Voyager Therapeutics Presents Data for Second-Generation, TRACER™-Generated Capsids and CNS Gene Therapy Programs Advancing Toward Clinical Trials at the ASGCT 27th Annual Meeting

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- Translational potential of TRACER-derived AAV capsids demonstrated by data across multiple species (murine, porcine, multiple NHPs, human cells) and receptor binding -

- Preclinical safety and efficacy demonstrated in Alzheimer's disease and ALS gene therapies; low IV doses provided broad CNS biodistribution and robust transduction of key cell types -

LEXINGTON, Mass., May 08, 2024 (GLOBE NEWSWIRE) -- Voyager Therapeutics, Inc. (Nasdaq: VYGR), a biotechnology company dedicated to advancing neurogenetic medicines, today announced the presentation of data related to its TRACER™ capsid discovery platform and TRACER-driven gene therapy programs at the American Society of Gene & Cell Therapy's (ASGCT) 27th annual meeting.

Second-generation, intravenously (IV)-delivered capsids, evolved through the TRACER platform, showed further enhanced blood-brain barrier (BBB) penetrance, greater liver detargeting, and transduction of 50-75% of cells across diverse brain regions, with upwards of 95% transduction in certain key cell types such as Purkinje Neurons. Further, a gene therapy in preclinical development for SOD1 amyotrophic lateral sclerosis (ALS), which combines a SOD1 RNAi transgene packaged in a second-generation capsid, reduced SOD1 messenger RNA (mRNA) expression by up to 80% in non-human primate (NHP) spinal cord motor neurons following a single IV delivery at a clinically relevant dose of 3E13 vg/kg. The potential translatability of these capsids is supported by data across multiple species, including mice and multiple species of NHP, as well as binding to Alkaline Phosphatase (ALPL, formerly called Receptor X) in multiple species and in human cells. These data are highlighted in the oral presentation, "Continued directed evolution of VCAP-101 and VCAP-102 identifies second generation capsids with increased brain tropism in non-human primates and mice (#119)" on Wednesday, May 8, 2024, 4:30 p.m. – 4:45 p.m. ET, as well as in multiple posters detailed below.

"Results across species, capsid generations, and disease models provide the most extensive validation to date of the high translational potential of our TRACER capsids for gene therapy in the CNS," said Todd Carter, Ph.D., Chief Scientific Officer of Voyager Therapeutics. "The strong performance of our capsids has enabled selection of three development candidates in Voyager's wholly-owned and partnered gene therapy programs for neurologic diseases, which are currently advancing towards anticipated IND filings in 2025."

Additional data demonstrating the potential translatability, activity against therapeutic targets, manufacturability and performance of Voyager's TRACER capsids are being presented across 12 oral and poster presentations throughout the ASGCT meeting as follows:

Second-Generation Capsids
Oral Presentation: Continued directed evolution of VCAP-101 and VCAP-102 identifies second generation capsids with increased brain tropism in non-human primates and mice (#119)

- Applying its TRACER capsid discovery platform, Voyager has evolved a second generation of capsids with further optimized features, including central nervous system (CNS) tropism and liver detargeting, compared to VCAP-101 or VCAP-102 capsids.
- With low doses (3E13 vg/kg) delivered IV in an NHP model, Voyager's second-generation capsids achieved transgene expression in up to 65% of neurons and up to 97% of astrocytes across diverse brain regions, including cortical and subcortical areas.
- A SOD1 RNAi transgene packaged in a second-generation capsid and delivered IV reduced SOD1 mRNA expression by up to 80% in NHP spinal cord motor neurons.
- The potential translatability of Voyager's capsids is supported by data across mice and multiple NHP models, as well as binding to ALPL, a highly conserved cell surface receptor expressed at the BBB that mediates enhanced brain tropism of Voyager's capsids in multiple species and in human cells.

Advancements in Wholly-Owned CNS Gene Therapy Programs
Intravenous administration of BBB-penetrant, MAPT-Silencing, AAV gene therapy provides broad and robust CNS Tau lowering in tauopathy mouse models (#1602)

- A single IV administration of a tau silencing gene therapy candidate in a mouse model expressing human tau resulted in dose-dependent increases in vector genomes and concomitant reductions in tau mRNA levels of up to 90%, which were associated with significant reductions (50-70%) in human tau protein levels across the brain.
- Voyager anticipates filing an investigational new drug (IND) application in this program in 2026.

Intravenous delivery of AAV gene therapy for the treatment of SOD1-ALS provides broad SOD1 lowering in NHP (#1647)

- A potent SOD1 RNAi transgene packaged in a novel TRACER™-evolved capsid and administered IV in NHPs led to a favorable safety profile and significant reductions of SOD1 mRNA in critical spinal cord and brain regions impacted in ALS, supporting continued development and advancement into clinical testing.
- Voyager anticipates filing an IND application in this program in mid-2025.

Mechanism of Action and Cross-Species Translation
Identification and characterization of a highly conserved cell surface receptor utilized by engineered BBB-penetrant AAV capsids with enhanced brain tropism in non-human primates and mice (#975)

- Voyager identified a highly conserved cell surface receptor that mediates enhanced brain tropism of the VCAP-101/102 engineered capsid class. The discovery of a conserved cross-species receptor facilitating BBB passage by a novel engineered AAV capsid class represents a significant step forward in the development of targeted CNS therapeutics and provides a foundation for the rational design of next-generation AAV vectors.

Establishment of a predictive transcytosis model to recapitulate capsid-receptor interaction and phenotype of BBB-penetrant AAV variants (#976)

- To further characterize the mechanism underlying VCAP-102's enhanced brain tropism, Voyager developed a transcytosis model expressing the VCAP-102 receptor in cultured cells and demonstrated that VCAP-102 and second-generation capsids, but not the AAV9 capsid, exhibited efficient transcytosis.

Evaluation of cross-species expression across four species and cellular tropism of VCAP-102, an engineered blood-brain barrier-penetrating AAV derived capsid from TRACER Platform screens (#1452)

- Across mice, marmosets, African Green Monkeys, and Cynomolgus macaques, VCAP-102 demonstrated higher biodistribution and widespread transgene expression in the CNS compared to AAV9, supporting potential translatability into humans.

High-resolution quantitative analysis of multiple AAV capsids in rodent and primate models using multiplexed reporter protein tagging platform (#511)

- To solve the bottleneck in capsid variant characterization, Voyager designed and optimized a cross-species platform to simultaneously analyze up to 10 capsids in a single animal, while providing transgene DNA and RNA quantitation and protein detection.

Reduced Immunogenicity, Developability, and Manufacturing
Discovery of TRACER AAV capsids escaping pre-existing neutralizing antibodies (#973)

- A new generation of AAV capsids was bioengineered via the TRACER™ platform to evade pre-existing neutralizing antibodies while retaining improved CNS tropism, potentially increasing patient eligibility to receive AAV gene therapies.

Oral Presentation: Developability assessment of novel AAV capsids and payloads at early preclinical stage to enable development of AAV gene therapies (#65)

- Developability refers to the likelihood that an AAV development candidate can be advanced towards the clinic as a manufacturable, safe, and efficacious drug. This study outlines analytical methods that can be utilized early in assessing critical quality attributes and may help enable efficient development of AAV gene therapies.

Machine Learning for AAV production-fitness modeling (#974)

- Voyager has advanced machine learning to predict production fitness of capsid variants with high accuracy, helping guide development of high-production-fit libraries.

Comparing CsCl density gradient ultracentrifugation and anion exchange chromatography for the enrichment of full adeno-associated viral (AAV) vectors (#1037)

- Robust manufacturing processes are needed to remove empty and partially filled capsids from recombinant AAV (rAAV) drug product. This study compares performance of ultracentrifugation and chromatographic separation methods.

Development of HEK293 cell line for optimal production of novel capsids with enhanced brain tropism (#1035)

- Voyager has internally developed an HEK293 cell line (VYGR-293). This cost-efficient cell line provides an AAV expression platform to produce drug candidates for neurological disorders.

About the TRACER™ Capsid Discovery Platform
Voyager's TRACER™ (Tropism Redirection of AAV by Cell-type-specific Expression of RNA) capsid discovery platform is a broadly applicable, RNA-based screening platform that enables rapid discovery of novel AAV capsids to enable gene therapy. Voyager has leveraged TRACER to create multiple families of novel capsids that, following intravenous delivery in preclinical studies, harness the extensive vasculature of the central nervous system (CNS) to cross the blood-brain barrier and transduce a broad range of CNS regions and cell types. In cross-species preclinical studies (rodents and multiple non-human primate species), intravenous delivery of TRACER-generated capsids resulted in widespread payload expression across the CNS at relatively low doses, enabling selection of multiple development candidates in Voyager's wholly-owned and partnered gene therapy programs for neurologic diseases.

About Voyager Therapeutics
Voyager Therapeutics, Inc. (Nasdaq: VYGR) is a biotechnology company dedicated to leveraging the power of human genetics to modify the course of – and ultimately cure – neurological diseases. Our pipeline includes programs for Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, and multiple other diseases of the central nervous system. Many of our programs are derived from our TRACER™ AAV capsid discovery platform, which we have used to generate novel capsids and identify associated receptors to potentially enable high brain penetration with genetic medicines following intravenous dosing. Some of our programs are wholly owned, and some are advancing with partners including Alexion, AstraZeneca Rare Disease; Novartis Pharma AG; Neurocrine Biosciences, Inc.; and Sangamo Therapeutics, Inc. For more information, visit www.voyagertherapeutics.com.

Voyager Therapeutics® is a registered trademark, and TRACER™ is a trademark, of Voyager Therapeutics, Inc.

Forward-Looking Statements
This press release contains forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995 and other federal securities laws. The use of words such as “potential,” “anticipate,” “expect,” “believe,” “could,” “may,” and other similar expressions are intended to identify forward-looking statements.

For example, all statements Voyager makes regarding Voyager’s ability to advance its AAV-based gene therapy programs, including expectations for Voyager’s achievement of preclinical and clinical development milestones for its potential development candidates such as the initiation of clinical trials; Voyager’s ability to advance gene therapy product candidates under its partnered programs; the potential for Voyager’s novel TRACER capsids to achieve desired results in humans, including achievement of a higher therapeutic index and increased patient eligibility to receive AAV gene therapies; and the ability of Voyager’s analytical methods to enable efficient development of AAV gene therapies are forward looking.

All forward-looking statements are based on estimates and assumptions by Voyager’s management that, although Voyager believes such forward-looking statements to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that Voyager expected. Such risks and uncertainties include, among others, the continued development of Voyager’s technology platforms, including Voyager’s TRACER platform and its antibody screening technology; the ability to initiate and conduct preclinical studies in animal models; the development by third parties of capsid identification platforms that may be competitive to Voyager’s TRACER capsid discovery platform; Voyager’s ability to create and protect intellectual property rights associated with the TRACER capsid discovery platform, the capsids identified by the platform, and development candidates for Voyager’s pipeline programs; the initiation, timing, conduct and outcomes of Voyager’s preclinical and clinical studies; the possibility or the timing of Voyager’s receipt of program reimbursement, development or commercialization milestones, option exercise, and other payments under Voyager’s existing licensing or collaboration agreements; the ability of Voyager to negotiate and complete licensing or collaboration agreements with other parties on terms acceptable to Voyager and the third parties; the ability to attract and retain talented directors, employees, and contractors; and the sufficiency of cash resources to fund its operations and pursue its corporate objectives.

These statements are also subject to a number of material risks and uncertainties that are described in Voyager’s most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission. All information in the press release is as of the date of this press release, and any forward-looking statement speaks only as of the date on which it was made. Voyager undertakes no obligation to publicly update or revise this information or any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

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