Voyager Therapeutics
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Unleashing the potential of AAV gene therapy

Voyager Therapeutics is unlocking the potential of adeno-associated virus gene therapy to treat a range of neurological disorders, broadening the therapeutic window while ensuring efficacy and safety.

There is an urgency for improved viral vector technology to meet the needs of the wide array of gene therapies that are in early-stage development. Conventional adeno-associated viruses (AAVs) are limited by insufficient delivery to the relevant tissue (that is, inadequate tissue tropism). When injected systemically, high doses are frequently required, leading to substantial—and at times life-threatening—toxicity. For central nervous system (CNS) applications, attempts are being made to deliver AAV gene therapy directly to the brain parenchyma or the cerebrospinal fluid (CSF) space by intra-cisterna magna or lumbar cistern injection; however, these routes result in suboptimal distribution across the brain and low transduction efficiency. This risk/benefit imbalance has resulted in numerous setbacks, delays, and losses of investment[1].

Enter Voyager Therapeutics (Cambridge, MA, USA), an altogether different gene therapy company, focused on developing life-changing treatments via innovative technology. Voyager is leading the development of next-generation AAV capsids—which are the outer viral protein shells that enclose genetic material—with the aim of overcoming the limitations currently hindering the field and unlocking the potential of gene therapy to enable much-needed life-changing treatments.

"At Voyager, we are working to fulfil the enormous promise AAV gene therapy holds for treating serious diseases," said CEO Al Sandrock. "Proprietary capsids born from our screening platform are creating opportunities to elevate the field and power our early-stage pipeline of programs in neurologic diseases and other therapeutic areas, targeting tissues and cells that have been previously inaccessible with conventional approaches."

TRACER: powering the next chapter

Underpinning Voyager's mission is its trademark AAV capsid-discovery platform, Tropism Redirection of AAV by Cell-type-specific Expression of RNA (TRACER). This broadly applicable, functional, RNA-based technology allows for rapid in vivo evolution of AAV capsids with desired cell-specific transduction properties in multiple species, including non-human primates (NHPs). TRACER facilitates the discovery of capsids that can cross the blood–brain barrier (BBB), have enhanced CNS tropisms across species, and achieve widespread biodistribution and transduction of multiple regions of the brain, including those that have traditionally been difficult to reach.

For example, using TRACER, Voyager has discovered a series of novel AAV capsids that, following intravenous (IV) administration, achieve up to 1,000-fold higher RNA expression in the brain and 100-fold higher RNA expression in the spinal cord of NHPs relative to AAV9, which is the naturally occurring AAV serotype that is currently understood to have the best penetration of the BBB in humans. "We believe Voyager's TRACER capsids should allow significantly enhanced gene delivery to specific types of cells in the brain at lower doses than conventional AAV9, enabling clinical development for Voyager and its partners across the field," said Mathieu Nonnenmacher, VP of Capsid Discovery.

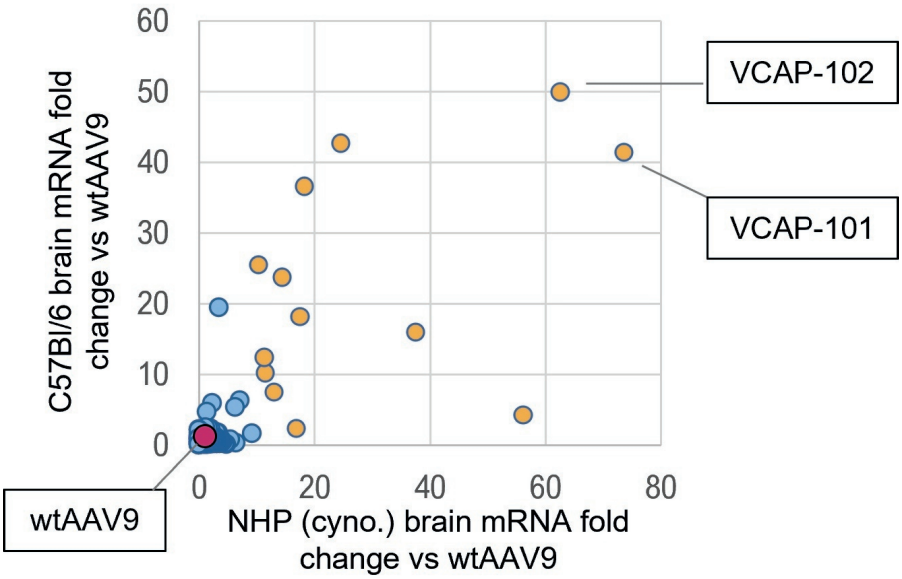

Fig. 1 | Cross-species functionality. Brain mRNA fold change of Voyager AAV9-derived capsids in NHP and mouse. mRNA, messenger RNA; NHP (cyno), non-human primate (cynomolgus); wtAAV9, wild type AAV9.

More recently, capsid evolution screens have yielded additional proprietary candidates, derived from AAV9 or AAV5, which demonstrate enhanced brain transduction relative to their parental serotypes at comparable levels in both NHPs and mice. "This cross-species functionality is critical to increasing a capsid's potential for translation into humans, while also enabling efficacy to be established in preclinical mouse disease models," pointed out Nonnenmacher (Fig. 1).

In addition to their improved tropism for the target tissues, a number of the capsids discovered by Voyager demonstrate significantly reduced delivery to off-target tissues, such as the dorsal root ganglia or the liver, which may help avoid toxicities commonly associated with AAV delivery.

Using TRACER, Voyager is also identifying capsids with the capacity for strong cardiac and skeletal muscle transduction, and the platform holds promise for producing candidates with enhanced tropism for liver, eye, and other tissue types (Fig. 2). The company is proceeding with additional capsid campaigns derived from AAV9, AAV5, and other AAV serotypes to identify novel capsids optimized for AAV delivery for specific therapeutic applications.

Designed to deliver

Voyager's next-generation capsids are designed to deliver innovative AAV-based gene therapies using various payloads. The company's team of experts initially identifies and selects suitable diseases, in which single-dose AAV gene therapy is expected to either increase or decrease the production of a specific protein, to prevent, halt, or slow disease progression, or to reduce symptom severity, therefore providing clinically meaningful impact to patients.

The team at Voyager works to match the capsid best suited to reach the necessary tissue and cell types with the therapeutic payload to be delivered. These genetic payloads comprise a promoter to drive expression of the transgene in the targeted cells and a therapeutic gene intended to replace one that is not being properly expressed, an artificial small-interfering RNA (siRNA) intended to knock-down deleterious expression of a harmful gene or allele, or an alternative payload, such as a gene encoding a therapeutic antibody. The team then optimizes the dose for IV delivery of the AAV vectors to target the cells that are critical to treating the disease of interest. "We believe that optimizing each of the capsid and transgene parameters,

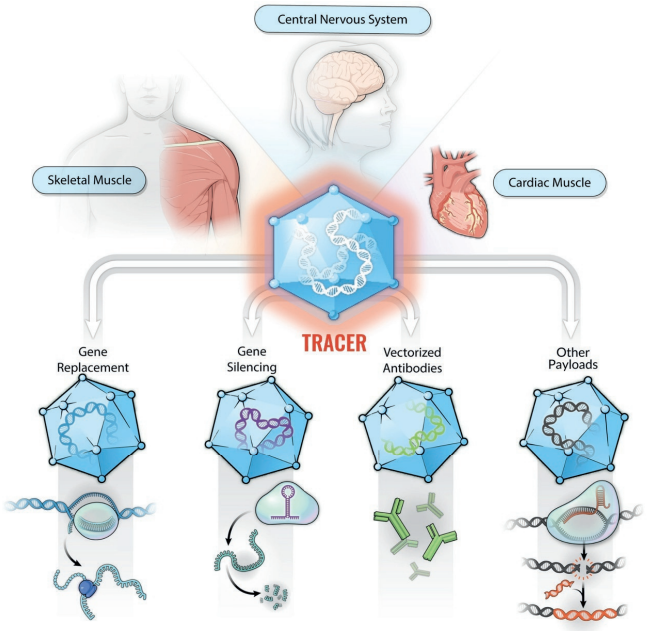

Fig. 2 | Tracer capsids in motion. The TRACER platform can be targeted to discover capsids for various tissue and cell types, and used to deliver various payloads.

including the promoter, is essential to achieving on-target delivery while minimizing off-target risks," explained Todd Carter, SVP of Research.

AAV–GBA1 gene replacement therapy

In addition to its TRACER capsid-discovery platform, Voyager has developed a strategy to accelerate the development of an *AAV*-glucocerebrosidase 1 (*GBA1*) gene replacement therapy designed to achieve superior CNS distribution with a non-invasive, one-time IV administration.

The *GBA1* gene encodes the lysosomal enzyme β-glucocerebrosidase (GCase). Homozygous *GBA1* loss-of-function (LOF) results in a deficit of GCase activity and a cellular build-up of glycosphingolipid substrate, which manifests as Gaucher's disease (GD). Enzyme-replacement therapy can have clinical impact in the periphery, but cannot adequately cross the BBB. Notably, LOF mutations in the *GBA* gene are one of the greatest genetic risk factors for Parkinson's disease (PD) and Lewy body dementia (LBD). Thus, Voyager's approach intends to use a next-generation AAV capsid with an optimized *GBA1* transgene cassette to increase GCase activity broadly across the brain and slow down pathogenesis in *GBA*-associated PD.

In vivo target-engagement studies have demonstrated that delivering *GBA1* transgenes using a BBB-penetrant AAV capsid resulted in therapeutically relevant levels of GCase in multiple brain regions in mouse models, following a single IV dose. As GCase-activity increases of 30–50% are anticipated to be clinically impactful, Voyager's results and several fold increases in activity suggest the potential of maintaining therapeutically relevant enzymatic activity with additional dose reductions.

GBA1 mutations are correlated with multiple disease manifestations in the CNS and peripheral tissues, and are present in 7–10% of PD patients. This strategy also holds the potential for treatment in patients with other manifestations of GBA dysfunction, such as GD and dementia with Lewy bodies (DLB).

"These findings illustrate the potential to ameliorate disease in models of GBA1," said Carter. "Multiple AAV-GBA1 constructs demonstrated dose-dependent GBA1 protein level and GCase activity increases, and correction of glycosphingolipid levels to match control human comparator cells in vitro, as well as widespread CNS delivery of protein and glycosphingolipid-substrate reduction in mouse models."

> **"Unlocking the full potential of AAV gene therapy... to reshape the treatment landscape for neurological disorders and other serious diseases**
>
> Al Sandrock, CEO, Voyager Therapeutics

Broader pipeline

Voyager's pipeline supports the company's strategic vision for developing best-in-class treatments by focusing on well-validated targets, following efficient pathways to preclinical and clinical proof-of-concept, and seeking opportunities to provide meaningful therapeutic benefit to patients in areas of significant unmet need.

Voyager has initiated gene therapy programs powered by its TRACER capsids for a broad spectrum of diseases, including PD, superoxide dismutase (SOD1)-linked amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), human epidermal growth factor receptor 2 (HER2)-positive breast cancer-associated brain metastases, and Huntington's disease (HD). These efforts have shown promise in preclinical studies, pointing to significant opportunity to provide patient benefit.

"Our gene therapy platforms enable us to engineer, optimize, manufacture, and deliver AAV-based gene therapies that we believe have the potential to safely provide durable efficacy," said Carter. "The diversity of our payloads and differentiated capsids create the potential to engage targets that would otherwise be undruggable or unreachable with gene therapy."

Partnering for potential

Voyager's goals are to elevate the field of AAV gene therapy to its highest potential and to develop and deliver life-changing treatments to people around the world. To that end, in addition to its commitment to excellence in research and development and its world-class expertise in AAV-vector engineering and neurobiology, the company is actively engaged in discussions with potential partners to make Voyager's TRACER capsids available for use in their gene therapy programs through licensing and collaboration.

"We believe that our experience in AAV gene therapy for severe neurological diseases, our TRACER platform, and our pipeline programs enabled by each provide us with unique opportunities to collaborate in different ways to maximize value creation for ourselves, our partners, and the field," said Allen Nunnally, CBO at Voyager.

Indeed, the company has already secured capsid option and license agreements with Novartis and Pfizer for target-specific use with CNS and cardiac muscle targets. Voyager also has an ongoing collaboration with Neurocrine Biosciences on a preclinical Friedreich's ataxia (FA) program and two undisclosed discovery programs in which the company's novel capsids may be deployed.

Voyager's capsids have demonstrated greater specificity at lower doses and with reduced risk of off-target effects compared to conventional AAVs in NHP studies. Nonetheless, the company is working relentlessly to iterate improved versions of its initial promising capsids and to develop other new candidates that will enable safe and effective delivery of genetic payloads that could change the trajectory of disease for millions of people. Voyager intends that its partnerships will create even more numerous opportunities to realize the promise of its technology in the development of life-changing therapies—within and beyond the CNS—than it could undertake on its own.

"We see each step in our journey as progress toward unlocking the full potential of AAV gene therapy—not just for Voyager, but for the entire field, to reshape the treatment landscape for neurological disorders and other serious diseases, and help as many people as possible," said Sandrock. "This is an opportunity to evolve, innovate, and close in on the breakthroughs with our TRACER capsids that hold enormous promise to change the trajectory of disease and help improve the future of medicine."

1. Chart: FDA clinical holds now double the historical average. *Jefferies* (27 February 2022). Via https://endpts.com/hold-the-phone-biopharma-fda-imposed-clinical-holds-are-on-the-rise/

CONTACT
Scott Santiamo, Senior Director, Corporate Communications
Voyager Therapeutics
Cambridge, MA, USA
Tel: +1-718-344-5843
Email: ssantiamo@vygr.com