a recombinant AAV9 vector. This technology was informed by—and transcends—many of the limitations of previous attempts at gene therapy (**Figure 1**).

Our platform centers around three basic technologies that overcome key issues associated with gene therapy failures of the past[3-5]:

- **A recombinant AAV9 capsid shell** able to deliver payload across the blood-brain barrier and into the nervous system and many other tissues.
- **Self-complementary (sc) AAV DNA technology**, featuring inverted terminal repeats (ITRs) for rapid onset of effect in quickly deteriorating patient populations.
- **An optimized expression cassette** designed to restore gene expression or suppress mutant gene expression safely.

The AveXis gene therapy pipeline is built on the successful extrapolation of data from years of research to make an AAV9 platform versatile enough to yield potential treatments for a variety of rare monogenic diseases. Our current AAV9 portfolio includes gene therapy candidates for SMA, Rett syndrome, *SOD1* amyotrophic lateral sclerosis (ALS), and Friedreich's ataxia, with several other AAV9-based candidates in the pipeline.

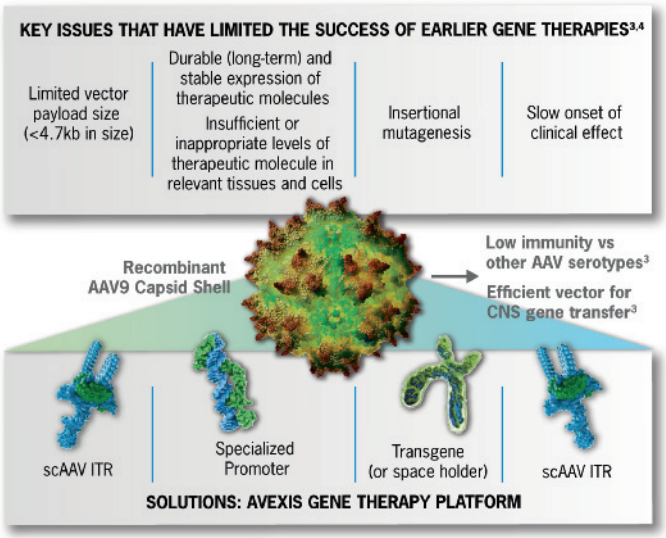

Figure 1. AAV, adeno-associated virus; CNS, central nervous system; kb, kilobases; scAAV ITR, self-complementary adeno-associated virus inverted terminal repeat.

AveXis is one of the first gene therapy companies in the world to have successfully scaled up its manufacturing capacity, with a manufacturing footprint of over one million square feet among four US locations—more than any other gene therapy company or contract manufacturing organization. This capacity and expertise will enable AveXis to manufacture both currently approved and pipeline therapies at quality and scale.

We continue to refine and evolve our platform and manufacturing capabilities to address the ongoing challenges inherent to gene therapy and to expand the applications into many new arenas of medicine.

At AveXis, we believe innovation and commitment can transform the lives of patients with rare genetic disease.

References

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