August 7, 2017

Research Published in Molecular Therapy Identifies Optimal Gene-based Therapeutic Construct for X-Linked Retinitis Pigmentosa

Preclinical research led by scientists from the University of Pennsylvania demonstrates effective delivery and expression of functional gene sequences, positive effects on retinal structure and function, and improved visual navigation in animal models

GAINESVILLE, Fla. and CAMBRIDGE, Mass. and PHILADELPHIA, Aug. 07, 2017 (GLOBE NEWSWIRE) -- Researchers from the University of Pennsylvania today announced the publication of preclinical proof of concept data supporting the clinical development of a gene-based therapy for the treatment of X-linked retinitis pigmentosa (XLRP), one of the most common inherited retinal disorders, which causes progressive vision loss in boys and young men.

The investigational gene therapy was developed by Applied Genetic Technologies Corporation (NASDAQ:AGTC), a biotechnology company conducting human clinical trials of adeno-associated virus (AAV)-based gene therapies for the treatment of rare diseases. AGTC is developing a gene-based therapy for XLRP in collaboration with Biogen.

The study, "Optimization of Retinal Gene Therapy for X-linked Retinitis Pigmentosa due to *RPGR* mutations," appears in the August issue of *Molecular Therapy* and was conducted by researchers from the University of Pennsylvania, the University of Florida, the University of Alabama, Emory University and AGTC.

Symptoms of XLRP begin with night blindness in young boys, followed by progressive constriction of the field of vision. Men with XLRP typically become legally blind at an average age of 45 years. The most common form of XLRP is caused by mutations in the RPGR gene. The treatment candidate used in the research and developed by AGTC is designed to provide a functional copy of this gene. XLRP is one of two lead development programs within AGTC's collaboration agreement with Biogen, announced in July 2015, along with X-linked retinoschisis.

"RPGR mutations resulting in XLRP are one of the most common forms of inherited retinal disease, and patients with these mutations currently have no treatment options," said co-lead study investigator William Beltran, DVM, Ph.D., Associate Professor of Ophthalmology, University of Pennsylvania School of Veterinary Medicine. "The results of these studies demonstrate important progress toward developing an effective therapy for patients living with this debilitating and progressive disorder."

To optimize the delivery and expression of a functional RPGR gene, researchers evaluated two promoter sequences in non-human primates; one from the IRBP gene and the other from the GRK1 gene. Results demonstrated that the IRBP promoter drove transgene expression only in rod photoreceptors, while the GRK1 promoter drove expression in both rod and cone photoreceptors. Subsequent analyses were conducted in a canine model of XLRP using vector constructs comprising the GRK1 promoter.

Additional analyses included evaluation of the safety and effects of a stabilized RPGR sequence delivered with an AAV2/5 vector (AAV2/5-GRK1-*hRPGRstb*) in canine models of early- and mid-stage disease; retinal and visual consequences of low- and high-dose vector administration at mid-stage disease compared with vehicle (balanced salt solution) control; and comparison of the AAV2/5-GRK1-*hRPGRstb* construct with AAV2/5-GRK1-*hRPGRco* (a new full-length stabilized and codon-optimized human RPGR).

Key findings from these analyses include:

- Injection of high or low doses of AAV2/5-GRK1-*hRPGRstb* to the eyes of animals with early- or mid-stage disease showed qualitative and/or quantitative preservation of retinal structure, as determined by the thickness of the outer nuclear layer (ONL) of the retina at two years of age. This preservation was not observed in animals receiving vehicle control. At higher vector doses, preservation of ONL thickness in animals with early-stage disease approached that of normal control animals.
- In short-term safety assessments, no ophthalmic alterations were seen and normal retinal lamination was retained; long-term safety assessments found no detectable ocular events or differences in ONL thickness; and

electroretinography (ERG) results showed no difference between treated and untreated regions of the same eye, and were similar to that of untreated eyes in control animals not affected by the canine form of XLRP.
- High and low doses of AAV2/5-GRK1-*hRPGRstb* rescued rod and cone function, as assessed with ERG at 103 weeks in animals treated at mid-stage disease compared with vehicle controls, with more pronounced and statistically significant effects observed at the high dose.
- High and low doses of AAV2/5-GRK1-*hRPGRstb* improved rod-mediated visual behavior in animals with mid-stage disease compared with vehicle controls, as assessed by maze and obstacle course testing under multiple illumination conditions, with greater improvements observed with the high dose.
- Comparison of AAV2/5-GRK1-*hRPGRstb* with AAV2/5-GRK1-*hRPGRco* showed no significant differences in ONL thickness between the two constructs based on retinal imaging; both vectors preserved ONL thickness, produced a typical localization of RPGR protein and corrected rod and cone opsin mislocalization, which is a key feature of photoreceptor disease.

The researchers conclude that the findings suggest that an AAV vector carrying a stabilized or a codon optimized full-length human RPGR gene sequence under the control of the human GRK1 promoter can be considered for advancement into a human clinical trial. This warranted further development of the drug candidate for XLRP.

"These data provide an important foundation for our XLRP development program," said Sue Washer, President and CEO of AGTC. "We are currently conducting studies that will support the filing of an Investigational New Drug application for our treatment candidate for XLRP caused by mutations in the RPGR gene, which we expect to submit to the U.S. Food and Drug Administration in the third quarter of 2017."

About AGTC

AGTC is a clinical-stage biotechnology company that uses its proprietary gene therapy platform to develop products designed to transform the lives of patients with severe diseases, with an initial focus in ophthalmology. AGTC's lead product candidates are designed to treat inherited orphan diseases of the eye, caused by mutations in single genes that significantly affect visual function and currently lack effective medical treatments.

AGTC's product pipeline includes ophthalmology programs in X-linked retinoschisis (XLRS), X-linked retinitis pigmentosa (XLRP), achromatopsia, wet age-related macular degeneration, and an optogenetics program with Bionic Sight. AGTC's non-ophthalmology programs include its adrenoleukodystrophy program and its otology program, which is in pre-clinical development, and the company expects to advance several otology product candidates into clinical development in the next few years. Each of AGTC's XLRS, XLRP and adrenoleukodystrophy programs is partnered with Biogen. AGTC employs a highly-targeted approach to selecting and designing its product candidates, choosing to develop therapies for indications having high unmet medical need that it believes are clinically feasible and present commercial opportunities. AGTC has a significant intellectual property portfolio and extensive expertise in the design of gene therapy products including capsids, promoters and expression cassettes, as well as, expertise in the formulation, manufacture and physical delivery of gene therapy products.

Forward Looking Statements

This release contains forward-looking statements that reflect AGTC's plans, estimates, assumptions and beliefs. Forward-looking statements include information concerning possible or assumed future results of operations, business strategies and operations, preclinical and clinical product development and regulatory progress, potential growth opportunities, potential market opportunities and the effects of competition. Forward-looking statements include all statements that are not historical facts and can be identified by terms such as "anticipates," "believes," "could," "seeks," "estimates," "expects," "intends," "may," "plans," "potential," "predicts," "projects," "should," "will," "would" or similar expressions and the negatives of those terms. Actual results could differ materially from those discussed in the forward-looking statements, due to a number of important factors. Risks and uncertainties that may cause actual results to differ materially include, among others: no gene therapy products have been approved in the United States and only two such products have been approved in Europe; AGTC cannot predict when or if it will obtain regulatory approval to commercialize a product candidate; uncertainty inherent in the regulatory review process; risks and uncertainties associated with drug development and commercialization; factors that could cause actual results to differ materially from those described in the forward-looking statements are set forth under the heading "Risk Factors" in the Company's Annual Report on Form 10-K for the fiscal year ended June 30, 2016, as updated by the Company's Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2017, as filed with the SEC. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Also, forward-looking statements represent management's plans, estimates, assumptions and beliefs only as of the date of this release. Except as required by law, we assume no obligation to update these forward-looking statements publicly or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future.

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