MeiraGTx Announces Five Posters at the European Society of Gene and Cell Therapy (ESGCT) 2024 Annual Congress

October 22, 2024

Multiple Posters Highlight the Breadth of Company's Novel Genetic Medicine and Cell Therapy Platforms

LONDON and NEW YORK, Oct. 22, 2024 (GLOBE NEWSWIRE) -- MeiraGTx Holdings plc (Nasdaq: MGTX), a vertically integrated, clinical-stage genetic medicines company, today announced the Company will exhibit five posters at the European Society of Gene and Cell Therapy (ESGCT) 2024 Annual Congress, which is being held from October 22-25, 2024, in Rome, Italy.

The posters are available on the Posters and Publications page of the Company's website.

The details of the poster presentations are as follows:

Poster Number: P0015
Abstract Title: *Evolution of a high-producing, modular upstream platform for AAV manufacturing*
Poster Session III: Tuesday 22 October from 19:30 to 21:00 CEST
Abstract:
The poster shows the evolution of MeiraGTx's upstream manufacturing platform, which was optimized and modulated through the choice of transfection reagents, adeno-associated virus (AAV) production enhancers, and transfection parameters, in fed-batch and perfusion culture mode. Over 3 years, we have achieved process optimizations yielding AAV titers up to $1x10^{12}$ VG/mL at harvest and >40% full capsids prior to polishing purification steps. Product quality attributes such as encapsidated residual plasmid DNA and host cell DNA are demonstrated to be controllable and maintained to satisfactory levels for patient safety through the combination of transfection reagent, small molecule enhancer, and transfection mix formulation parameters. Operating a perfusion-based process has also increased volumetric VG yield by approximately 40% and reduced plasmid DNA usage by at least 25%, without compromising on AAV productivity and product quality, demonstrating additional cost savings.

Poster Number: P0020
Abstract Title: *AAV-based evaluation of novel in silico promoters to drive expression in rod photoreceptors*
Poster Session II: Wednesday 23 October from 13:30 to 15:00 CEST
Abstract:
As rods outnumber cones by a ratio of 1:20 or greater in the retina and defects are common in rods leading to various ocular diseases, we sought to design and test novel promoters to drive expression specifically and at high expression levels in rods. Using an AI-assisted promoter engineering approach, ten novel promoter sequences were initially designed, cloned into an adeno-associated virus (AAV) backbone carrying eGFP and finally packaged into AAV5 or AAV7m8. In addition, AAV5 and AAV7m8 vectors were produced carrying the commonly used rhodopsin kinase (RK) promoter and eGFP. Following the initial screen, five second-generation, improved promoter sequences were designed combining elements from preferred performers of the first screen and again packaged into AAV5 and AAV7m8 for additional analysis. Wild-type mice received subretinal injections with the AAV5 vectors to assess promoter activity in the murine retina. Four weeks post vector administration, eyes were harvested for immunohistochemical analysis and qPCR expression analysis to determine specificity and expression levels, respectively. In parallel, the AAV7m8 vectors were used to assess promoter activity in human pluripotent stem cell (hPSC)-derived retinal organoids. Three weeks post-transduction, organoids were fixed and dissociated into single cells for FACS analysis or cryosectioned for immunohistochemistry. Sections were stained with markers of rod and cone photoreceptors and quantitatively assessed for eGFP co-expression. Lead candidates were identified based on promoter specificity to rod photoreceptors, determined by immunohistochemistry, and promoter strength, measuring expression level using qPCR or signal intensity using FACS.

Poster Number: P0129
Abstract Title: *Identification of highly potent and tissue-specific promoters with massively parallel screening*
Poster Session III: Tuesday 22 October from 19:30 to 21:00 CEST
Abstract:
Promoters are an integral component of any effective gene therapy. A potent promoter may allow for a therapeutic effect with a lower dosage, which could lower immune responses and manufacturing costs. A short promoter leaves more space for the transgene and mitigates the cargo capacity constraints of current gene therapy delivery methods. In addition, shorter promoters are especially useful for central nervous system applications as neuronal genes tend to have a longer coding region compared to non-neuronal genes. Here, we developed a massively parallel reporter assay (MPRA) to screen a synthetic library of over 240,000 promoters that are 182 bp long. This flexible AAV-based platform can be applied to diverse model systems including primary human tissue, iPSC-derived organoids, and non-human primates. Initial screening in transfected mouse Neuro2A cells identified hundreds of potent promoter candidates, of which 34 were selected for independent validation using flow cytometry. We identified 15 promoters exhibiting folds higher expression than CAG despite a 10-fold reduction in size in Neuro2A cells. Furthermore, 5 of these promoters are stronger than CMV and 3-fold smaller. In the human Huh7 cell line, all 15 promoters have lower expression than CAG indicating their specificity. In parallel, potent promoters were identified by this platform in human myotubes, primary mouse neurons, mouse liver, and the mouse gastrocnemius muscle. Independent validation of single candidates confirms the strength of our candidate promoters *in vivo*. These selected promoters can be further engineered using machine learning coupled with rational design to increase promoter potency. This approach allows the screening of hundreds of thousands of rationally designed small promoters (<200bp) capable of driving strong transgene expression in complex model systems. Our selected promoters harbor great potential for future gene therapy applications.

Poster Number: P0351

Abstract Title: *AAV-mediated gene therapy attenuates loss of vision in a mouse model of Bardet-Biedl-Syndrome 10*
Poster Session I: Tuesday 22 October from 19:30 to 21:00 CEST
Abstract:
Bardet-Biedl syndrome (BBS) is a group of inherited, autosomal recessive ciliopathies characterized by disturbances of cilia function in multiple cell types, leading to obesity, renal failure, and blindness. More than 20 causative genes are known with many mutations disabling the function of the BBSome, a protein complex regulating the movement of cargo proteins in and out of cilia. Mutations in the BBS10 gene are the second most common cause of BBS and account for more than 20% of all cases. In this study, we set out to optimize and identify an AAV vector carrying the human *BBS10* gene providing sustained efficacy and a good safety profile for clinical translation.

Human *BBS10* either under the control of the ubiquitous CAG promoter or the photoreceptor-specific rhodopsin kinase (RK) promoter was packaged into AAV8 and tested in Bbs10 KO mice at different doses. Whilst the CAG construct did not show efficacy, treatment with the RK construct rescued retinal function and thickness up to six months post-treatment when delivered at a high dose, accompanied by a partial correction of the localization of Syntaxin 3, a partner protein of BBS10. Interestingly, a 5-fold lower dose of AAV8.RK.hBBS10 was not therapeutic, although the equivalent dose of an AAV8.RK carrying mouse *Bbs10* was efficacious. These findings support the hypothesis that due to a species difference, the potency of the AAV8.RK.hBBS10 is potentially underestimated when assessed in Bbs10 KO mice. In parallel to the work in mutants, we performed a long-term safety study to overexpress human BBS10 under the RK promoter in wild-type mice. Up to six months post-injection, no significant detrimental effects on retinal function or retinal morphology were observed paving the way toward translation. Application for rare pediatric disease designation is currently underway.

Poster Number: P0753
Abstract Title: *Riboswitch-regulated gene and cell therapy*
Poster Session III: Thursday 24 October from 14:00 to 15:30 CEST
Abstract:
Controlled expression of delivered transgene is critical for both gene and cell therapies. Here, we report that by linking our synthetic aptamer to our alternative splicing gene expression platform, we have created a robust, synthetic mammalian riboswitch cassette that regulates gene expression tightly and dynamically in response to small-molecule inducers. In the presence of the small molecule, the splicing-based expression platform creates an “on” switch by sequestering a splice site of an alternative exon. Riboswitches that respond to these novel small-molecule inducers regulate transgene expression with high dynamic range in a dose-dependent manner. When delivered through an adeno-associated viral (AAV) vector to the liver or the muscle in mice, the engineered riboswitches reversibly regulate transgene expression via an orally delivered small-molecule inducer, providing precise control of transgene expression, with high dynamic range. With these riboswitches and orally available small-molecule inducers, we were able to regulate hormones such as human growth hormone, growth factors such as erythropoietin (Epo), and therapeutic antibodies such as anti-HER2 antibodies to efficacious levels *in vivo*. RiboCAR-T cells with riboswitch-controlled chimeric antigen receptors (CARs) had more stem/memory-like phenotypes, exhibiting superior anti-tumor activities against lymphoma when compared with conventional CAR-T cells that expressed constitutive CAR.
This robust gene regulation system enables both temporal and spatial control of gene expression, providing not only improved efficacy but also a safety mechanism for gene and cell therapies.

About MeiraGTx

MeiraGTx (Nasdaq: MGTX) is a vertically integrated, clinical-stage genetic medicines company with a broad pipeline of late-stage clinical programs supported by end-to-end manufacturing capabilities. MeiraGTx has internal plasmid production for GMP, two GMP viral vector production facilities as well as an in-house Quality Control hub for stability and release, all fit for IND through commercial supply. In addition, MeiraGTx has developed a proprietary manufacturing platform with leading yield and quality aspects and commercial readiness, core capabilities in viral vector design and optimization, and a transformative riboswitch gene regulation platform technology that allows for the precise, dose-responsive control of gene expression by oral small molecules. MeiraGTx is focusing the riboswitch platform on the delivery of metabolic peptides, including GLP-1, GIP, Glucagon, and PYY, using oral small molecules, as well as cell therapy for oncology and autoimmune diseases. MeiraGTx has developed the technology to apply genetic medicine to more common diseases, increasing efficacy, addressing novel targets, and expanding access in some of the largest disease areas where the unmet need remains high.

For more information, please visit www.meiragtx.com

Forward Looking Statement

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including, without limitation, statements regarding our product candidate development and anticipated milestones regarding our pre-clinical and clinical data, reporting of such data and the timing of results of data and regulatory matters, as well as statements that include the words “expect,” “will,” “intend,” “plan,” “believe,” “project,” “forecast,” “estimate,” “may,” “could,” “should,” “would,” “continue,” “anticipate” and similar statements of a future or forward-looking nature. These forward-looking statements are based on management’s current expectations. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, our incurrence of significant losses; any inability to achieve or maintain profitability, raise additional capital, repay our debt obligations, identify additional and develop existing product candidates, successfully execute strategic transactions or priorities, bring product candidates to market, expansion of our manufacturing facilities and processes, successfully enroll patients in and complete clinical trials, accurately predict growth assumptions, recognize benefits of any orphan drug designations, retain key personnel or attract qualified employees, or incur expected levels of operating expenses; the impact of pandemics, epidemics, or outbreaks of infectious diseases on the status, enrollment, timing and results of our clinical trials and on our business, results of operations and financial condition; failure of early data to predict eventual outcomes; failure to obtain FDA or other regulatory approval for product candidates within expected time frames or at all; the novel nature and impact of negative public opinion of gene therapy; failure to comply with ongoing regulatory obligations; contamination or shortage of raw materials or other manufacturing issues; changes in healthcare laws; risks associated with our international operations; significant competition in the pharmaceutical and biotechnology industries; dependence on third parties; risks related to intellectual property; changes in tax policy or treatment; our ability to utilize our loss and tax credit carryforwards; litigation risks; and the other important factors discussed under the caption “Risk Factors” in our Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, as such factors may be updated from time to time in our other filings with the SEC, which are accessible on the

SEC's website at www.sec.gov. These and other important factors could cause actual results to differ materially from those indicated by the forward-looking statements made in this press release. Any such forward-looking statements represent management's estimates as of the date of this press release. While we may elect to update such forward-looking statements at some point in the future, unless required by law, we disclaim any obligation to do so, even if subsequent events cause our views to change. Thus, one should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this press release.

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