

Optimizing gene therapy for severe central nervous system diseases

Voyager Therapeutics is developing potentially life-changing gene therapies to treat advanced Parkinson's disease and other serious neurological disorders with a significant unmet medical need.

Over the past decade, gene therapy has shown tremendous promise for the treatment of severe diseases of the central nervous system (CNS). Clinical trials have demonstrated that adeno-associated virus (AAV) vectors in particular are safe and effective for delivering therapeutic genes to the brain and spinal cord. Because targeted cells in the CNS are long-lived and non-dividing, a single dose of this type of therapy could potentially be sufficient for lifelong treatment of disease. Yet the promise of an AAV gene therapy has not yet been realized for the millions of patients whose symptoms are not treatable or adequately controlled by currently available therapies.

To close that clinical gap, Voyager is developing potentially life-changing gene therapies that specifically target the underlying pathobiology of CNS diseases by either expressing missing proteins or inhibiting disease-causing proteins. The company, headquartered in Cambridge, Massachusetts, is committed to advancing the field of AAV gene therapy by innovating and investing in areas such as vector optimization, engineering and delivery, as well as manufacturing.

Launched in 2014, the public clinical-stage company has already developed a robust product engine that could transform treatment for a wide range of severe neurological diseases with known genetic causes. Its most advanced clinical candidate, VY-AADC01, is currently in a phase 1b clinical trial for the treatment of advanced Parkinson's disease, and additional preclinical programs are rapidly advancing toward the clinic.

"Voyager's mission is to become the leading gene therapy company focused on developing, manufacturing and commercializing products for serious diseases of the central nervous system," said Voyager's president and CEO Steven Paul. "We have made solid progress toward achieving our goal of developing revolutionary treatments that can truly make a difference to patients."

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Steven Paul, CEO

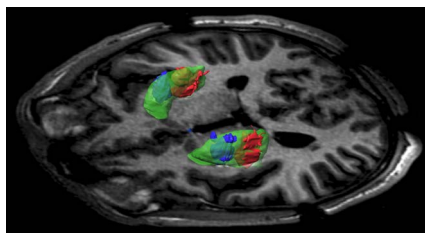


Figure 1: MRI image of putamen coverage of VY-AADC01. Green, putamen; blue/red, VY-AADC01 injections.

Turning back the clock in Parkinson's disease

Voyager's lead program centers on developing a much needed therapy for advanced Parkinson's disease. Currently, the most efficacious treatment for Parkinson's disease is a drug called levodopa, which gets converted in neurons in the brain to dopamine by an enzyme called aromatic L-amino acid decarboxylase (AADC). But as the disease progresses, patients lose the ability to convert levodopa into dopamine as endogenous neurons in the midbrain that contain AADC die. These later-stage patients have erratic, short-lived responses to levodopa and related drugs, and subsequently experience worsening and debilitating symptoms of immobility such as tremor, rigidity and slowness of movement. Consequently, they require higher and more frequent doses of levodopa, but it is often difficult to find a medication schedule that provides consistent relief of their motor symptoms throughout the day, and levodopa side effects such as dyskinesia and non-motor behavioral symptoms tend to increase with the dose.

To address this problem, Voyager's goal with VY-AADC01 is to bypass the brain region where neurons are dying and, with a single infusion, deliver the gene that encodes AADC directly to the putamen, a brain region where intrinsic neurons remain intact, to create a new reservoir of dopamine in response to orally administered levodopa. This approach could provide advanced patients with more reliable control of their motor symptoms in response to levodopa dosing, essentially setting the clock back to a time when they were less symptomatic and more responsive to levodopa (Fig. 1).

Patients studied in a previously completed phase 1 study continued to show sustained expression of the AADC enzyme after initial administration suggesting the potential for a long-term, durable benefit after a single treatment. A phase 1b dose-escalation trial in advanced Parkinson's disease is under way, with preliminary results, including measurements of motor

function, expected at the end of 2016 and in the first half of 2017. "Our goal is to turn back the clock on the treatment of these motor symptoms for the estimated 100,000 patients in the US alone who suffer from the advanced stages of the disease, allowing them to now respond the way they initially did during the earlier stages of the disease," Paul said.

Advancing AAV therapies for severe neurological diseases

Voyager's preclinical AAV programs for the treatment of severe CNS diseases include gene knockdown or silencing for the treatment of amyotrophic lateral sclerosis, Huntington's disease and chronic pain, and gene replacement for the treatment of Friedreich's ataxia and spinal muscular atrophy. A newer approach involves delivering genes that encode certain monoclonal antibodies. For example, VY-TAU01 is an AAV vector containing a gene encoding a monoclonal antibody that targets tau protein aggregates for removal. This therapy is intended to treat frontotemporal dementia and Alzheimer's disease.

In all of its gene therapy programs, Voyager is committed to advancing the AAV field by selecting, designing and manufacturing high-quality vectors. To tailor each gene therapy for a particular disease, the company focuses on engineering all three key elements of AAV vectors—the capsid, promoter and transgene—and selects the most suitable dose, route of administration and delivery technique to achieve optimal gene expression or gene knockdown in the right cells at the right time.

Moreover, the company has established a global strategic collaboration with Sanofi Genzyme, has a state-of-the-art process development laboratory at its headquarters and is collaborating with MassBiologics, a US Food and Drug Administration-licensed commercial-scale good manufacturing practice (GMP) manufacturer affiliated with the University of Massachusetts Medical School. "Through additional partnerships and collaborations, we are confident that we will be able to leverage our transformative product engine to improve the lives of patients suffering from severe disease of the CNS," Paul said.

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