MeiraGTx Announces the Presentation of Four Posters at the American Society of Gene and Cell Therapy (ASGCT) 2025 Annual Meeting

May 13, 2025

Multiple Poster Presentations Highlight the Depth and Novelty of MeiraGTx's Technology Platforms for Gene and Cell Therapy

LONDON and NEW YORK, May 13, 2025 (GLOBE NEWSWIRE) -- MeiraGTx Holdings plc (Nasdaq: MGTX), a vertically integrated, clinical stage genetic medicines company, today announced the Company will exhibit four poster presentations at the American Society of Gene and Cell Therapy (ASGCT) 2025 Annual Meeting, which is being held from May 13-17, 2025, in New Orleans, LA.

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

The details of the poster presentations are below:

Poster 507: *An Ultra-Low Dose of a Localized CNS Gene Therapy for Severe Pediatric Obesity*
Poster Session: Tuesday, May 13, 6:00-7:30 pm CDT
Abstract:
Brain-derived neurotrophic factor (BDNF) is a secreted growth factor that promotes neuronal health throughout the central nervous system and is a key signaling component of metabolic homeostasis. In the ventromedial hypothalamus (VmH), elevated leptin signals melanocortin 4 receptor (MC4R) expressing neurons to release BDNF, which then acts through tropomyosin receptor kinase B (TrkB) to signal fullness and reduce food intake. Patients with loss-of function mutations along this pathway develop severe early-onset obesity syndromes characterized by hyperphagia and food-related distress as young as six months old. Current therapeutic approaches such as bariatric surgery and glucagon-like peptide 1 (GLP1) agonists may be effective for generalized obesity, but do not result in significant, durable treatment for individuals with MC4R or BDNF deficiency. By directly delivering BDNF to the VmH through an adeno-associated virus (AAV)-based gene therapy, we aim to treat these individuals early in childhood in a safe, effective, and lasting way. Treating these children early could significantly improve their physical and emotional well-being and prevent the development of irreversible sequelae such as cancer and diabetes.

To achieve this, we developed a more potent vector which could decrease the AAV gene therapy dose required to maintain effective weight loss, potentially mitigating adverse effects associated with high levels of AAV administration. Our optimized BDNF clinical construct, designed by altering various cis-regulatory components, expresses BDNF up to 143-fold greater than basal levels *in vivo*, significantly higher than the original academic construct. This is well in excess of the levels shown to prevent weight gain in the diet-induced obesity (DIO) wild-type mouse model. This highly potent AAV-BDNF vector showed efficacy in DIO mice with significant dose-dependent weight loss observed across a wide therapeutic window, with a 60-fold-dose range. Delivery of AAV-BDNF to a single hemisphere of obese mice on high-fat diet resulted in dramatic weight loss up to approximately 40%, which plateaued at the level of wild-type lean controls. In comparison, weight loss in DIO animals injected daily with a GLP-1 agonist, semaglutide, plateaued at approximately 12%. Weight loss in AAV-BDNF treated mice has been maintained for at least three months and continues to be monitored to further assess the durability of AAV-BDNF. In addition to lower body weight, AAV-BDNF-expressing mice showed significantly improved glucose tolerance compared to control AAV-GFP-expressing obese mice.

To assess the safety of AAV-BDNF gene therapy administered directly to the hypothalamus, we performed biodistribution, hematology, serum chemistry, and brain histology. Because the hypothalamus controls additional behaviors besides feeding, we also assessed animals using the open field, novelty-suppressed feeding, food intake measurements, and standard opponent tests to survey other behavioral attributes. As previously reported, locomotion increased in AAV-BDNF-treated animals. More importantly, animals did not display heightened aggression after AAV-BDNF treatment and exhibited normal pro-social behaviors. Furthermore, AAV-BDNF treatment did not ablate the ability of animals to feed. Overall, our data suggest that AAV-BDNF is an effective and safe therapeutic strategy for severe-early onset pediatric obesity syndromes.

Poster 893: *Novel Rationally Designed Promoters Surpass CAG in Mouse and Human Models*
Poster Session: Tuesday, May 13, 6:00-7:30 pm CDT
Abstract:
Promoters are essential for gene expression and can be engineered to develop optimized gene therapies. Ideal promoters are short in length and confer tissue specificity as well as potent transgene expression. Approximately 50% of gene therapy clinical trials rely on the CAG or CMV promoters. However, high doses of gene therapies have recently led to serious adverse events in patients. Thus, there is a need to increase gene therapy vector potency to improve the safety profile of gene therapies. Accordingly, we aimed to engineer novel CAG-based constitutive promoters which are both shorter than the original sequence and lead to stronger transcriptional activity. CMV was excluded because it reportedly inactivates *in vivo*. These optimizations would allow for a lower effective dose which could potentially reduce immune responses after treatment and lower the cost of goods for gene therapy applications.

The CAG promoter is a hybrid promoter, 1.8 kb in length, consisting of the CMV immediate early enhancer, the chicken β-actin promoter, and a hybrid rabbit β-globin intron. We rationally designed a series of 82 new CAG promoter variants by systematically introducing modifications to each of the promoter elements and tested them in human and mouse *in vitro* and *in vivo* models. In our library of engineered CAG promoter variants, 51 are smaller than the original CAG, of which 22 are fewer than 1000 base pairs in length.

In HEK293T cells, 67 CAG promoter variants are stronger than the original CAG sequence with the strongest promoter exhibiting 13-fold improvement in potency. In both primary human hepatocytes and primary human myotubes, four CAG variants drove 15-fold higher transgene expression than the original while being ~40% shorter in length. These four variants and an additional strong CAG variant were packaged into AAV9 and administered either systemically or directly into the gastrocnemius muscle of C57BL/6 mice. After systemic administration, one variant in particular, C178, was found

to be stronger than the original CAG in the muscle, liver, heart, and brain while being 700 base pairs shorter in length. In the mouse muscle, four of these variants led to 0.5 to 2.5-fold stronger transgene expression three months after direct injection. In contrast, muscle-specific promoters that are used in the clinic such as Ck8e are significantly weaker than the original CAG promoter when assessed using the same bioimaging paradigm. Expression will continue to be evaluated to determine if these potent promoters have durable activity *in vivo*.

Here, we have shown several rationally designed CAG-based constitutive promoters which are both shorter than the original CAG sequence and yield higher transcriptional activity in human and mouse in vitro and in vivo models. These promoters show potential for the development of future gene therapies. In particular, these smaller, more potent CAG variants could be advantageous for the design of gene therapies for the muscle and central nervous system where transgenes are typically large, and packaging constraints are of major concern.

Poster 897: *Differential Usage of Transcription Factor Binding Sites to Boost Synthetic Promoter Activity*
Poster Session: Tuesday, May 13, 6:00-7:30 pm CDT
Abstract:
Transcription factor binding sites (TFBS) play a crucial role in regulating gene expression and can either enhance or repress expression depending on their function and context. Here, we designed a library of short synthetic promoters to evaluate the effect of differential TFBS usage in N2A, mouse neuroblastoma, and C2C12, mouse myoblasts, cell lines.

A massively parallel reporter assay was created to assess the transcriptional strength of 244,000 synthetic promoter sequences. These 182 bp sequences include a variable regulatory upstream region and one of six core promoters with known tissue specificity. Two ubiquitous, JeT and AdML, two muscle-specific, MCK and DES, and two liver-specific promoters, mTTR and AAT, were chosen to assess the impact of alternative TFBS usage on promoter specificity. Regulatory regions were generated to evaluate (i) the effect of each TFBS in isolation, and (ii) the combinatorial effect of selected and tissue-enriched TFBS. Promoter activity in each cell line was calculated as a normalized expression score, referred to as SoR, using Illumina-based sequencing data. Subsequently, the TFBS fold change, or Boost SoR, over the activity of the parent core promoter without any regulatory region was calculated.

Using Boost SoR, we categorized all TFBS as activators (Boost SoR ≥ 0.1, n=85,711), repressors (Boost SoR ≤ -0.1, n=53,146), or as having minimal impact on promoter performance (Boost SoR between -0.1 and 0.1, n=13,814). The top five activating TFBS tested with muscle-specific MCK achieved a four-fold or greater increase in expression compared to MCK alone, with the top boosting TFBS exhibiting a six-fold Boost SoR. The five most repressive TFBS combined with MCK reduced transcription by over five-fold. For JeT, the five strongest activating TFBS increased expression by three-fold or more, while the five most repressive TFBS decreased expression by four-fold or more. In total, 21.6% of all TFBS combined with JeT were characterized as activators with the strongest activators boosting expression by more than four-fold. Except for DES, all core promoters exhibited the highest boost in expression through homotypic, or repetition of the same TFBS, designs rather than through combinatorial approaches. Amongst the two hundred strongest activating homotypic TFBS designs for each of the core promoters, only six were consistently observed across promoters, emphasizing their high degree of selectivity. To further evaluate TFBS-promoter selectivity, we correlated the Boost SoR of TFBS across core promoters. On average, TFBS tested with JeT and MCK exhibited a lower correlation with other core promoters (R2JeT = 0.14, R2MCK=0.23), suggesting a higher TFBS selectivity of those promoters. Conversely, the constitutive promoter, AdML, showed a significantly higher correlation with the liver promoter, mTTR, and MCK, a muscle promoter (R2mTTR = 0.29, pmTTR=1.4E-81; R2MCK = 0.28 pMCK= 9.6E-77).

We successfully characterized TFBS that positively and negatively boost the expression from core promoters. By quantifying the boosting effects of differential TFBS, we demonstrated the ability to enhance the performance of the widely used and optimized JeT promoter. Furthermore, we identified TFBS uniquely associated with each promoter and sequences that should be excluded from active regulatory element design. This analysis represents a key asset when designing stronger synthetic promoters for gene therapy.

Poster 1040: *Preclinical Efficacy and Potency Assay Development of An Optimized AAV-hUPF1 Gene Therapy for Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD)*
Poster Session: Wednesday, May 14, 5:30-7:00 pm CDT
Abstract:
Amyotrophic lateral sclerosis (ALS) is a devastating progressive neurodegenerative disease that damages motor neurons in the brain and spinal cord. While the pathogenesis of ALS can result from either sporadic or familial inherited mutations, the underlying pathology in over 95% of cases is associated with dysregulation of TAR DNA-binding protein 43 (TDP-43). Here, we present the optimization and preclinical efficacy of AAV-hUPF1, a central regulator in nonsense-mediated RNA decay (NMD), in multiple ALS models. Our data and the mechanism of Up-frameshift 1 (hUPF1) action suggest that the efficacy of this therapy would be agnostic to patients' genetic background.

To improve AAV packaging and thus convey manufacturing benefits, we reduced the size of the original hUPF1 construct by 1.5kb while improving therapeutic efficacy in both *in vitro* and *in vivo* models. Using an efficient capsid for CNS delivery and a highly potent expression cassette, our therapeutic strategy is to minimize AAV dosage while maintaining a high level of expression and subsequent efficacy. The optimized AAV-hUPF1 effectively mitigated toxicity in TDP-43 and C9orf72 iNeuron models and restored the normal function of neurons derived from C9orf72 patient cell lines at a lower multiplicity of infection (MOI) than used for the original. Mechanistically, UPF1 target engagement was confirmed in transduced C9orf72 patient-derived neurons by the downregulation of known NMD targets. In a Fused in Sarcoma (FUS) mouse model of ALS, optimized AAV-hUPF1 significantly improved motor neuron survival to levels comparable to wild-type controls at approximately 36% transduction.

To further develop the AAV-hUPF1 program, we piloted different TDP-43 induced toxicity models as *in vitro* potency assays for manufacturing release. To induce cell death, TDP-43 was overexpressed in primary mouse neurons using AAV9 transduction, and in human SH-SY5Y cells using the doxycycline-inducible TET-ON system. While toxicity was reliably and robustly induced in the primary neuronal model, UPF1 co-expression did not result in a measurable global effect and thus did not meet the requirements for our assay development. In contrast, repeated experimentation in the stably transduced and differentiated SH-SY5Y cells showed that TET-inducible overexpression of TDP-43 caused significant toxicity in only about 50% of the cases, demonstrating that the TET-inducible system is too variable to be implemented as a reliable potency assay. After exploring gross neuronal toxicity as a strategy to establish a validated potency assay, we now aim to explore other approaches that are based on the proposed underlying mechanism of action for UPF1, including RNA homeostasis. Developing a robust potency assay is a major component in the manufacturing of clinical therapeutics and our goal towards treating ALS patients safely and effectively with AAV-hUPF1.

Collectively, the data from *in vitro* and *in vivo* studies using FUS, TDP-43, and C9orf72 models demonstrate that hUPF1 holds significant potential for treating the majority of patients with ALS and other degenerative diseases caused by TDP43 pathology such as Frontotemporal Dementia, as we continue the development of this program.

About MeiraGTx

MeiraGTx (Nasdaq: MGTX) is a vertically integrated, clinical-stage genetic medicines company with a broad pipeline with four late-stage clinical programs. Each of these programs use local delivery of small doses resulting in disease modifying effects in both inherited and more common diseases, in the eye, Parkinson's disease and radiation-induced xerostomia. MeiraGTx uses its innovative technology in optimization of capsids, promoters and novel translational control elements to develop best in class, potent, safe viral vectors. MeiraGTx's broad pipeline is supported by end-to-end in-house manufacturing. MeiraGTx has built the most comprehensive manufacturing capabilities in the industry, with 5 facilities globally, including two that are licensed for GMP viral vector production and a GMP QC facility with clinical and commercial licensure. In addition, MeiraGTx has developed a proprietary manufacturing platform process over 9 years based on more than 20 different viral vectors with leading yield and quality aspects and commercial readiness. Uniquely, MeiraGTx has developed a novel technology for in vivo delivery of any biologic therapeutic using oral small molecules. This transformative riboswitch gene regulation technology allows precise, dose-responsive control of gene expression by oral small molecules. MeiraGTx is focusing the riboswitch platform on the regulated *in vivo* delivery of metabolic peptides, including GLP-1, GIP, Glucagon, Amylin, PYY and Leptin, as well as cell therapy, CAR-T for liquid and solid tumors and autoimmune diseases, and additionally PNS targets addressing long term intractable pain. MeiraGTx has developed the technology to apply genetic medicine to 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 our pre-clinical data and reporting of such data and the timing of results of data, 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 or rare pediatric disease 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 March 31, 2025, 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.

Contacts

Investors:
MeiraGTx
Investors@meiragtx.com

or

Media:
Jason Braco, Ph.D.
LifeSci Communications
jbraco@lifescicomms.com